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Interventions to improve adherence to inhaled steroids for asthma (Review)

Normansell R, Kew KM, Stovold E

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[Intervention Review]

Interventions to improve adherence to inhaled steroids for asthma

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ABSTRACT

Background

Despite its proven efficacy in improving symptoms and reducing exacerbations, many patients with asthma are not fully adherent to their steroid inhaler. Suboptimal adherence leads to poorer clinical outcomes and increased health service utilisation, and has been identified as a contributing factor to a third of asthma deaths in the UK. Reasons for non-adherence vary, and a variety of interventions have been proposed to help people improve treatment adherence.

Objectives

To assess the efficacy and safety of interventions intended to improve adherence to inhaled corticosteroids among people with asthma.

Search methods

We identified trials from the Cochrane Airways Trials Register, which contains studies identified through multiple electronic searches and handsearches of other sources. We also searched trial registries and reference lists of primary studies. We conducted the most recent searches on 18 November 2016.

Selection criteria

We included parallel and cluster randomised controlled trials of any duration conducted in any setting. We included studies reported as full-text articles, those published as abstracts only and unpublished data. We included trials of adults and children with asthma and a current prescription for an inhaled corticosteroid (ICS) (as monotherapy or in combination with a long-acting beta$_2$-agonist (LABA)). Eligible trials compared an intervention primarily aimed at improving adherence to ICS versus usual care or an alternative intervention.

Data collection and analysis

Two review authors screened the searches, extracted study characteristics and outcome data from included studies and assessed risk of bias. Primary outcomes were adherence to ICS, exacerbations requiring at least oral corticosteroids and asthma control. We graded results and presented evidence in 'Summary of findings' tables for each comparison.

We analysed dichotomous data as odds ratios, and continuous data as mean differences or standardised mean differences, all using a random-effects model. We described skewed data narratively. We made no a priori assumptions about how trials would be categorised but conducted meta-analyses only if treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

Main results

We included 39 parallel randomised controlled trials (RCTs) involving adults and children with asthma, 28 of which (n = 16,303) contributed data to at least one meta-analysis. Follow-up ranged from two months to two years (median six months), and trials were conducted mainly in high-income countries. Most studies reported some measure of adherence to ICS and a variety of other outcomes such as quality of life and asthma control. Studies generally were at low or unclear risk of selection bias and at high risk of biases associated with blinding. We considered around half the studies to be at high risk for attrition bias and selective outcome reporting.

We classified studies into four comparisons: adherence education versus control (20 studies); electronic trackers or reminders versus control (11 studies); simplified drug regimens versus usual drug regimens (four studies); and school-based directly observed therapy (three studies). Two studies are described separately.

All pooled results for adherence education, electronic trackers or reminders and simplified regimens showed better adherence than controls. Analyses limited to studies using objective measures revealed that adherence education showed a benefit of 20 percentage points over control (95% confidence interval (CI) 7.52 to 32.74; five studies; low-quality evidence); electronic trackers or reminders led to better adherence of 19 percentage points (95% CI 14.47 to 25.26; six studies; moderate-quality evidence); and simplified regimens led to better adherence of 4 percentage points (95% CI 1.88 to 6.16; three studies; moderate-quality evidence). Our confidence in the evidence was reduced by risk of bias and inconsistency.

Improvements in adherence were not consistently translated into observable benefit for clinical outcomes in our pooled analyses. None of the intervention types showed clear benefit for our primary clinical outcomes - exacerbations requiring an oral corticosteroid (OCS) (evidence of very low to low quality) and asthma control (evidence of low to moderate quality); nor for our secondary outcomes - unscheduled visits (evidence of very low to moderate quality) and quality of life (evidence of low to moderate quality). However, some individual studies reported observed benefits for OCS and use of healthcare services. Most school or work absence data were skewed and were difficult to interpret (evidence of low quality, when graded), and most studies did not specifically measure or report adverse events.

Studies investigating the possible benefit of administering ICS at school did not measure adherence, exacerbations requiring OCS, asthma control or adverse events. One study showed fewer unscheduled visits, and another found no differences; data could not be combined.

Authors' conclusions

Pooled results suggest that a variety of interventions can improve adherence. The clinical relevance of this improvement, highlighted by uncertain and inconsistent impact on clinical outcomes such as quality of life and asthma control, is less clear. We have low to moderate confidence in these findings owing to concerns about risk of bias and inconsistency. Future studies would benefit from predefining an evidence-based 'cut-off' for acceptable adherence and using objective adherence measures and validated tools and questionnaires. When possible, covert monitoring and some form of blinding or active control may help disentangle effects of the intervention from effects of inclusion in an adherence trial.

PLAIN LANGUAGE SUMMARY

Strategies to help people with asthma take their steroid inhaler as prescribed

Background to the question

Inhalers containing steroids improve asthma-related symptoms and reduce asthma attacks when taken regularly. But many people with asthma do not take them as prescribed. This leads to more symptoms and flare-ups, which have been linked to a third of asthma deaths in the UK.

Missing doses is sometimes called 'non-adherence'. Reasons for missing doses vary from person to person. For example, people often forget to take their inhaler or have a busy and unpredictable lifestyle that makes it difficult to fit this in. Some people do not appreciate the need for taking inhalers as prescribed. Some people choose to reduce or discontinue taking steroids. This can happen for many reasons, including side effects, fear of side effects or a perception that benefits do not outweigh disadvantages.

The aim of this review was to find out whether strategies to help people with asthma take their steroid inhaler really work, and whether improved adherence leads to other benefits.

Study characteristics

We found 39 studies including more than 16,000 adults and children with asthma who were taking a steroid inhaler. Most studies collected data at six months, so we can really apply the messages in this review only over six months - we cannot say whether these methods are effective in a few years time, for example. We searched multiple sources for relevant studies. This review is current as of November 2016.

Different studies tried different ways to help people take their inhaler more regularly. We grouped studies according to four ways of helping people take their inhaler: providing education about adherence (20 studies); using electronic monitoring or reminders to take the inhaler (11 studies); making the drug easier to take (e.g. once instead of twice a day, one inhaler instead of two) (four studies); and giving the inhaler during school hours (three studies).

We mainly looked for whether strategies helped people to take their inhaler as prescribed, and whether people had fewer asthma attacks and better asthma control.

Key results

People who were given education were better at taking their inhaler than controls; 20% more people took their treatment (likely to be somewhere between 8% and 33% more). Those given trackers or electronic reminders were 19% better at using their inhaler than controls (14% and 25%). People who were given an easier way of taking their inhaler (e.g. fewer times a day) were only 4% better than those who carried on as usual (2% and 6%).

Unfortunately, these efforts to help people take their inhaler as prescribed generally did not lead to obvious benefit for things like asthma control and number of attacks, but in most cases, we could not tell either way. We also did not see a difference for quality of life or time people needed off school or work, but the evidence was often uncertain.

Studies investigating the possible benefit of giving children their inhaler during school hours did not actually measure how often they missed doses.

Quality of the evidence

It's difficult to tell whether these different strategies are worth using because studies were quite different from one other. This variation means that we cannot be sure what the real benefit is, beyond improving adherence. Sometimes we did not find enough studies to detect a difference between groups. The fact that most people knew which group they were in also reduced our confidence in the findings because this can affect things like how positively people respond to questionnaires. We had concerns about how many people dropped out of about half the studies, and we are uncertain whether studies reported everything they measured.

Key message

The studies we found suggest that various strategies can help people with asthma take their inhaler better, compared with "control" (e.g. usual asthma care). However, many of these studies were quite different from one another, and we are not certain about whether people will find that their asthma is improved as a result of this approach.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Adherence education compared with controls for asthma

Patient or population: asthma
Setting: community
Intervention: adherence education
Comparison: control group (no education)

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with controls	Risk with adherence education				
% Adherence WMD of follow-up 71.7 weeks (all studies)	**Objective measures**	Mean adherence in the control group was **46.7%**	Mean adherence with adherence education was **20.13% higher** (7.52 higher to 32.74 higher)	-	280 (5 RCTs)	⊕⊕◯◯ **LOW**[a,b,c]	Only studies in which adherence was measured with an electronic monitor
	All measures	Mean adherence in the control group was **57.1%**	Mean adherence with adherence education was **11.59% higher** (3.72 higher to 19.46 higher)	-	1693 (10 RCTs)	⊕⊕◯◯ **LOW**[a,b,c]	
Exacerbations requiring OCS (people with 1 or more) WMD of follow-up 30.8 weeks		**149 per 1000**	**242 per 1000** (148 to 370)	OR 1.82 (0.99 to 3.36)	349 (3 RCTs)	⊕⊕◯◯ **LOW**[a,d]	
Asthma control (ACQ) WMD of follow-up 28.5 weeks		Mean ACQ score was **1.52**	Mean score with adherence education was **0.03 better** (0.49 better to 0.43 worse)	-	455 (4 RCTs)	⊕⊕⊕◯ **MODERATE**[a,e]	Lower score indicates better control. Scale 0 to 6. MCID 0.5

Asthma control (ACT) WMD of follow-up 29.5 weeks	Mean ACT score was **18.88**	Mean score with adherence education was **0.30 better** (1.43 better to 0.82 worse)	-	333 (3 RCTs)	⊕⊕⊕○ **MODERATE**[a,e]	Higher score indicates better control. Scale 5 to 25. MCID 3
Unsheduled visits to a healthcare provider (people with 1 or more) WMD of follow-up 67.2 weeks	**159 per 1000**	**83 per 1000** (35 to 184)	OR 0.48 (0.19 to 1.19)	688 (4 RCTs)	⊕○○○ **VERY LOW**[a,b,d,f]	Includes visits to ED, GP, hospital for any cause
Absenteeism WMD of follow-up 63.3 weeks	We did not perform an analysis of absences because the data were heavily skewed		-	109 (2 RCTs)	Not graded	
Quality of life (AQLQ) WMD of follow-up 27.4 weeks	Mean AQLQ score was **5**	Mean score with adherence education was **0.01 better** (0.20 worse to 0.23 better)	-	734 (6 RCTs)	⊕⊕⊕○ **MODERATE**[a,e]	Higher score indicates better QOL. Scale 1 to 7. MCID 0.5

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI)

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; CI: confidence interval; ED: emergency department; GP: general practitioner; MCID: minimal clinically important difference; OCS: oral corticosteroid; OR: odds ratio; QOL: quality of life; RCT: randomised controlled trial; WMD: weighted mean duration

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded once primarily owing to risk of bias from open-label trials and some concerns regarding attrition bias, selective reporting and selection bias (-1 risk of bias)
[b] Downgraded once owing to inconsistency between study results (-1 inconsistency)
[c] Funnel plot examined; no clear evidence of publication bias (no downgrade for publication bias)
[d] Confidence intervals include no difference and/or potential important harm or benefit of the intervention (-1 imprecision)

[e] Confidence intervals fall within the established MCID for this scale (no downgrade for imprecision)

[f] Studies contributing to this analysis reported different types of unscheduled visits and some recorded visits for any cause rather than asthma alone (-1 indirectness)

[g] Unclear how absenteeism was defined or reported, and different participants may have different thresholds for missing work or school. One study was conducted in children and the other in adults. Combined, this makes the outcome hard to interpret

BACKGROUND

Description of the condition

Asthma is a chronic breathing condition that affects more than 300 million adults and children worldwide (Global Asthma Report 2014). 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 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 (CDC 2016). Asthma is under-diagnosed and under-treated worldwide. 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).

The mainstay of asthma treatment for all but the mildest cases consists of inhaled corticosteroids (ICSs) (Barnes 1993), which are also known as 'preventer' or 'controller' medications (i.e. the intention is that they are used once or twice daily (depending on the preparation), even when well, to maintain control over symptoms). Inhaled corticosteroids, which are delivered directly to a patient's airways via an inhaler or a nebuliser, work by suppressing the multiple inflammatory cascades that are activated in the airways of a person with asthma. Inflammation leads to increased mucus production and airway constriction, which in turn contribute to symptoms of asthma. Reduction in underlying inflammation through sustained use of an ICS can result in symptom improvement and reduced asthma-related morbidity and mortality (Barnes 2003; Bårnes 2015).

Inhaled corticosteroids commonly used today include budesonide, beclomethasone, fluticasone (propionate and furoate), mometasone and ciclesonide. They can be given alone or in combination with other preventer medications such as long-acting beta$_2$-agonists (LABAs) or leukotriene receptor antagonists (LTRAs) (BNF).

Description of the intervention

Despite its proven efficacy, many patients are not fully adherent to their prescribed ICS (Bårnes 2015). Adherence is described by the World Health Organization (WHO) as "the degree to which use of medication by the patient corresponds with the prescribed regimen"; WHO emphasises the "diversity and complexity of adherence behaviour". In addition, patients with asthma may be fully adherent to preventer medication when symptomatic but poorly adherent when well (WHO Report 2003). This may reflect the fact that, unlike rescue medication, which gives immediate relief of symptoms (i.e. a 'reliever' or 'rescue' inhaler containing a short-acting beta$_2$-agonist (SABA) such as salbutamol), an ICS given for airway inflammation may take several weeks to provide maximal benefit.

Reasons for non-adherence to asthma therapies, including ICSs, vary among individuals. Commonly cited reasons include complexity of the treatment regimen; cost; administration route; and patient beliefs about therapy, including safety, necessity and risk of dependence. Lower socioeconomic status, inclusion in a minority ethnic group and fewer years of education have also been associated with reduced adherence (Bårnes 2015; Bender 2005; Clark 1999; Cochrane 1999).

Understanding the underlying reasons for non-adherence is essential for tackling the problem. The WHO Report 2003 has subcategorised these reasons as follows.

- 'Erratic non-adherence' - perhaps most common and largely the result of forgetfulness or a busy, unpredictable lifestyle.
- 'Unwitting non-adherence' - usually the result of failure to appreciate the specifics of regimens or the need for adherence.
- 'Intelligent non-adherence' - the result of a purposeful choice to reduce or discontinue ICS use for many reasons, including side effects, fear of side effects or a perception that the benefits do not outweigh the disadvantages.

Similarly, Horne 2002, which reported a cross-sectional survey of people with asthma who completed validated questionnaires, identified that adherence was primarily associated with doubts about the necessity for the medication and concerns about the side effects of treatment. This study reported that a more negative perception of the consequences of illness is associated with poorer adherence to preventer medication. A possible explanation for this unexpected finding is that those who are already poorly adherent may be more likely to experience poorer asthma control and thus may rate the consequences of illness more negatively.

Interventions to improve adherence to ICS may take many forms, including audiovisual reminders (Charles 2007), electronic monitoring of dosing with clinician feedback (Onyirimba 2003), interactive voice response system via mobile phone (Mulvaney 2013), text message reminders (Johnson 2015) and more comprehensive patient or parent education (Bender 2002).

How the intervention might work

How the intervention works will be directly related to the type of non-adherence targeted and the type of intervention offered. The simplest interventions proposed to tackle 'erratic non-adherence' might work by providing a very basic prompt to patients to remember to use their inhaler. Multi-faceted interventions that involve tackling 'unwitting' or 'intelligent' non-adherence might comprise patient education and partnership building between healthcare professionals and patients and are likely to work through more complex psychological and behavioural pathways.

A recently updated Cochrane Review assessing the evidence for interventions to improve adherence across the whole spectrum of health care identified 109 randomised controlled trials (RCTs) for inclusion. Review authors concluded that a small number of trials, which implemented complex interventions, demonstrated improvement in adherence and clinical outcomes, suggesting that the more rudimentary interventions generally have little impact. This may reflect the likelihood that any individual under treatment for asthma will likely have a combination of reasons for non-adherence, possibly both intentional and unintentional (Horne 2002). However, the highly complex nature of the interventions implemented in these 'successful' trials casts doubts on their feasibility in a real-life setting (Nieuwlaat 2014).

Medication adherence is recognised to deteriorate often during adolescence (Dinwiddie 2002). Patients in this age group might be particularly receptive to newer technologies for assisting with adherence, for example, Internet-based care and text message reminders. However, the authors of Nieuwlaat 2014 concluded that evidence is currently insufficient to show with certainty whether these newer methods of improving adherence are effective.

Lower levels of adherence in minority communities and among those from lower socioeconomic groups suggest that even when access to health care and prescription coverage is equal (Krishnan 2001), cultural tailoring of interventions may be required for successful treatment.

Why it is important to do this review

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 2015 demonstrated that patients who are adherent to their preventer medication make fewer claims for oral corticosteroid prescriptions, reflecting a lower rate of exacerbation. Williams 2003 identified an association between hospitalisations and emergency department visits and non-adherence to ICS. Murphy 2012 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, both of which are markers of poorly controlled asthma. 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 is incurred by controlled asthma (Barnes 1996; Global Asthma Report 2014).

Evidence shows that many people with asthma benefit greatly from regular use of an ICS. However, ways that healthcare professionals can best assist patients in maintaining adherence remain unclear. We are conducting this review to explore this topic.

OBJECTIVES

To assess the efficacy and safety of interventions intended to improve adherence to inhaled corticosteroids among people with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel and cluster RCTs of any duration conducted in any setting. If we identified cross-over trials, we included only data from the first part of the study because of the potential for carry-over effects of the intervention.

We included studies reported as full-text articles, those published as abstracts only and unpublished data.

Types of participants

We included adults and children of any age with a diagnosis of asthma, according to international or national guidelines or as diagnosed by a healthcare professional, and currently prescribed an ICS alone or in combination with a LABA. We excluded participants with other respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) or bronchiectasis. If we identified trials in which only a subset of participants had received a diagnosis of asthma, we included these participants if we could obtain disaggregated data. If we identified trials targeting improved adherence to asthma therapies generally, and at least 80% of participants were using an ICS at baseline, we included these trials in the review. We also included trials in which the intervention was targeted at a healthcare professional (the trial "participant"), who in turn would deliver the adherence intervention to patients with asthma.

Types of interventions

We included trials that compared an intervention primarily aimed at improving adherence to ICS (± LABA) versus:

- usual care/no additional intervention;
- an alternative intervention that does not primarily aim to increase adherence; or

- an alternative intervention of a different type or intensity, also aimed at improving adherence.

Interventions may range from simple automated reminders to more complex behavioural, psychological and motivational interventions. Interventions may be delivered to the participant or to the parent/career by any healthcare professional or trained peer. Interventions may also be delivered to a healthcare professional. We allowed other co-interventions in the management of asthma provided they were provided in the same way for intervention and comparison groups, for example, a personalised asthma action plan (PAAP) + adherence prompt versus PAAP alone.

Types of outcome measures

Primary outcomes

- Adherence to ICS (as reported by trialists; e.g. self-report via diary or questionnaire, electronic monitoring, prescription monitoring/pharmacy claims data).
- Exacerbations requiring at least oral corticosteroids.
- Asthma control (ideally measured on a validated scale such as the Asthma Control Test (ACT)).

Secondary outcomes

- Unscheduled visits to a healthcare provider.
- Absenteeism from work/school.
- Quality of life (ideally measured on a validated scale such as the Asthma Quality of Life Questionnaire (AQLQ)).
- All adverse events*.

We chose adherence as a primary outcome, as studies will be aiming to improve this outcome. However, we believe it is important to assess whether improvement in adherence translates into improved clinical outcomes; thus, we have included exacerbations and asthma control as primary outcomes in the belief that these are important to patients. Outcomes of adverse events, absenteeism and quality of life are also important to patients. Unscheduled visits to a healthcare provider are important to patients as well and serve as a marker of usage of healthcare services.

If outcomes were reported at multiple time points, we extracted and included the latest reported time point. If studies reported post-intervention follow-up, we extracted this information and presented it narratively.

Reporting one or more of the outcomes listed here was not a criterion for inclusion of trials in this review.

*If we identified serious adverse events reported as 'asthma', we described these narratively, as they are likely to represent a severe exacerbation requiring at least hospitalisation.

Search methods for identification of studies

Electronic searches

We identified trials 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.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org/).
- Weekly searches of MEDLINE Ovid SP 1946 to date.
- Weekly searches of Embase Ovid SP 1974 to date.
- Monthly searches of PsycINFO Ovid SP.
- Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
- Monthly searches of the Allied and Complementary Medicine Database (AMED) EBSCO.
- 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 provided in Appendix 1. See Appendix 2 for search terms used to identify studies for this review. We conducted the primary search on 20 May 2016, and updated the search on 18 November 2016.

We conducted additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (all years to 18 November 2016) and MEDLINE Ovid (1946 to 18 November 2016) to identify adherence trials targeting mixed populations including people with asthma (Appendix 2).

We searched the following trials registries on 20 May 2016 and 18 November 2016.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We did not apply any restrictions on the language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturer websites for trial information.

We searched on 23 November 2016 for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

We used the Rayyan Web app (Elmagarmid 2014) to independently screen titles and abstracts of all studies identified by the search for possible inclusion, and we coded each study as 'include' (eligible or potentially eligible/unclear) or 'exclude'. KK screened all titles and abstracts, and RN and ES each screened one-half. We retrieved full-text study reports/publications, and two review authors (RN and KK) independently screened them to identify studies for inclusion, and to identify and record reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted the third review author (ES). We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

We planned to use Covidence 2015 to extract study characteristics and outcome data, but we found it too time consuming and instead used an Excel data extraction form that we each piloted on at least one study. We planned that one review author (RN) would extract the following study characteristics from included studies, but instead we shared the studies equally between all three review authors (RN, ES and KK).

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

Each review author extracted outcome data independently from two-thirds of the studies so that data from each study were extracted twice. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. We resolved disagreements by reaching consensus or by involving a third review author (RN, KK or ES). One review author (RN) transferred data to the Review Manager (RevMan 2014) file. We double-checked that data had been entered correctly by comparing data presented in the systematic review against study reports. A second review author (KK or ES) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

As for numerical data extraction, each review author independently assessed risk of bias for two-thirds of the included studies, so that each study was assessed twice. We used the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with the third review author who had not already assessed the study (RN, KK or ES). We assessed risk of bias according to the following domains.

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

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for an unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering a treatment effect, we took into account the risk of bias for studies that contributed to that outcome.

Assesment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data using Mantel-Haenzsel odds ratios (ORs) with a random-effects model and 95% confidence intervals (CIs). When rare events were reported, we used Peto ORs. When data were reported as rates or times-to-events (e.g. exacerbations), we analysed them as time-to-event or rate ratios. We transformed reported rate ratios into log-rate ratios and analysed them using a random-effects model and generic inverse variance (GIV) in Review Manager 5 (RevMan 2014). We entered data presented as a scale with a consistent direction of effect.

We analysed continuous outcomes (e.g. ACT, AQLQ) as mean differences (MDs) or as standardised mean differences (SMDs) using a random-effects model and 95% CIs. We used change from baseline scores when available.

We undertook meta-analyses only when this was meaningful (i.e. if treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

We narratively described skewed data reported as medians and interquartile ranges.

When multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. intervention A vs usual care, intervention B vs usual care) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

If both change from baseline and endpoint scores were available for continuous data, we used change from baseline unless most studies reported endpoint scores. Similarly, we preferred adjusted data examined by analysis of variance (ANOVA) to account for baseline differences when available.

When both per-protocol/completer and intention-to-treat (ITT) analyses were provided in a single report, we used the latter.

Unit of analysis issues

We analysed dichotomous data using participants (rather than events) as the unit of analysis. However, if exacerbations were reported as rate ratios, we analysed them on this basis. We meta-analysed data from cluster RCTs only if available data had been, or could be, adjusted to account for clustering. We adjusted data from Foster 2014 for meta-analysis using an intracluster correlation coefficient (ICC) of 0.037 (based on the ACT score, kindly supplied by the study author team). However, this adjustment had very little impact on the meta-analyses, and so we have used the raw unadjusted data.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to request missing numerical outcome data when possible (e.g. when a study is identified as abstract only). When this was not possible, and missing data were thought to introduce serious bias, we considered this in the GRADE rating for the affected outcome.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported this and explored possible causes through prespecified subgroup analyses.

Assessment of reporting biases

When we were able to pool more than 10 studies, we created and examined a funnel plot to explore possible small study and publication biases.

Data synthesis

We used a random-effects model and performed a sensitivity analysis using a fixed-effect model.

'Summary of findings' table

We created four 'Summary of findings' tables, one for each of the comparisons, using the following outcomes: adherence to ICS; exacerbations requiring at least an oral corticosteroid (OCS); asthma control; quality of life; unscheduled visits to a healthcare provider; absenteeism from work/school; and adverse events. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Type of intervention: interventions meeting the definition of a complex intervention* versus simpler interventions.
- Age of participants: adults versus adolescents versus children.
- To whom the intervention is delivered: participant/parent/career versus healthcare professional.

We constructed an additional table to present other potential factors across studies that may alter the treatment effect (e.g. type, delivery, dose and schedule of ICS; whether treatment was given in a combination inhaler with a LABA; baseline severity of asthma). We used the following outcomes in subgroup analyses.

- Adherence to ICS.
- Exacerbations requiring at least an OCS.
- Asthma control.

We used the formal test for subgroup interactions provided in RevMan 2014.

*Complex interventions are conventionally described as those including 'several interacting components' (Campbell 2000). From a public health point of view, complex interventions, which are likely to involve a substantial educational element, and population-based interventions, which may include cluster RCTs, are thought to have greater overall impact on patient behaviour. Simpler interventions, such as cue reminders, will not address the more complex issues of adherence, and effects may be less likely to persist beyond removal of the intervention. Thus, we considered this an important subgroup analysis for inclusion.

Sensitivity analysis

We planned the following sensitivity analyses.

- Excluding unpublished data.
- Excluding trials considered at high risk of selection bias.
- Excluding trials in which not all participants were prescribed ICS at baseline.
- Excluding trials in which adherence was measured via non-objective methods (e.g. diary, self-report). In a post hoc change to our analysis plan, we have presented studies using objective measures (i.e. electronic inhaler monitors) as the primary analysis for % adherence, as we deemed this to be a more useful analysis. An analysis including studies using all measures then follows.

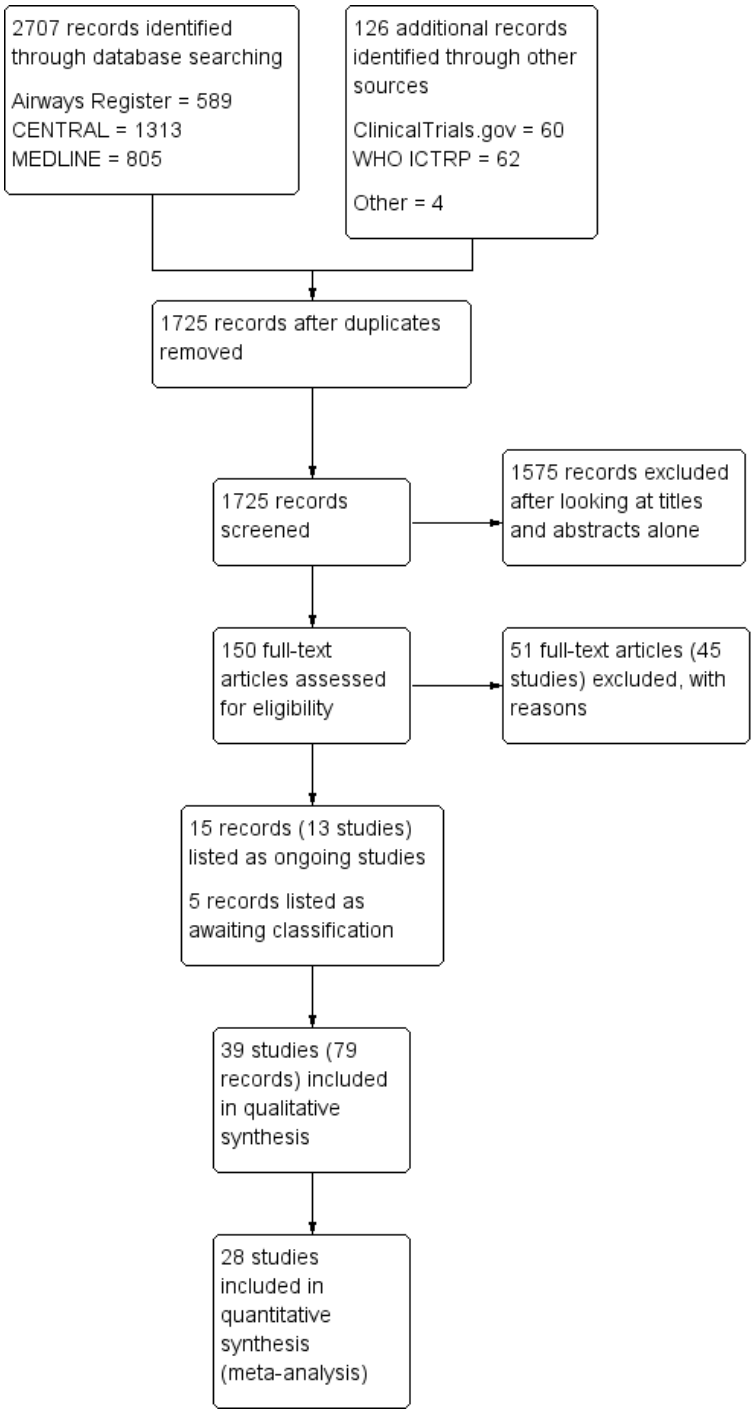
RESULTS

Description of studies

Results of the search

Through database searches, we retrieved 2707 references. Our searches of other resources, including trials registries, revealed 127 additional records. Once duplicates had been removed, we had a total of 1725 records left to screen. We excluded 1575 records on the basis of titles and abstracts. We obtained the full text of the remaining 150 records. We excluded 45 studies (51 references), added five studies to Studies awaiting classification and listed 13 studies as ongoing (15 records). We included 39 studies (79 references). For further details of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Thirty-nine studies met our inclusion criteria, and 28 of these contributed data to at least one meta-analysis. These studies included a total of 16,303 participants who were randomly assigned to comparisons of interest in this review. The largest study was a pragmatic trial that included 9603 pre-existing users of ICS, and the smallest included 12. The median total number of participants was 102. Investigators reported three trials as conference abstracts only (Black 2008; Hart 2002; NCT02451709), one on the clinicaltrials.gov website (NCT02413528) and one as a pharmaceutical company report (ADERE PEDIATRIC 1). The remainder were full-text peer-reviewed journal articles. We present a summary of the characteristics of included studies in Table 1.

Methods

As per our protocol, all included trials were RCTs with parallel design that compared an intervention to improve adherence to inhaled corticosteroids versus usual care or an alternative intervention not specifically designed to improve adherence, or of a lower intensity. Two studies used a cluster randomised design (Foster 2014; NCT00459368); the remainder were randomised at an individual participant level. One study included four relevant arms (personalised adherence discussion (PAD); inhaler reminders and feedback (IRF); PAD + IRF; and usual care; Foster 2014). Two studies included three relevant arms: NCT00233181 randomised participants to adherence monitoring and education, education or usual care; and NCT00166582 randomised participants to a team work intervention, an asthma education intervention (not deemed relevant to this review) or usual care. The remainder were two-arm parallel-group trials.

Intevention length varied, and follow-up continued from two months to two years. The median duration of follow-up was 24 weeks. Several studies reported a previous run-in period during which participants were stabilised on an asthma treatment regimen. Outcome data were extracted at the last time point reported to assess enduring effects of the intervention. Trials were conducted in a variety of mainly high-income countries worldwide. Most were carried out in the USA (Bender 2010; Gerald 2009; Halterman 2004; Kamps 2008; Mann 1992; NCT00115323; NCT00149487; NCT00166582; NCT00233181; NCT00414817; NCT00459368; NCT00958932; NCT01169883; NCT01175434; NCT01714141; NCT02413528; Onyirimba 2003), the UK (Bosley 1994; Hart 2002; Koufopoulos 2016; NCT01064869; NCT02451709; Price 2010), New Zealand (ACTRN12606000508572; Black 2008; Chan 2015; Charles 2007) and Australia (ACTRN12607000489493; Burgess 2007; Foster 2014). The remainder were carried out in Brazil (ADERE PEDIATRIC 1; Chatkin 2006), Norway (Gallefoss 1999), Sweden (NCT00516633), The Netherlands (Vasbinder 2015 E-MATIC), Canada (NCT01132430), Belgium (Mehuys 2008), Denmark (Strandbygaard 2010) and Denmark and Switzerland (Ulrik 2009).

Participants

We included studies involving both children and adults. Eighteen studies included only children, 20 studies included adults and/or adolescents only and one study recruited both adults and children. Most studies did not specify the ethnicity of participants.

All studies included participants with a diagnosis of asthma. Almost all studies required participants to be using ICS at baseline, although in two studies (Strandbygaard 2010; Ulrik 2009), some participants were commenced on ICS during the run-in period. Asthma severity at baseline was inconsistently reported, so it is not possible to characterise the population in this review as a whole. When available, we extracted information about baseline severity and reported this in the Characteristics of included studies tables.

Interventions

Studies included a variety of comparisons, which we classified into four broad groups. Some studies appear in more than one comparison, as they included three or more arms. Most studies did not specify which additional medications were allowed or disallowed, so we assume that most participants continued their usual asthma medication regimen. We have outlined below the four broad comparisons.

Adherence education versus control (Table 1)

We included the following studies in this group: Bender 2010; Chatkin 2006; Foster 2014; NCT00115323; NCT00149487; NCT00166582; NCT00958932 (PAD and PAD + IRF groups vs IRF and control groups); ADERE PEDIATRIC 1; Gallefoss 1999; Hart 2002; Kamps 2008; Mehuys 2008; NCT00233181 (adherence monitoring and education vs control and education alone vs control); NCT00516633; NCT01064869; NCT01132430; NCT01169883; Onyirimba 2003 (adherence education and usual care arms); and Ulrik 2009; and NCT00414817. As per our protocol, we further classified these studies into those delivering a complex intervention versus those not delivering a complex intervention. We performed subgroup analysis when possible according to this classification.

Included studies tested a wide range of educational interventions, including one-to-one and group face-to-face adherence education

sessions; motivational interviewing; family-based problem-solving interventions; team work interventions; nurse-led psychoeducation; telephone interventions; and interactive voice recognition systems. Full details can be found under Characteristics of included studies and are summarised in Table 1.

We classified most of the education interventions as complex (i.e. they involved multiple interacting components and were tailored to the individual). However, we classified as non-complex three studies using voice recognition software to deliver adherence education and reminders (Bender 2010; NCT00414817; NCT00958932). Participants in Chatkin 2006 received a maximum 10-minute phone call from a trained nursing student to promote adherence; we judged this intervention to be non-complex, although we lacked detail about the contents of the call. Another study, which deviated from protocol and for which we do not have results, stated that participants received telephone 'medical guidance'; we classified this intervention as non-complex (ADERE PEDIATRIC 1).

Electronic trackers or reminders versus control (Table 2)

Studies that used electronic adherence trackers plus feedback to participants included ACTRN12607000489493; Foster 2014 (IRF and IRF + PAD groups vs PAD and control groups); NCT00233181 (adherence education and monitoring vs education alone); NCT01714141; NCT02451709; and NCT00459368.

Studies that used electronic reminders alone, without an adherence feedback discussion, included Black 2008; Chan 2015; Charles 2007; Strandbygaard 2010; and Vasbinder 2015 E-MATIC.

We classified studies in this group as non-complex if they tested automated reminders such as text messages or an inhaler device with an audible or visual alarm system. However, if participants received tailored feedback from a healthcare professional based on adherence data acquired through electronic monitoring, we classified this intervention as complex (ACTRN12607000489493; Foster 2014; NCT00233181; NCT00459368; NCT02451709). Full details can be found under Characteristics of included studies and are summarised in Table 2.

Simplified drug regimen versus usual drug regimen (Table 3)

Studies that aimed to improve adherence by randomising participants to a simplified therapeutic regimen included ACTRN12606000508572; Bosley 1994; Mann 1992; and Price 2010. We classified all four studies as providing a non-complex intervention.Full details can be found under Characteristics of included studies and are summarised in Table 3.

School-based directly observed therapy (Table 4)

Gerald 2009, Halterman 2004 and NCT01175434 randomised children to receive their ICS at school or usual care. Gerald 2009 and Halterman 2004 were classified as non-complex, as the intervention was largely limited to providing school-based ICS therapy. NCT01175434 was classified as complex, as participants also underwent web-based screening to assess children's asthma, which generated a report that was sent to their primary care provider and was used to adjust the medication regimen. Full details can be found under Characteristics of included studies and are summarised in Table 4.

Finally, we were unable to classify several studies according to the above categories. Burgess 2007 used an "incentive" inhaler device (the "Funhaler") to encourage children to adhere to their inhaled medication. Koufopoulos 2016 trialled use on an online community of people with asthma ("AsthmaVillage") to improve adherence.

We have provided additional details of these studies under Characteristics of included studies.

Outcomes

Outcomes reported were not consistent across reviews, and investigators did not always use validated scales. Almost all included studies reported some measure of adherence, usually as a percentage, with 100% showing complete adherence, but the way in which this was captured and calculated varied between studies. When possible, we extracted and presented this information in Characteristics of included studies and Table 1. The three studies in which the intervention consisted of supervised ICS therapy at school did not report adherence as an outcome (Gerald 2009; Halterman 2004; NCT01175434).

Many included studies used an objective measure of adherence; this was often an electronic inhaler monitoring device. Named devices used included the "SmartInhaler" (ACTRN12606000508572; Burgess 2007; Charles 2007; NCT02451709); the "SmartTrack" device (Chan 2015; Foster 2014); the "MDILog or MDILog-II (Bender 2010; Kamps 2008; NCT00149487; NCT00166582); the "Doser Clinical Trials" (Doser-CT) device (Bender 2010; NCT01169883); the "E-haler/ Adhaler" (Vasbinder 2015 E-MATIC); the "Tubuhaler Inhalation Computer (TIC)" (Bosley 1994); the "Diskus Adherence Monitor" (Bender 2010); the "MDI Chorolog" (Onyirimba 2003); and the "Nebuliser Chronolog" (Mann 1992). Hart 2002 and NCT00115323 report using dose-counting devices but do not name the specific product used. ADERE PEDIATRIC 1, Chatkin 2006, Price 2010, Strandbygaard 2010 and Ulrik 2009 report counting the doses actuated/remaining on the returned inhaler but do not describe use of a monitoring device.

With the exception of the MDILog-II, these devices record the time and date of inhaler actuation, and most disregard multiple actuations in a short space of time ("dose-dumping"). The MDI-Log-II also includes a measure of whether the drug was inhaled via a "temperature sensitive thermistor". Data can be uploaded onto a computer (for review and discussion in some studies) but in most

cases were not visible to the participant day-to-day. In Vasbinder 2015 E-MATIC, the device sent data back to the study database via the mobile phone network, which allowed real-time tailoring of adherence reminder text messages for participants. Some of the devices described above (e.g. the SmartInhaler) are capable of producing audiovisual inhaler reminders; studies investigating this as an intervention disabled this function in control groups (see comparison 2).

Remaining studies used canister weight (Bender 2010; NCT00516633) or a combination of pharmacy data and self-report (Gallefoss 1999; Mehuys 2008; NCT00233181; NCT00414817; NCT00459368; NCT00958932; NCT01064869; NCT01132430). Two studies relied on self-report (Koufopoulos 2016; NCT01714141).

The three studies that investigated school-based therapy (Gerald 2009; Halterman 2004; NCT01175434) did not measure or report adherence.

Included studies reported the following outcomes: lung function (e.g. FEV_1, peak expiratory flow rate (PEFR)) (n = 15); quality of life (e.g. AQLQ) (n = 13); rescue medication use (n = 11); asthma control (e.g. ACT, Asthma Control Questionnaire (ACQ)) (n = 10); hospitalisations (n = 9); exacerbations (n = 8); asthma symptoms (n = 8); absences from school/work (n = 7); emergency department (ED) visits (n = 7); OCS use (n = 4); participant satisfaction (n = 4); use of healthcare services (n = 5); beliefs about medication (n = 3); costs (n = 3); primary care/general practitioner (GP) visits (n = 3); adverse events (n = 3); unscheduled visits to a healthcare provider (n = 3); self-efficacy (n = 2); anxiety and depression (e.g. Hospital Anxiety and Depression Scale (HADS)) (n = 2); asthma knowledge (n = 2); fractional exhaled nitrous oxide (n = 2); asthma morbidity (n = 1); parent and adolescent conflict (n = 1); functional severity index (n = 1); episodes of poor asthma control (n = 1); inhaler technique (n = 1); feasibility (n = 1); activity limitation (n = 1); parent sleep interruption (n = 1); and change in family plans due to the child's asthma (n = 1).

We extracted and reported only our prespecified outcomes of interest.

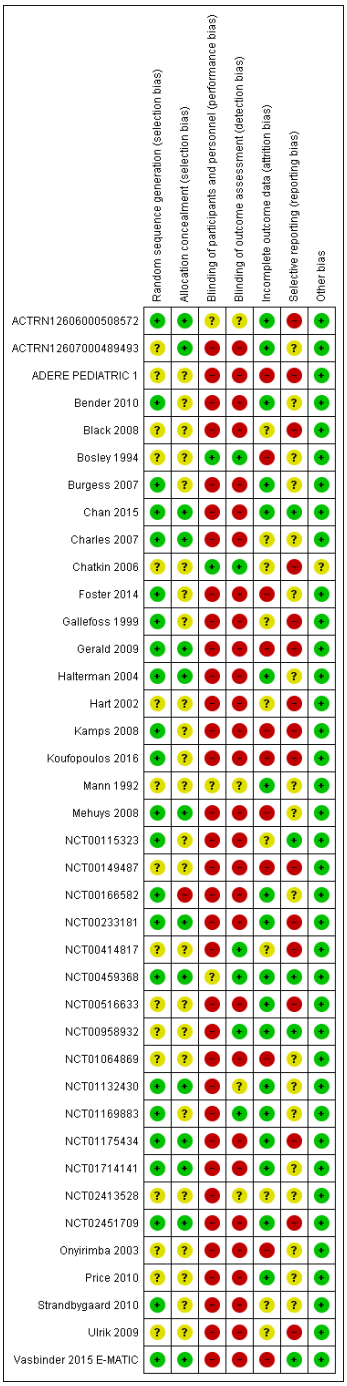
Excluded studies

After full-text review, we excluded 52 records, which were related to 45 unique studies. The most common reason for exclusion (n = 20) was that adherence to ICS was not the primary focus of the intervention, for example, the study involved multi-faceted asthma education or shared decision making. The second most common reason (n = 12) was that the study was a trial of different ICS types, regimens or inhaler devices, in which adherence was *observed and reported* but improved adherence was not the main intention of the intervention. Nine studies were not of appropriate design for inclusion, one study recruited a mixed disease population, one recruited participants among whom less than 50% were using ICS and one study aimed to improve treatment adherence generally in asthma, rather than ICS specifically, and did not report the proportion using ICS. A final study aimed to investigate if Symbicort Maintenance and Reliever Therapy (SMART) could improve adherence, but our outcomes of interested would have been confounded by the different drugs and doses used in each arm; therefore, we excluded this study.

Risk of bias in included studies

As planned, we assessed each trial according to the Cochrane 'Risk of bias' tool (Figure 2). In some cases, we assessed blinding, or lack or blinding, as associated with a different level of risk, depending on the outcome in question. We have noted in the Characteristics of included studies tables when this was the case, and we factored this into our GRADE decisions for these outcomes (e.g. a study at high risk of detection bias for patient-reported outcomes, such as quality of life, might be at lower risk for other, more objective outcomes, such as electronically monitored adherence).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We considered all included studies to be at low (n = 23) or unclear (n = 16) risk of bias for the random sequence generation domain. We considered the following studies to be at low risk because study authors described an accepted method of generating a random sequence (e.g. using a computer-generated random sequence): ACTRN12606000508572; Bender 2010; Burgess 2007; Chan 2015; Foster 2014; Gallefoss 1999; Gerald 2009; Halterman 2004; Kamps 2008; Koufopoulos 2016; Mehuys 2008; NCT00115323; NCT00166582; NCT00233181; NCT00459368; NCT01132430; NCT01169883; NCT01175434; NCT01714141; NCT02451709; Strandbygaard 2010; Vasbinder 2015 E-MATIC. We were unable to make a judgement on the following studies considered at unclear risk because investigators described them as 'randomised' but provided no other details: ACTRN12607000489493; ADERE PEDIATRIC 1; Black 2008; Bosley 1994; Chatkin 2006; Hart 2002; Mann 1992; NCT00149487; NCT00414817; NCT00516633; NCT00958932; NCT01064869; NCT02413528; Onyirimba 2003; Price 2010; Ulrik 2009.

Only 14 included studies (ACTRN12606000508572; ACTRN12607000489493; Chan 2015; Charles 2007; Gerald 2009; Halterman 2004; Mehuys 2008; NCT00233181; NCT00459368; NCT01132430; NCT01175434; NCT01714141; NCT02451709; Vasbinder 2015 E-MATIC) described the method of allocation concealment adequately to be considered at low risk of bias in this domain. Accepted methods included use of sequentially numbered, sealed, opaque envelopes. We considered one study (NCT00166582) to be at high risk because the sequence was available to the research assistant who recruited participants. We judged the remaining 24 studies to be at unclear risk, as investigators did not describe methods used to conceal allocation (ADERE PEDIATRIC 1; Bender 2010; Black 2008; Bosley 1994; Burgess 2007; Chatkin 2006; Foster 2014; Gallefoss 1999; Hart 2002; Kamps 2008; Koufopoulos 2016; Mann 1992; NCT00115323; NCT00149487; NCT00414817; NCT00516633; NCT00958932; NCT01064869; NCT01169883; NCT02413528; Onyirimba 2003; Price 2010; Strandbygaard 2010; Ulrik 2009).

Blinding

Owing to the nature of the intervention, blinding of participants and personnel was not possible in most trials, and we judged 34 of the 39 included studies to be to be at overall high risk of performance bias. We judged two studies (Bosley 1994; Chatkin 2006) to be at low risk of performance bias. Bosley 1994 measured only outcomes of lung function and electronically monitored adherence, which are more objective outcomes and therefore are less likely to be susceptible to performance bias. In addition, participants were unaware that they were being monitored. Similarly, Chatkin 2006 did not describe blinding but reported only the outcome of electronically monitored adherence. We assessed three studies (ACTRN12606000508572; Mann 1992; NCT00459368) to be at unclear risk of performance bias. Mann 1992 did not describe procedures used to mask participants or personnel, and although some outcomes were more objective and were less prone to bias, others, including asthma symptoms, were more at risk. Therefore, we judged this study to be at unclear risk overall. Similarly, for ACTRN12606000508572, participants were unaware that the main outcome of interest was adherence and they were monitored covertly, but other outcomes, such as ACQ, were at greater risk of bias. Finally, NCT00459368 randomised healthcare practitioners rather than individuals. Practitioners were aware of their group allocation, and it is unclear how this knowledge may have influenced adherence of their patients in ways unintended by the intervention itself.

Many of the outcomes of interest in this review are patient reported (e.g. asthma control, quality of life), and the unblinded participant is often the outcome assessor. We therefore judged 29 of the included studies to be at high risk of bias in the outcome assessment domain. We judged six studies to be at low risk (Bosley 1994; Chatkin 2006; NCT00414817; NCT00459368; NCT00958932; NCT01169883). We made this judgement because the outcomes measured were objective and were unlikely to be influenced by outcome assessors' knowledge of group allocation (e.g. usage of healthcare services from medical records, data from electronic monitoring devices), and for some specific measures, studies described masking outcome assessors to group allocation. We judged the remaining four studies (ACTRN12606000508572; Mann 1992; NCT01132430; NCT02413528) to be at unclear risk of bias. NCT01132430 included a mixture of outcomes objectively assessed by a blinded outcome assessor and patient-reported outcomes, so overall we judged this study to be at unclear risk. Similarly, Mann 1992 and ACTRN12606000508572 included a mix of objective outcomes and patient-reported outcomes. NCT02413528 reported very minimal details, so we could not make a judgement.

Incomplete outcome data

We judged 18 studies to be at low risk of attrition bias; drop-out was low and balanced, and withdrawn participants were adequately described (ACTRN12606000508572; ACTRN12607000489493; Bender 2010; Burgess 2007; Chan 2015; Halterman 2004; Mann 1992; NCT00166582;

NCT00233181; NCT00459368; NCT00516633; NCT00958932; NCT01132430; NCT01169883; NCT01175434; NCT01714141; NCT02451709; Price 2010). We judged 11 studies to be at high risk, usually owing to high and/or unbalanced drop-out from study arms (ADERE PEDIATRIC 1; Bosley 1994; Foster 2014; Gerald 2009; Kamps 2008; Koufopoulos 2016; Mehuys 2008; NCT00149487; NCT01064869; Onyirimba 2003; Vasbinder 2015 E-MATIC). We judged another 10 studies to be at unclear risk, usually because drop-outs were not adequately described to allow a judgement (Black 2008; Charles 2007; Chatkin 2006; Gallefoss 1999; Hart 2002; NCT00115323; NCT00414817; NCT02413528; Strandbygaard 2010; Ulrik 2009).

Selective reporting

We judged five trials to be at low risk of reporting bias. We were able to identify a prepublished protocol or prospective trial registration and found that all stated outcomes of interest were appropriately reported (Chan 2015; NCT00115323; NCT00459368; NCT00958932; Vasbinder 2015 E-MATIC). We judged 15 studies to be at high risk of selective reporting. Reasons included that the study was identified only as a conference abstract with minimal details, that key outcomes were reported only narratively or in a way that prevented meta-analysis or that we noted an important deviation between protocol/registration and published results (ACTRN12606000508572; ADERE PEDIATRIC 1; Black 2008; Chatkin 2006; Gallefoss 1999; Gerald 2009; Hart 2002; Kamps 2008; Koufopoulos 2016; NCT00149487; NCT00233181; NCT00414817; NCT00516633; NCT02451709; Ulrik 2009). We judged the remaining 18 studies to be at unclear risk, primarily because we were unable to identify a prepublished protocol or prospective trial registration.

Other potential sources of bias

We did not note any additional potential sources of bias in any included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Adherence education compared with controls for asthma; **Summary of findings 2** Electronic trackers or reminders (± feedback) compared with controls for asthma; **Summary of findings 3** Simplified compared with usual regimens for asthma; **Summary of findings 4** School-based ICS therapy compared with home therapy for asthma

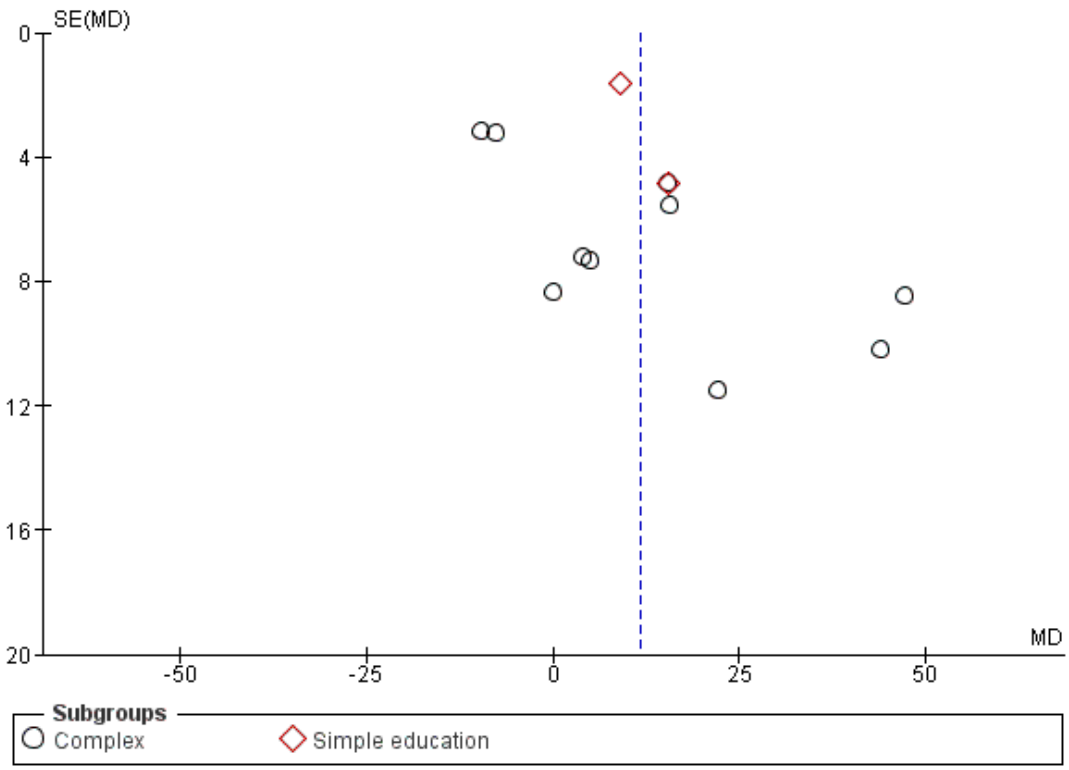
Comparison 1. Adherence education versus controls

Adherence

Our primary analysis of adherence included only studies that used an objective electronic monitor to measure adherence. Mean adherence for those receiving adherence education was 20% better than for those in the control group (Analysis 1.1; mean difference (MD) 20.13, 95% confidence interval (CI) 7.52 to 32.74; 280 participants; five studies; low-quality evidence). A benefit favouring adherence education is seen when studies using both objective and subjective measures are included, but the effect is attenuated (Analysis 1.2; MD 11.59, 95% CI 3.72 to 19.46; 1693 participants; 10 studies; low-quality evidence).

We noted great variation between individual study results in both analyses (I^2 = 81% and 88%, respectively), and concerns about effects of performance bias and selection bias reduced our confidence in the results. We created a funnel plot to look for evidence of publication bias (Figure 3) and found none.

Figure 3. Funnel plot of comparison: 1 Adherence education vs controls, outcome: 1.2 % Adherence (all measures).



One larger study (Chatkin 2006) dichotomised participants into those who achieved greater than 85% adherence and those who did not; results showed benefit of the educational intervention (Analysis 1.3; odds ratio (OR) 2.68, 95% CI 1.61 to 4.46; 271 participants; one study).

A test for subgroup differences between interventions judged to be 'complex' (i.e. multi-faceted) and interventions offering simpler forms of education detected no differences between the two types of interventions (I^2 = 0%), but it should be noted that we classified as 'simple' only one study using objective measures. Testing suggested no important differences between studies of adults, studies of adults and adolescents and studies of children (Analysis 5.1) when all measures of adherence were considered. If the same subgroup analysis is performed only on studies using objective measures, only one study in the child subgroup remains; although this analysis suggests that the intervention is more effective in children, we interpret this finding with extreme caution. We planned a subgroup analysis based on the recipient of the intervention, but this was not necessary, as all interventions were delivered to adults or children with asthma or their parents.

Exacerbations requiring OCS

It was not possible to discern with certainly whether education had an effect on the odds that a patient would need oral steroids for an exacerbation (OR 1.82, 95% CI 0.99 to 3.36; 349 participants; three studies; I^2 = 10%; low-quality evidence). The point estimate lay in favour of control, but confidence intervals around the pooled estimate showed no differences between groups (Analysis 1.4). We downgraded the evidence for risk of bias and for imprecision. We did not perform subgroup analyses on this primary outcome because we identified too few studies and we did not observe significant heterogeneity in the analysis.

Three other studies (NCT00233181; NCT00958932; NCT01064869) reported the mean number of exacerbations per person over six or 12 months, but the data were skewed so we did not pool the results. NCT00233181 reported a significant reduction in OCS use (incident rate ratio 0.83; 95% CI 0.73 to 0.95; P = 0.008) when both intervention groups were compared with the control group. Conversely, NCT00958932 reported increased oral steroid use in the intervention group over the 24 months of the study (mean

(standard error (SE)) oral steroid bursts per person per year 0.21 (0.18) in the control group and 0.27 (0.23) in the intervention group; P = 0.05). NCT01064869 reported a small reduction in courses of oral steroids at 12-month follow-up in the intervention group compared with the control group, but this finding was not significant (mean (standard deviation (SD)) 1.7 (1.1) in the intervention group and 2.0 (1.4) in the control group; P = 0.41).

Asthma control

Studies used the Asthma Control Questionnaire (Bender 2010; NCT00115323; NCT01064869; NCT01132430) and the Asthma Control Test (Foster 2014; Mehuys 2008; NCT01132430) as validated measures of asthma control (Analysis 1.5) and reported no differences between adherence education and control on the ACQ (MD -0.03, 95% CI -0.49 to 0.43; 455 participants; four studies; I^2 = 38%; moderate-quality evidence) nor on the ACT (MD 0.30, 95% CI -0.82 to 1.43; 333 participants; three studies; I^2 = 40%; moderate-quality evidence). We noted some variation in study results, but our confidence in these results was mainly reduced by risk of performance and detection bias. Upper and lower confidence limits for both estimates fell within the minimal clinically important differences (MCIDs) for the scales (0.5 point for the ACQ and 3 points for the ACT), so we did not consider the evidence imprecise. It was not possible to perform subgroup analyses on this primary outcome because we identified too few studies and we did not observe substantial heterogeneity in the analysis.

Unscheduled visits

Studies reported unscheduled visits inconsistently as hospital visits, ED visits or GP visits, and this made the estimate difficult to interpret (Analysis 1.6). The pooled estimate lay predominantly in favour of adherence education, but the effect was imprecise and the upper confidence limit crossed the line of no difference (OR 0.48, 95% CI 0.19 to 1.19; 688 participants; four studies; I^2 = 59%). We considered evidence for this outcome to be of very low quality owing to risk of bias, inconsistency between study results, imprecision and variation in the way unscheduled visits were defined. Also, effects presented separately suggest possible benefit of adherence education for ED and GP visits, but we did not set out to assess these outcomes separately, so this must be interpreted with caution.

Three other studies (Gallefoss 1999; NCT00233181; NCT00958932) reported the mean number of unscheduled visits per person, but the data were skewed so we have not presented a mean difference. Gallefoss 1999 reported a reduction in the mean (SD) number of GP consultations in the intervention group compared with the control group: 0.7 (2.0) versus 2.6 (3.6); P < 0.001. NCT00233181 also reported a significant reduction in the number of ED visits in the intervention group (incident rate ratio 0.88; 95% CI 0.78 to 0.99; P = 0.03), NCT00958932 reported ED and after-hours visits but did not detect a significant between-group difference for either outcome (P = 0.23 and P = 0.12, respectively).

Absence from work/school

Two studies reported rates of absenteeism per person over 12 months (Gallefoss 1999) or 18 months (NCT00516633). The mean number of absence days per person in Gallefoss 1999 was eight in the adherence education group (n = 25) and 26 in the control group (n = 24), but standard deviations were 32 and 70 days, respectively, suggesting that the data were heavily skewed. Consequently, we did not consider it appropriate or useful to analyse the data for a mean difference. The other study reporting this outcome (NCT00516633) observed a mean of 2.1 days in the adherence education group (n = 32) and 3.9 days in the control group (n = 28); the P value for this difference as reported in the paper was 0.08.

Quality of life

Results showed no difference between adherence education and control on the Asthma Quality of Life Questionnaire (Analysis 1.7; MD 0.01, 95% CI -0.20 to 0.23; 734 participants; six studies; I^2 = 34%; moderate-quality). Upper and lower confidence limits fell within the 0.5 MCID for the scale, so we did not downgrade for imprecision. We had concerns regarding performance and detection bias because the scale is self-rated.

All adverse events

No studies measured or reported adverse events other than the need for oral steroids or unscheduled visits, which have already been considered.

Comparison 1 sensitivity analyses

No unpublished data were included in the analyses, so we found that this sensitivity analysis was not necessary.

Only one study in the objective % adherence outcome was rated at high risk for either of the selection bias domains, and results without this study showed a slightly smaller pooled effect than was evident in the main analysis (MD 16.23, 95% CI 3.86 to 28.60). No studies in the 'Exacerbation requiring OCS' or 'Asthma control' analyses were at high risk in either of the selection bias domains.

Mehuys 2008 and Gallefoss 1999 were the only Comparison 1 studies in which not all participants were taking an ICS at baseline (although proportions were between 89.5% and 97% in each group). Mehuys 2008 did not contribute to the objective % adherence outcome, as researchers did not measure adherence using an electronic monitor. Both studies contributed to 'Exacerbations requiring OCS' and their exclusion left just the two Foster 2014

comparisons (PAD vs control and IRF + PAD vs IRF) in the analysis. The point estimate favours control over education (OR 3.44, 95% CI 1.35 to 8.81; 131 participants; one study), but results were reported by a single small study and should be interpreted with caution. Mehuys 2008 contributed to the ACT analysis, but our conclusions did not change when we excluded this study (MD 0.72, 95% CI -0.58 to 2.02).

As described previously, instead of excluding studies that did not measure adherence objectively in a sensitivity analysis, we have presented this as our main analysis (Analysis 1.1).

Comparison 2. Electronic trackers or reminders versus controls

Adherence

As for Comparison 1, our primary analysis of adherence included only studies that used an objective electronic monitor to measure adherence. Mean adherence of those using electronic trackers or reminders was 20% better than mean adherence of those in the control group (Analysis 2.1; MD 19.86, 95% CI 14.47 to 25.26; 555 participants; six studies; I^2 = 34%; moderate-quality evidence). As with Comparison 1, our confidence in the estimate was reduced by possible performance and selection bias. Pooling studies using any measure of adherence had little impact on the estimate, but greater inconsistency was evident (MD 18.41, 95% CI 11.82 to 25.00; 762 participants; eight studies; I^2 = 66%; low-quality evidence).

Subgroup analyses for the objectively measured adherence outcome provides weak evidence that inhaler reminders combined with individual feedback may be more effective than inhaler reminders alone (test for subgroup difference: I^2= 65.2%; P = 0.09; Analysis 2.1). The test for subgroup differences between interventions judged to be 'complex' (i.e. multi-faceted) and simpler interventions also provides weak evidence that complex interventions may be more effective, but this effect was seen only when the analysis was limited to studies using objective measures of adherence (I^2 = 65.2%; P = 0.09; Analysis 5.2). Testing also suggested no important differences between studies of adults (or adults and adolescents) and children (I^2 = 0%; Analysis 5.3). As with Comparison 1, the subgroup analysis based on the recipient of the intervention was not necessary, as all interventions were delivered to adults or children with asthma or their parents.

Three other studies reported data about adherence that could not be pooled with data from studies reporting % adherence. Data from Chan 2015 were skewed and were reported as medians; this study showed large benefit of an audiovisual inhaler reminder, with an intervention median adherence of 84% (10th to 90th percentile 54 to 96; N = 110) compared with a control median adherence of 30% (10th to 90th percentile 8 to 68; N = 110). NCT00459368, a large cluster study, reported adherence as a refill rate and showed similar results between groups (21.3 in the feedback group (SE 2.5), 23.2 in the control group (SE 2,2)). NCT01714141 collected adherence data in several ways from a self-report questionnaire, none of which were comparable with those of other studies; scores generally favoured the treatment group.

Exacerbations requiring OCS

It was not possible to say with certainty whether electronic trackers or reminders improved the odds of needing oral steroids for an exacerbation (OR 0.72, 95% CI 0.37 to 1.39; 3063 participants; four studies; I^2 = 60%; very low-quality evidence). Confidence limits included important benefit in one direction and important harm in the other (Analysis 2.3). We downgraded the evidence further for risk of bias and inconsistency.

Again, as with the first comparison, we did not perform subgroup analyses on this primary outcome because we identified too few studies. Similarly, some studies (NCT00233181; NCT00459368; NCT02451709; Vasbinder 2015 E-MATIC) reported the mean number of exacerbations per person over a period of time and the data were skewed, so we did not consider a mean difference to be a valid measure for comparison. NCT00233181 reported no difference between the adherence monitoring with feedback group and the asthma education group for oral steroid use (P = 0.32). Similarly, NCT00459368 reported oral steroid use and found no clear benefit of adherence feedback over usual care (P = 0.277). Vasbinder 2015 E-MATIC reported exacerbations as requiring OCS, an ED visit or hospitalisation and reported no advantage of the text messaging intervention over control (P = 0.432). Finally, NCT02451709 adjusted the analysis to account for the skew and found that children receiving adherence feedback had fewer exacerbations per 100 days compared with controls (rate ratio 0.23, 95% CI 0.08 to 0.64).

Asthma control

Studies used the Asthma Control Questionnaire (NCT02451709; Strandbygaard 2010) or the Asthma Control Test (Chan 2015; Foster 2014; NCT01714141; Vasbinder 2015 E-MATIC) as validated measures of asthma control (Analysis 2.4). Results did not show an important difference between reminders/trackers and controls on the ACQ (MD 0.24, 95% CI -0.29 to 0.78; 109 participants; two studies; I^2 = 0%; low-quality evidence) nor on the ACT (MD 0.74, 95% CI -0.20 to 1.69; 596 participants; four studies; I^2 = 47%; low-quality evidence). The upper limit for the ACQ estimate includes the MCID for the scale (0.5), so trackers and reminders could have an important effect on this measure of asthma control; we downgraded the evidence for imprecision for this reason. We noted some variation between ACT results, but confidence limits fell below the 3 point MCID for the scale, so we did not consider the estimate imprecise.

It was not possible to perform subgroup analyses on this primary outcome because we identified too few studies and we did not observe significant heterogeneity in the analysis.

Unscheduled visits

Some studies reported unscheduled visits as ED visits and some as hospital visits (Analysis 2.5); we did not pool the two because NCT00459368 reported both. It was not possible to say with certainly whether electronic trackers or reminders reduced the odds of unscheduled visits to the ED (OR 1.14, 95% CI 0.88 to 1.47; 2918 participants; two studies; I^2 = 0%; moderate-quality evidence) or to the hospital (OR 0.97, 95% CI 0.53 to 1.78; 2865 participants; two studies; I^2 = 0%; not graded), as the estimates were imprecise.

NCT02451709 reported data that could be analysed as rate ratios (Analysis 2.6) and showed a reduction in hospital visits (rate ratio 4.38, 95% CI 1.46 to 13.14) but not in GP or ED visits (rate ratio 1.15, 95% CI 0.83 to 1.59).

Absence from work/school

Chan 2015 reported that the number of parents taking at least one absence favoured controls but results were imprecise (Analysis 2.7; OR 1.42, 95% CI 0.82 to 2.47; low-quality evidence). We considered evidence for the outcome to be of low quality owing to imprecision and risk of bias. NCT02451709 reported absences per 100 child days that favoured reminders, but results were imprecise (Analysis 2.8; rate ratio 1.16, 95% CI 0.97 to 1.39; evidence quality not graded).

Quality of life

Studies reported no difference between electronic trackers or reminders and controls on the Asthma Quality of Life Questionnaire (MD -0.03, 95% CI -0.20 to 0.13; 369 participants; four studies; I^2 = 0%; moderate-quality evidence). Upper and lower confidence limits lay well within the 0.5 point MCID for the scale, so we did not consider the effect imprecise, although we had the usual concerns related to risk of bias.

All adverse events

Only Vasbinder 2015 E-MATIC measured and reported adverse events; this study reported serious adverse events of any cause and observed none in either group.

Comparison 2 sensitivity analyses

No unpublished data contributed to any of the three primary outcomes, so this sensitivity analysis was not necessary. Similarly, we rated no contributing studies at high risk of selection bias, so this was also not necessary.

Before the study commenced, not all participants in Strandbygaard 2010 were taking an ICS (59%), but all were taking an ICS at the start of the study. Excluding this study made little difference in the objective % adherence analysis (MD 20.62, 95% CI 14.30 to 26.95) but greatly decreased the precision of the ACQ analysis (MD 0.19, 95% CI -1.37 to 1.75). This study did not contribute to exacerbations requiring oral steroids.

As for Comparison 1, instead of excluding studies that did not measure adherence objectively in a sensitivity analysis, we have presented this as our main analysis (Analysis 2.1).

Comparison 3. Simplified versus usual drug regimens

Adherence

All three studies contributing to this outcome assessed adherence using an objective measure. Adherence was 4% better with simplified drug regimens than with usual drug regimens (Analysis 1.1; MD 4.02, 95% CI 1.88 to 6.16; 1310 participants; three studies; I^2 = 0%). We downgraded the evidence only for risk of bias and rated it as moderate quality. The effect is difficult to interpret as two studies compared combined versus separate inhalers (Bosley 1994; ACTRN12606000508572), and one study compared once-daily versus twice-daily dosing (Price 2010).

Adherence data in Mann 1992 could not be combined with those from other studies. Twice-daily and four-times-daily groups in Mann 1992 took a similar mean number of correct daily inhalations. Data from the same study showing the percentage of days with missed inhalations favoured twice daily but were skewed (twice daily 36.8%, SD 48.3; four times daily 57.1%, SD 49.6).

Exacerbations requiring OCS

It was not possible to tell whether simplifying drug regimens had an effect on exacerbations, as only one study of 16 people reported this outcome (Analysis 3.2; OR 2.33, 95% CI 0.17 to 32.58; low-quality evidence). This study compared twice-daily treatment versus treatment given four times daily (Mann 1992).

Asthma control

One study (ACTRN12606000508572) comparing combined inhalers (simplified regimen) versus separate inhalers showed no difference between regimens on the ACQ (MD -0.03, 95% CI -0.34 to 0.28; 103 participants; one study). Both confidence limits fell within the 0.5 MCID for the ACQ, so we did not downgrade for imprecision. We had the usual concerns regarding risk of bias through lack of blinding, so we rated the evidence as moderate quality.

Unscheduled visits

Price 2010 did not show benefit of once-daily dosing (simplified regimen) versus twice-daily dosing for unscheduled visits (Analysis 3.4; OR 1.17, 95% CI 0.72 to 1.90; 1037 participants; one study; low-quality evidence). The effect lay close to no difference, and confidence limits showed important benefit in one direction and important harm in the other; we downgraded the evidence for this imprecision and for risk of bias.

Absence from work/school

On the basis of data from one study (Price 2010), it was, again, not possible to tell whether once-daily dosing (simplified regimen) showed benefit for this outcome compared with twice-daily dosing; only one study reported this, and confidence intervals included important benefit and harm (Analysis 3.5; OR 0.93, 95% CI 0.37 to 2.30; low-quality evidence).

Quality of life

One study comparing once-daily dosing (simplified) versus twice-daily dosing (Price 2010) reported quality of life on the Therapeutics Group Asthma Short Form (Analysis 3.6); the lower confidence limit crossed the line of no effect, so we were not confident in the estimate (MD 6.00, 95% CI -0.76 to 12.76; 1037 participants; low-quality evidence). The scale ranges from 1 to 100, and we could find no information on an agreed MCID.

All adverse events

Price 2010 reported adverse events and observed fewer in the simplified regimens group (once-daily dose) than in the control group (twice-daily dose), but confidence intervals included no difference (OR 0.76, 95% CI 0.56 to 1.04; low-quality evidence). We downgraded the evidence for imprecision and for risk of performance bias.

Comparison 3 subgroup and sensitivity analyses

We did not perform any subgroup analyses for this comparison as we included no more than three studies in any single analysis. None of the sensitivity analyses were necessary because we located no unpublished data, no contributing studies were at high risk of selection bias and all used objective measures of adherence.

Comparison 4. School-based ICS therapy versus control

The three studies performing this comparison provided no data for adherence, exacerbations requiring OCS, asthma control or adverse events. Gerald 2009 reported a composite measure of episodes of poor asthma control (EPAC), which we could not combine with any other measures. We identified too few studies to consider any of the planned subgroup or sensitivity analyses, but we have presented below data that could be analysed.

Unscheduled visits

Two studies reported unscheduled visits, but the data could not be combined. Halterman 2004 reported that 18 of 89 children in the intervention group and 26 of 91 in the control group had three or more visits over 10 months. NCT01175434 reported that 9 of 48 children in the intervention group and 11 51 in the control group had one or more unscheduled visits over six to eight months.
Both studies reported the number of people who had one or more hospitalisations for any cause during the study; confidence intervals showed an important benefit in either direction, so it was not possible to say whether school-based ICS has a beneficial effect (OR 0.58, 95% CI 0.16 to 2.05; 279 participants; two studies; I^2 = 0%; low-quality evidence).

Absence from work/school

Halterman 2004 reported mean absences per child over the 10-month study: 6.8 absences (SD 9.5) for the intervention group and 8.8 days (SD 8.8) for the control group. NCT01175434 reported a mean of 0.37 absences (SD 0.7) in the intervention group over two weeks and 0.85 (SD 1.3) in the control group. Both sets of data were skewed and were not suitable for combination in a mean difference analysis.

Quality of life

The same two studies reported results of the Paediatric Asthma Quality of Life Questionnaire (PAQLQ). A statistically significant effect favoured giving ICS at school, but the upper end of the confidence limit lay under the 0.5 MCID for the scale, so the difference is unlikely to be clinically important (MD 0.25, 95% CI 0.01 to 0.49; 279 participants; two studies; I^2 = 0%; moderate-quality evidence).

Adverse events

NCT01175434 reported that no one in the intervention group (n = 48) and no one in the control group (n = 51) had any adverse events.

Unclassified studies

We were unable to classify Koufopoulos 2016 and Burgess 2007, as both tested interventions that did not fit into any of our four main categories.
Burgess 2007 reported that a novel spacer device, the 'Funhaler', did not improve adherence to ICS in children over the 12-week study period. End of follow-up median adherence (range) was 46%

(2% to 100%) in the intervention group and 53% (0 to 100%) in the control (Aerochamber) group. Investigators measured adherence with a SmartInhaler. Study authors reported the number of children experiencing an exacerbation requiring an OCS: 11 of 24 in the intervention group and 6 of 20 in the control group.

Koufopoulos 2016 investigated whether an online asthma community ("AsthmaVillage") can improve self-reported adherence, measured on the Simplified Medication Adherence Questionnaire (SMAQ). Results show that the control group reported better adherence to ICS during the study period and control group participants were more likely to use the online diary than those in the AsthmaVillage group.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Electronic trackers or reminders (±feedback) compared with controls for asthma

Patient or population: asthma
Setting: community
Intervention: electronic trackers or reminders (± feedback)
Comparison: control group

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with controls	Risk with electronic trackers or reminders (± feedback)				
% Adherence WMD of follow-up 47.6 weeks	**Objective measures only**	Mean adherence in the control group was **53.27%**	Mean adherence was **19.86% higher** (14.47 higher to 25.26 higher)	-	555 (6 RCTs)	⊕⊕⊕◯ **MODERATE**[a]	Only studies in which adherence was measured with an electronic monitor
	All measures	Mean adherence in the control group was **56.06%**	Mean adherence with trackers was **18.41% higher** (11.82 higher to 25.00 higher)	-	762 (8 RCTs)	⊕⊕◯◯ **LOW**[a,b]	
Exacerbations requiring OCS (people with at least 1) WMD of follow-up 48.6 weeks		**218 per 1000**	**169 per 1000** (94 to 280)	OR 0.72 (0.37 to 1.39)	3063 (4 RCTs)	⊕◯◯◯ VERY **LOW**[a,b,c]	
Asthma control (ACQ) WMD of follow-up 43.0 weeks		Mean ACQ score in the control group was **0.89**	Mean score with trackers or reminders was **0.24 better** (0.29 worse to 0.78 better)	-	109 (2 RCTs)	⊕⊕◯◯ **LOW**[a,c]	Lower score indicates better control. Scale 0 to 6. MCID 0.5

Asthma control (ACT) WMD of follow-up 34.0 weeks	Mean ACT score in the control group was **20.04**	Mean score with trackers or reminders was **0.74 better** (0.20 worse to 1.69 better)	-	596 (4 RCTs)	⊕⊕◯◯ **LOW**[a,b,d]	Higher score indicates better control. Scale 5 to 25. MCID 3
Unscheduled healthcare visits to a healthcare provider (ED) WMD of follow-up 50.0 weeks	**84 per 1000**	**95 per 1000** (75 to 119)	OR 1.14 (0.88 to 1.47)	2918 (2 RCTs)	⊕⊕⊕◯ **MODERATE**[c]	Two studies (n = 2865) also reported hospitalisations. OR 0.97 (0.53 to 1.78)
Absenteeism (people with at least 1 absence) Follow-up 26 weeks	**327 per 1000**	**409 per 1000** (285 to 546)	OR 1.42 (0.82 to 2.47)	220 (1 RCT)	⊕⊕◯◯ **LOW**[c,e]	
Quality of life (AQLQ) WMD of follow-up 36.8 weeks	Mean AQLQ score in the control group was **5.15**	Mean score with trackers or reminders was **0.03 worse** (0.13 better to 0.20 worse)	-	369 (4 RCTs)	⊕⊕⊕◯ **MODERATE**[a,d]	Higher score indicated better QOL. Scale 1 to 7. MCID 0.5

*__The risk in the intervention group__ (and its 95%confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; CI: confidence interval; ED: emergency department; MCID: minimal clinically important difference; OCS: oral corticosteroid; OR: odds ratio; QOL: quality of life; RCT: randomised controlled trial; WMD: weighted mean duration

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded once primarily owing to risk of bias from open-label trials and some concerns regarding attrition bias, selective reporting and selection bias (-1 risk of bias)
[b]Downgraded once for inconsistency between study results (-1 inconsistency)
[c]Confidence intervals include no difference and potential important harm and benefit of the intervention (-1 imprecision)

[d] Confidence intervals fall within the MCID for this scale (no downgrade for imprecision)
[e] Downgraded once owing to risk of performance and detection bias (-1 risk of bias)

Simplified compared with usual regimens for asthma

Patient or population: asthma
Setting: community
Intervention: simplified regimens
Comparison: usual regimens

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with usual regimens	Risk with simplified regimens				
% Adherence (objective measures) WMD of follow-up 12.9 weeks	Mean adherence in the control group was **86.73%**	Mean adherence with simplified regimens was **4.02%** higher (1.88 higher to 6.16 higher)	-	1310 (3 RCTs)	⊕⊕⊕◯ **MODERATE**[a]	Only studies in which adherence was measured with an electronic monitor
Exacerbations requiring OCS People with 1 or more Follow-up 12 weeks	**125 per 1000**	**250 per 1000** (24 to 823)	OR 2.33 (0.17 to 32.58)	16 (1 RCT)	⊕⊕◯◯ **LOW**[b]	
Asthma control (ACQ) Follow-up 24 weeks	Mean ACQ score in the control group was **0.89**	Mean score with simplified regimens was **0.03 better** (0.34 better to 0.28 worse)	-	103 (1 RCT)	⊕⊕⊕◯ **MODERATE**[c]	Lower score indicates better control. Scale 0 to 6. MCID 0.5
Unscheduled visits Follow-up 12 weeks	**63 per 1000**	**72 per 1000** (46 to 113)	OR 1.17 (0.72 to 1.90)	1037 (1 RCT)	⊕⊕◯◯ **LOW**[a,d]	
Absence from work/ school Follow-up 12 weeks	**19 per 1000**	**18 per 1000** (7 to 43)	OR 0.93 (0.37 to 2.30)	1037 (1 RCT)	⊕⊕◯◯ **LOW**[a,d]	

Change in quality of life (ITG-ASF) Follow-up 12 weeks	Mean change in quality of life in the control group was **14**	Mean change with simplified regimens was **6 points better** (0.76 worse to 12.76 better)	-	1037 (1 RCT)	⊕⊕◯◯ **LOW**[a,e]	Higher score indicates better QOL. Range 0 to 100. MCID not known
All adverse events Follow-up 12 weeks	**175 per 1000**	**139 per 1000** (106 to 181)	OR 0.76 (0.56 to 1.04)	1233 (1 RCT)	⊕⊕◯◯ **LOW**[a,f]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
ACQ: Asthma Control Questionnaire; CI: confidence interval; ITG-ASF: Integrated Therapeutics Group - Asthma Short Form; MCID: minimal clinically important difference; OCS: oral corticosteroid; OR: odds ratio; QOL: quality of life; RCT: randomised controlled trial; WMD: weighted mean duration

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded once primarily owing to lack of blinding and some concerns regarding attrition bias, selective reporting and selection bias (-1 risk of bias)
[b] One very small trial resulting in very wide confidence intervals (-2 imprecision)
[c] Although confidence intervals fall within the MCID, only one study contributed to this outcome (-1 imprecision)
[d] Confidence intervals include both important potential harm and benefit of the intervention (-1 imprecision)
[e] Confidence intervals do not exclude no difference (-1 imprecision)
[f] Confidence intervals range from no difference to an important benefit of simplified regimens (-1 imprecision)

School-based ICS therapy compared with home therapy for asthma

Patient or population: children with asthma
Settings: school
Intervention: ICS given at school
Comparison: ICS given at home

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	School-based ICS therapy				
Unscheduled visits 1 or more hospitalisations for any cause WMD of follow-up 35.8 weeks	**49 per 1000**	**29 per 1000** (8 to 96)	OR 0.58 (0.16 to 2.05)	279 (2 RCTs)	⊕⊕◯◯ **LOW**[a,b]	
Quality of life (PACQLQ) 1 to 7; higher is better WMD of follow-up 35.8 weeks	Mean PAQLQ score in the control group was **6.31**	Mean score in the intervention groups was **0.25 higher** (0.01 to 0.49 higher)	-	279 (2 RCTs)	⊕⊕⊕◯ **MODERATE**[a]	
Adverse events Follow-up 30 weeks	No events observed in either arm		-	99 (1 RCT)	Not graded	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; ICS: inhaled corticosteroid; OR: odds ratio; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; RCT: randomised controlled trial; WMD: weighted mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

No data could be meta-analysed for adherence, exacerbations requiring OCS, asthma control or absenteeism. Some data are presented narratively in the review

[a] Both contributing studies considered at high risk for performance and detection bias

[b] Confidence intervals include both potential harm and benefit of the intervention

DISCUSSION

Summary of main results

This review found 39 eligible parallel randomised controlled trials (RCTs), 28 of which (n = 16,303) contributed data to at least one meta-analysis. Eighteen studies included only children, 20 included adults and/or adolescents and one recruited individuals of all ages; all participants had asthma and a vast majority were using an inhaled corticosteroid (ICS) at baseline. Follow-up of analysed studies ranged from two months to two years (median six months). Trials were conducted mainly in high-income countries. Outcomes reported were not consistent across reviews, and investigators did not always use validated scales. Almost all included studies reported some measure of adherence, usually as a percentage, but the way in which this information was captured and calculated varied between studies. Studies were generally at low or unclear risk of selection bias and at high risk of bias associated with blinding (although this varied by outcome). Review authors considered around half of these studies to be at high risk for attrition bias and selective outcome reporting.

Studies were classified into four comparisons by consensus: adherence education versus control (20 studies); electronic trackers or reminders versus control (11 studies); simplified drug regimens versus usual drug regimens (four studies); and school-based directly observed therapy (three studies). Two multi-arm studies appeared in two comparisons (Foster 2014; NCT00233181), and two studies were described separately (Burgess 2007; Koufopoulos 2016).

All pooled results for adherence education, electronic trackers or reminders and simplified regimens led to better adherence than for controls, both when adherence was measured objectively and when all measures were considered. However, our confidence in the evidence was reduced by risk of bias and inconsistency. When measured objectively (e.g. using a dose counter), adherence education showed 20% benefit over controls (95% confidence interval (CI) 7.52 to 32.74; five studies; low-quality evidence), and the effect was attenuated to 12% when all measures were considered. Electronic trackers or reminders led to 20% (18% if all measures were included) better adherence than for controls (95% CI 14.47 to 25.26; six studies; low-quality evidence). Simplified regimens led to 4% better adherence than usual care (95% CI 1.88 to 6.16; three studies; moderate-quality evidence), but the effect is difficult to interpret, as two studies compared combined versus separate inhalers (ACTRN12606000508572; Bosley 1994) and one study compared once-daily versus twice-daily dosing (Price 2010). When we were able to conduct subgroup analyses, we found that 'complex' or multi-faceted educational interventions were not statistically better than simpler interventions, but weak evidence suggested that complex interventions involving adherence reminders and feedback may be more effective than simpler interventions within this comparison. Similarly, weak evidence from subgroup analysis suggested that combining reminders with feedback is more effective than using reminders alone. Overall, results for adults and children were similar.

Improvements in adherence were inconsistently translated into observable benefit for clinical outcomes, with some studies reporting a reduction in usage of healthcare services or courses of oral steroids favouring the intervention, and other studies reporting the opposite, or no difference. None of the pooled analyses showed clear benefit for exacerbations requiring an oral corticosteroid (OCS) (evidence of low quality), unscheduled visits (evidence of very low to moderate quality), asthma control or quality of life (evidence for both of low to moderate quality). School or work absence data were mostly skewed and were difficult to interpret (evidence of low quality, when graded), and most studies did not report adverse events.

Studies investigating the possible benefit of administering an ICS at school did not measure adherence, exacerbations requiring OCS, asthma control or adverse events. One study showed fewer unscheduled visits, and another found no difference; data could not be combined.

Overall completeness and applicability of evidence

The findings of this review appear to support the premise that interventions specifically intended to improve adherence to ICS are effective in improving percent adherence in both adults and children. However, a wide range of interventions have been used in the included studies, and even within the four comparisons, interventions are variable. We cannot be sure to what extent improvement in adherence was a result of the intervention itself, rather than a result of participation in a trial in which the stated aim was to improve adherence (the "Hawthorne effect" (McCambridge 2014)). Indeed, in many trials all participants showed improvement in several outcomes, irrespective of the group to which they were assigned. In some included trials, participants' adherence was covertly monitored to minimise the impact of performance bias, but participants would likely have been aware of the overall aims of the trial nonetheless. In addition, many of the interventions, especially in Comparison 1, would require considerable investment of resources and in a budget-constrained healthcare system would be unlikely to be widely adopted. All three considerations limit the applicability of review findings to a real-world setting.

Although all three of the comparisons that measured percentage adherence demonstrated improvement (albeit with low to moderate confidence), it is not always clear whether this was a clinically meaningful improvement, with no established minimal clinically important difference for this outcome. Studies have suggested that median ICS adherence to maintain asthma control is in excess of 80% (Lasmar 2009). It may have been helpful for interpretation if more trialists had prespecified what they considered to be 'acceptable' adherence, for example, greater than 80%, and had dichotomised participants into those achieving this level

of adherence and those not achieving it. The clinical applicability and usefulness of observed improvements in percent adherence could be further disputed by observation of an inconsistent impact on clinical outcomes such as asthma control, quality of life or exacerbations. Most participants, despite improvements in percent adherence, may not have reached the 'threshold' necessary for discernible clinical improvement (Comparisons 1 and 2), or baseline/control group adherence was already at a high level (Comparison 3), thus allowing little room for discernible improvement (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). It must be noted that very few studies specifically measured or reported adverse events beyond asthma-related events such as exacerbations. Therefore, we cannot comment on the safety of the interventions studied.

Objectvely measured adherence would generally be considered more reliable than patient-reported measures or pharmacy data. In a post hoc decision, we presented objectively measured adherence as our main adherence analysis. It came as a surprise that in Comparison 1, limiting the analysis to objectively measured adherence resulted in a greater effect size. One possible explanation for this is that when participants were asked to self-report and had received an educational intervention, they were able to make a more realistic assessment of their adherence than were participants in the control group, who may have consciously or unconsciously inflated their adherences rates. This could have resulted in an underestimation of the effect of the intervention.

Our protocol clearly stated that we would include only studies for which adherence to ICS was the main aim of the trial. This resulted in the exclusion of many studies for which adherence education was just one component of a broader asthma education or self-management education intervention. This may have led to the exclusion of potentially informative studies; however, their inclusion would have further hampered interpretation, as it would be almost impossible to be sure which element of the intervention had led to observed clinical benefit. Mann 1992 included a comparison (four-times-daily dosing) that is not relevant in current practice, but we did not state that we would exclude 'historical' comparisons, and this study was not combined with any other study in a meta-analysis.

Some included studies specifically targeted people with poorly controlled asthma, those known to have suboptimal adherence levels or those in especially high-risk groups, such as adolescents. We did not plan to analyse such trials separately from those that recruited a more general asthma population. It may have been illuminating to do so, as it is conceivable that these groups would benefit most from a potentially resource-consuming intervention and could be therefore be targeted in a real-world setting.

We were not able to carry out all of our planned subgroup analyses, and our subgrouping by complexity may have imposed some limitations. This was inevitably a subjective judgement, although we involved all three review authors in the assessment and revised three of our classifications after peer review. Some of the included studies provided only a brief description of the intervention, which also hampered our confidence in our classification. Although subgroup analysis did not provide strong evidence that more complex interventions are more effective than less complex interventions, a different classification process may have led to different conclusions.

Quality of the evidence

Studies were generally at low or unclear risk of selection bias, but we downgraded many of the analyses for inherent risk of bias associated with studies of behavioural interventions that cannot be blinded. To some extent, performance and detection biases varied by outcome, and by the nature of interventions within a given comparison, but we agreed that performance biases can be present even for more objective outcomes (such as unscheduled visits or exacerbations) because people who know they are receiving the intervention, or know they are not, might be more or less likely to visit their doctor or report a negative outcome. Lack of blinding was a problem especially for self-rated outcomes such as asthma control and quality of life and may have affected how participants, study investigators and healthcare professionals behaved in each group, producing a more indirect effect on other, more objective outcomes, including adherence itself. Thus, our confidence in many of the outcomes was reduced by risk of bias, especially when we had additional concerns about attrition or uncertainties about the selection process.

Inconsistency between study results tended to be more of an issue for adherence, and this may be explained at least in part by methodological differences such as measurements used and length of the study, or by differences in the underlying populations. Subgroup analyses generally did not help to explain observed heterogeneity. Most studies showed better adherence in the intervention group, but some outliers showed an effect close to no difference or in the opposite direction, which reduced our confidence in the findings.

Dichotomous analyses of fairly rare events such as exacerbations and unscheduled visits tended to be limited by imprecision. For these outcomes, confidence intervals stretched from an important benefit of the intervention to a possible benefit of controls, which prevented firm conclusions.

Indirectness of evidence was less of an issue in this evidence base, as we applied eligibility criteria stringently. In only a couple of instances, indirectness in the measurement of an outcome reduced our confidence in the effect (absences and unscheduled visits in Comparison 1). Similarly, we did not detect or strongly suspect publication bias for any outcomes.

Potential biases in the review process

As much as possible, we carried out this review as presented in the published protocol (Kew 2016) and recorded deviations from it under Differences between protocol and review. We could not perform planned subgroup or sensitivity analyses on some outcomes because studies were too few or fell into a single subgroup. We did not attempt to contact study authors for additional outcome data or risk of bias clarification owing to the number of studies identified. Therefore, we may have overstated the uncertainty in risk of bias, particularly as related to allocation concealment. Published reports may not have provided unpublished data that were not included in the meta-analyses. However, it is unlikely that eligible studies were missed by the searches conducted because they covered multiple sources and were sifted in duplicate.

We could not anticipate all the ways in which intervention groups and control groups would differ across studies; as a result, our post hoc classification of studies into four comparisons could have introduced bias. It is conceivable that a different classification system may have yielded different results.

Agreements and disagreements with other studies or reviews

Several recent reviews have investigated adherence interventions in people with chronic diseases, such as asthma. Both Ershad 2016 and Yasmin 2016 examined the effectiveness of text messaging interventions for people with chronic disease. Ershad 2016 presented a narrative review that included six asthma studies. In keeping with our review, these review authors found that text messaging was effective in promoting adherence among different patient populations, although three of the asthma studies showed no differences between groups in adherence to treatment. Yasmin 2016 included two asthma studies of text message and voice call interactions. These review authors concluded that people with chronic disease showed improvement in adherence, but review authors did not see a significant impact on clinical outcomes, which is consistent with our findings. In addition, these review authors found variation in types of interventions provided and outcome measurements assessed, which made it difficult to draw firm conclusions, and cost-effectiveness remains questionable. Anglada-Martinez 2014 reviewed m-health interventions proposed to increase medication adherence and concluded that studies provided mixed evidence of the benefits of these interventions, probably because of variation in study methods. We also encountered problems with between-study heterogeneity.

Hall 2014 considered effects of medical device dose memory functions on medication adherence and included one study on asthma medication adherence. These review authors found evidence of benefit for these device functions in terms of medication adherence and patient confidence in managing their condition. We did not attempt to extract outcomes related to participant confidence or self-efficacy. Wu 2014 reviewed adherence interventions delivered by healthcare providers and included 23 studies of people with asthma, most of whom were children. Review authors found that interventions delivered by a healthcare provider improved adherence and recommended that future reviews should focus on particular patient populations and adherence behaviours. They planned to perform subgroup analyses based on the identified recipient of the intervention but were unable to do so, as all interventions were delivered directly to study participants.

Recent reviews of adherence interventions among asthma populations show a similar picture. Dibello 2014 brought together trials of text messaging services aimed at adults 18 to 45 years of age. Review authors found that adherence improved and noted some impact on control and lung function. However, they were not able to perform a meta-analysis because of heterogeneity. Tran 2014 reviewed studies of patient reminder systems. These review authors were not able to pool the data but concluded, "All studies in our analysis suggest that reminder systems increase patient medication adherence, but none documented improved clinical outcomes".

Bårnes 2015 provides a wide-ranging review of adherence in asthma and includes studies on adherence levels and effects of poor adherence, as well as studies of interventions aimed at improving adherence. In the intervention studies, review authors found mixed results, with most studies showing improved adherence, although this did not always translate to improvement in other outcomes.

The results of our review of interventions to improve adherence in asthma are consistent with the findings of other reviews examining asthma populations and the broader category of chronic disease, as described. We found that adherence rates increased, but that the impact on clinical outcomes was unclear, and our conclusions must be considered in the light of variation across studies. Our review differs in that we have drawn different types of interventions together into a single review that focuses on people with asthma rather than on a broader category of chronic disease, and, when appropriate, we have been able to pool study results.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest that interventions to improve ICS adherence in adults and children with asthma can increase adherence, whether objectively or subjectively measured. This finding was consistent across the three comparisons performed to measure this. The clinical relevance of this improvement, highlighted by uncertain and inconsistent impact on clinical outcomes such as quality of life and asthma control, is less clear. Overall, we have low to moderate confidence in these findings owing to concerns about risk of bias and inconsistency.

Implications for research

Guidelines for asthma management consistently call for routine

discussion of adherence with patients, and evidence suggests that poor adherence may contribute to unfavourable outcomes. This fact emphasises the importance of research conducted to investigate interventions that may be recommended to practitioners and their patients. Future studies would benefit from ensuring that investigators use validated tools for outcome measurement, such as the Asthma Control Test (ACT), the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ), and provide adequate details regarding baseline asthma severity among participants. Given that our confidence in our findings was reduced by concerns about performance and detection biases, we suggest that some form of blinding or active control is important to include, when possible. This would help to elucidate the contribution of the intervention itself to improved adherence, beyond the potential benefit of inclusion in an adherence trial. It may be helpful for trialists to prespecify a threshold for 'acceptable' adherence and to perform a dichotomous analysis of those achieving this level and those not achieving it. The inconsistent impact observed in terms of clinical outcomes may have occurred because most participants did not achieve this threshold (Comparisons 1 and 2), or because baseline/control group adherence was already at a high level (Comparison 3). Targeting those at high risk or known to have poor adherence may provide evidence that is more 'useful' in the real world, which may be affected by budget constraints.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACTRN12606000508572

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 24 weeks **Setting:** Medical Research Institute of New Zealand and the P3 Research Clinical Trials Unit at Bowen Hospital, Wellington, New Zealand **Trial registration:** ACTRN12606000508572
Participants	**Population:** 111 adolescents and adults with asthma randomised to intervention (combination inhaler) (n = 57) or control (separate inhaler) (n = 54) **Age:** 16 to 65 years; mean (SD) age in the adherence group 45.5 (13.8) years and in the control group 49.2 (11.2) years **Baseline asthma severity:** Those with a significant exacerbation in the last month were excluded **Inclusion criteria:** adults in the Wellington region 16 to 65 years of age; diagnosis of asthma; and currently taking ICS at a stable dose with or without a separate LABA inhaler **Exclusion criteria:** diagnosis of chronic obstructive pulmonary disease, current use of a combination ICS/LABA inhaler, pregnant or lactating women, history of other clinically significant disease, significant exacerbation of asthma in the previous month requiring clinic or hospital attendance **Percentage withdrawn:** 5.3% from the adherence group and 9.3% from the control group **Other allowed medication:** not reported
Interventions	**Intervention summary:** 125 mg FP and 25 mg salmeterol in a combination Smartinhaler, 2 actuations twice daily. The Smartinhaler casing recorded the date and time of each actuation. Participants were not told that adherence would be monitored **Control summary:** 125 mg FP and 25 mg salmeterol in separate Smartinhalers, 2 actuations twice daily. The Smartinhaler casing recorded the date and time of each actuation. Participants were not told that adherence would be monitored **Complex intervention:** no
Outcomes	**Outcomes measured:** FEV_1, ACQ, Asthma Exacerbation Questionnaire, need for oral steroids or doctor visits over previous 6 weeks. Primary adherence measure was percentage of doses taken over last 6 weeks of the study; secondary adherence measures were adherence during the other 6-week periods of the study, percentage of fully adherent days, proportion who were > 50%, > 80% or > 90% adherent over each 6-week period, overuse defined as > 2 doses taken within a 6-hour period or > 4 doses within a 24-hour period (% of days when this occurred) **Adherence calculation:** electronic Smartinhaler data - number of doses taken as a percentage of those prescribed. All calculations were made after exclusion of dose dumping, defined as 6 or more actuations within a 5-minute period

ACTRN12606000508572 (*Continued*)

Notes	**Type of publication:** single peer-reviewed journal article **Funding:** GlaxoSmithKline (GSK) **GSK ID number:** SAM106689

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was by computer-generated random code supplied by a statistician. The sequence was imbedded in a Microsoft Access Database (Microsoft Corp, Redmond, Wash) by a third party and concealed from the researchers until the time the subject was enrolled and entered into the database"
Allocation concealment (selection bias)	Low risk	"The sequence was imbedded in a Microsoft Access Database (Microsoft Corp, Redmond, Wash) by a third party and concealed from the researchers until the time the subject was enrolled and entered into the database"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although participants were aware that they were taking combined or separate inhalers, adherence was measured covertly with a SmartInhaler; this was the main outcome measured. However, ACQ may be at risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although blinding of outcome assessors was not described, adherence was measured objectively with a SmartInhaler; this was the only outcome measured. However, ACQ is participant reported and may be at risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 8 participants withdrew (3 from the combined inhaler group and 5 from the separate inhaler group). All are accounted for in the flow diagram, and drop-out occurred for similar reasons
Selective reporting (reporting bias)	High risk	Prospectively registered trial (ACTRN12606000508572). All outcomes listed in trial registration have been clearly reported, but the study mentions the Asthma Exacerbation Question-

ACTRN12606000508572 (*Continued*)

		naire and the need for oral steroids and doctor visits over the previous 6 weeks, which are not reported in the paper
Other bias	Low risk	None noted

ACTRN12607000489493

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 4 months **Setting:** 1 paediatric asthma clinic within an outer metropolitan general hospital in Australia **Trial registration:** not reported
Participants	**Population:** 26 children with asthma randomised to receive adherence feedback (n = 14) or usual care (n = 12) **Age:** 6 to 14 years; mean age in the adherence feedback group 9.1 years and in the control group 9.3 years **Baseline asthma severity:** intervention group: FEV_1 % predicted = 72.9, mean fluticasone dose (mcg/d) 300; number with symptoms or reliever use 3 or more times per week = 10. Control group: FEV_1 % predicted = 77.5, mean fluticasone dose (mcg/d) 250, number with symptoms or reliever use 3 or more times per week = 8 **Inclusion criteria:** Children given a diagnosis of asthma at between 6 and 14 years of age (inclusive) were eligible for enrolment if their asthma was not well controlled despite prescribed preventive medication. Suboptimal control was based on reported history of asthma symptoms (wheeze or limitation of activity) occurring more than twice a week and requiring reliever medication and/or reduced lung function (reproducible FEV_1 < 80% predicted) **Exclusion criteria:** not reported **Percentage withdrawn:** no withdrawal from trial **Other allowed medication:** not reported
Interventions	**Intervention summary:** Adherence data collected via Smartinhaler were shared with the child, parent and physician during consultation for those allocated to the intervention group. These data were incorporated in the management plan for the coming month. Reviews were performed monthly with the child's usual physician **Control summary:** Children in the control group had their Smartinhaler collected and were given a new device. Their adherence remained unknown to parent, child and respiratory physician. Reviews were performed monthly with the child's usual physician **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence, symptoms (via questionnaire), lung function **Adherence calculation:** Adherence was calculated as a percentage of prescribed doses registered by the Smartinhaler, between midnight and midday or between midday and midnight for morning and evening doses, respectively, or at any time during the day for once-daily dosing

ACTRN12607000489493 (*Continued*)

Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"After providing informed written consent, children were randomly allocated to either the intervention or control group through the use of sealed opaque envelopes" Not clear how the order of sealed envelopes was generated
Allocation concealment (selection bias)	Low risk	"After providing informed written consent, children were randomly allocated to either the intervention or control group through the use of sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Although primary outcome - adherence - was measured by an electronic counter, other outcomes (such as SABA use) may be subject to performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Main outcome - adherence - objectively measured, but other outcomes (such as reported SABA use) subject to detection bias as the unblinded parent is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified; symptoms measured but not reported so could not be included in meta-analysis. No measure of variance is given for the adherence outcome, nor for the secondary outcomes of FEV_1 and controller medication use. P values are not exact (1 decimal place) . Other outcomes reported appropriately
Other bias	Low risk	None noted

ADERE PEDIATRIC 1

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 90 weeks **Setting:** 1 site. Brazil **Trial registration:** ADERE PEDIATRIC 1 (GSK trial register)
Participants	**Population:** 298 children with asthma randomised to a telephone follow-up intervention (n = 149) or to usual care (n = 149) **Age:** 6 to 14 years; mean age (SD) in the intervention group 8.9 (2.4) years and in the control group 9.0 (2.5) years **Baseline asthma severity:** Of those who completed the trial in the intervention group, 67 had moderate and 41 severe asthma, and in the control group, 74 had moderate and 37 severe asthma **Inclusion criteria:** moderate or severe asthma defined by SPT II Brazillian Consensus on Asthma Management **Exclusion criteria:** comorbidities that may interfere with study evaluation, systemic steroids required for more than 7 days; patients treated with allergen immunotherapy **Percentage withdrawn:** 28% from the intervention group and 27% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** medical guidance and follow-up telephone call from a health-care professional every 15 days **Control summary:** medical guidance; no telephone follow-up **Complex intervention:** no
Outcomes	**Outcomes measured:** level of compliance, disease control evaluated by 5-point questionnaire, quality of life (SF-36) **Adherence calculation:** percentage of actual number of doses of salmeterol/fluticasone propionate divided by number of expected doses
Notes	**Type of publication:** pharmaceutical company report **Funding:** GlaxoSmithKline **NB:** participants from non-intervention group not followed up, no conclusions drawn from protocol. No peer-reviewed publication

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized to intervention or non-intervention" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel; described as open-label

ADERE PEDIATRIC 1 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors; described as open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	> 25% drop-out in both groups. Control group not followed up as planned, so missing data for entire outcomes for this group. Study protocol was violated
Selective reporting (reporting bias)	High risk	Multiple planned outcomes, including primary outcome (adherence 'not available'), or available only for the intervention group
Other bias	Low risk	None noted

Bender 2010

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** 10 weeks **Setting:** single site; participants recruited through newspaper adverts; in association with community allergy practices. USA **Trial registration:** not reported
Participants	**Population:** 50 adults with asthma randomised to an interactive voice response (IVR) intervention (n = 25) or usual care (UC) (n = 25) **Age:** 18 to 65 years; mean age (SD) in IVR group 39.6 (12.8) years and in UC group 43.5 (14.3) years **Baseline asthma severity:** physician-diagnosed asthma for which they were prescribed daily inhaled corticosteroid treatment; no other severity information given **Inclusion criteria:** adults 18 to 65 years old who had physician-diagnosed asthma for which they were prescribed daily inhaled corticosteroid treatment. Participants were recruited through newspaper advertising and in co-operation with community allergy practices and received $25 for each completed study visit **Exclusion criteria:** significant disease or disorder that, in the opinion of the investigator, might influence results of the study or the patient's ability to participate in the study (this included other chronic health disorders, current substance abuse or dependence, mental retardation or psychiatric disorder); current participation in another asthma-related research or clinical trial **Percentage withdrawn:** no withdrawal **Other allowed medication:** not specifically reported
Interventions	**Intervention summary:** 2 automated IVR telephone calls separated by 1 month, with 1 additional call if recently reported symptoms of poorly controlled disease or failure to fill a prescription. Calls were completed in less than 5 minutes and included content designed to inquire about asthma symptoms, deliver core educational messages, encourage refilling of inhaled corticosteroid prescriptions and increase communication with providers **Control summary:** usual care **Complex intervention:** no

Bender 2010 (*Continued*)

Outcomes	**Outcomes measured:** AQLQ, ACT, BMQ, adherence with use of an electronic monitor **Adherence calculation:** electronic adherence device or canister weight to give a mean % adherence (exact details of calculation not provided)
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** supported by the Investigator-Sponsored Study Program of AstraZeneca

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomization table generated before study initiation determined group assignment by order of entry into the study
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants described. Main outcome - adherence - objectively measured, but other outcomes such as ACQ and AQLQ subject to performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators remained blind to treatment until final data set was completed. However, for participant-reported outcomes such a AQLQ and ACQ, the participant is the outcome assessor; therefore these outcomes are at high risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although attrition not specifically reported, end of study data given for all 50 randomised participants
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, but all outcomes stated in methods clearly reported
Other bias	Low risk	None noted

Black 2008

Methods	**Design:** parallel-group randomised controlled trial; blinding not stated **Duration:** 2 months **Setting:** set in New Zealand; no other details reported **Trial registration:** not reported
Participants	**Population:** 40 children with asthma randomised to an inhaler alarm intervention (n = 20) or usual care (n = 20) **Age:** 7 to 17 years; no further details reported **Baseline asthma severity:** 'symptomatic asthma despite being on inhaled corticosteroids' **Inclusion criteria:** children aged 7 to 17 years with symptomatic asthma despite taking inhaled corticosteroids **Exclusion criteria:** not reported **Percentage withdrawn:** withdrawal not reported **Other allowed medication:** not reported
Interventions	**Intervention summary:** inhaler alarm with 14 different tones, 1 for each morning and evening of the week **Control summary:** usual care (inhaler alarm turned off) **Complex intervention:** no
Outcomes	**Outcomes measured:** AQLQ, prebronchodilator FEV_1, use of salbutamol, adherence to inhaled steroid **Adherence calculation:** Adherence was expressed as a percentage; exact calculation not reported
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Some outcomes (e.g. AQLQ) may be influenced by knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessor described, and not clear how adherence data were collected and calculated. Self-report outcomes (e.g. AQLQ) may be subject to detection bias

Black 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not reported
Selective reporting (reporting bias)	High risk	Conference abstract; no trial registration identified. Study reported only as a conference abstract from 2008 and does not appear to have been published in full. Therefore, limited details about methods and outcomes, in particular, no measure of variance for the AQLQ
Other bias	Low risk	None noted

Bosley 1994

Methods	**Design:** open-label, multi-centre, parallel-group randomised controlled trial **Duration:** 12 weeks **Setting:** 4 general practices and a hospital outpatient clinic. UK **Trial registration:** not reported
Participants	**Population:** 102 adults with asthma randomised to receive a combined inhaler (n = 51) or separate inhalers (n = 51) **Age:** 18 to 70 years; mean age of all trial completers (36 in each group) 44 years (range 20 to 69 years) **Baseline asthma severity:** mean duration of illness 13.9 years (range 0.25 to 54 years). No details of baseline asthma severity given **Inclusion criteria:** patients with asthma, 18 to 70 years of age, who required treatment with regular inhaled steroids and beta-agonists (as assessed by their own doctor) **Exclusion criteria:** not reported **Percentage withdrawn:** 30% from each trial arm **Other allowed medication:** not reported
Interventions	**Intervention summary:** Treatment group was given 1 Turbuhaler inhaler containing a fixed combination of terbutaline (250 μg per dose) and budesonide (100 μg per dose) **Control summary:** Control group was given 2 Turbuhaler inhalers - 1 containing terbutaline (250 μg per dose) and 1 containing budesonide (100 μg per dose) **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence, lung function measures (FVC and FEV_1) **Adherence calculation:** percent adherence = number of doses taken × 100/number of doses prescribed - measured using Turbuhaler Inhalation Computer
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** study funded by the Astra Clinical Research Unit, which also provided the Turbuhaler Inhalation Computer

Risk of bias		***Risk of bias***

Bosley 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly divided into treatment and control groups" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label design; although outcomes (adherence with an electronic monitor and lung function) are unlikely to be highly susceptible to influence according to participants' and personnel's knowledge of group allocation. "In order to obtain as accurate a picture of "normal" behaviour as possible, patients were not told that the Turbuhalers contained TICs [Turbuhaler Inhalation Computer] or that their compliance was being monitored"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label design, although outcomes (adherence with a covert electronic monitor and lung function) are unlikely to be highly susceptible to influence according to outcome assessors' knowledge of group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximately 30% drop-out in both arms of the trial. Participants who dropped out were younger but otherwise did not differ from those who completed according to trial report. However, no flow diagram presented, so unclear if reasons for drop-out were balanced
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, but all outcomes stated in methods clearly reported
Other bias	Low risk	None noted

Burgess 2007

Methods	**Design:** parallel-group randomised controlled trial; blinding not stated **Duration:** 13 weeks **Setting:** private and public paediatric respiratory clinics. Australia **Trial registration:** not reported
Participants	**Population:** 47 children with asthma randomised to receive a 'Funhaler' (n = 26) or a control spacer (n = 21) **Age:** 18 months to 7 years; mean age in the Funhaler group 3.4 years and in the control group 3.8 years **Baseline asthma severity:** intervention group: mean frequency of wheeze (5-point scale) = 1.9; number with exacerbation in previous month = 8; mean fluticasone dose (mg/d) = 166. Control group: mean frequency of wheeze (5-point scale) = 1.9; number with exacerbation in previous month = 3; mean fluticasone dose (mg/d) = 193 **Inclusion criteria:** children with diagnosis of asthma, 18 months to 7 years of age, taking preventive asthma medication on a daily basis **Exclusion criteria:** not reported **Percentage withdrawn:** 8% from the intervention arm and 5% from the control arm **Other allowed medication:** not reported
Interventions	**Intervention summary:** small-volume spacer that incorporates an incentive toy (spinning disk and whistle) that is driven by the child's expired breath (the 'Funhaler') **Control summary:** a control spacer (Aerochamber Plus) **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence, symptoms (from a 'symptoms questionnaire'), exacerbations (defined as the child having received a course of prednisolone initiated by the parent in response to an escalation of symptoms requiring regular reliever medication more than 4th-hourly for 24 hours as per asthma management plan or prescription of prednisolone by the child's primary care physician) **Adherence calculation:** Adherence was evaluated as a percentage of prescribed doses registered by the Smartinhaler between midnight and midday and between midday and midnight for morning and evening doses, respectively, or at any time during the day for once-daily dosing
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** not reported

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All subjects were then randomized to either the FunHaler or a control spacer using a minimization computer program (Minim) with equal weighting for age, sex and level of maternal education"
Allocation concealment (selection bias)	Unclear risk	No details

Burgess 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Although primary outcome - adherence - was measured by an electronic counter, other outcomes (such as symptoms) may be subject to performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Main outcome - adherence - objectively measured, but other outcomes (such as symptoms) subject to detection bias, as the unblinded parent is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and balanced (< 10% in both arms) and all drop-outs accounted for
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified; symptoms measured but not reported numerically so could not be included in meta-analysis. Other outcomes reported appropriately
Other bias	Low risk	None noted

Chan 2015

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 6 months **Setting:** participants recruited from emergency departments, followed up in community. New Zealand **Trial registration:** ACTRN12613001353785
Participants	**Population:** 220 children with asthma randomised to receive an audiovisual inhaler reminder (n = 110) or usual care (n = 110) **Age:** 5 to 15 years; mean age (SD) in audiovisual reminder group was 8.9 (2.5) years and in control group was 8.9 (2.6) years **Baseline asthma severity:** intervention group: mean (SD) asthma morbidity score 9.3 (2.2); mean (SD) Childhood Asthma Control Test score 18.8 (4.4); mean (SD) FEV_1 (% predicted) 92 (17). Control group: mean (SD) asthma morbidity score 9.2 (2.5) ; mean (SD) Childhood Asthma Control Test score 18.8 (4.2); mean (SD) FEV_1 (% predicted) 90 (17) **Inclusion criteria:** children and adolescents 6 to 15 years of age who attended the regional emergency department in Auckland, New Zealand, with a suspected diagnosis of asthma exacerbation and were screened for eligibility; patients with a diagnosis of acute asthma who were on treatment or needed treatment with twice-daily inhaled corticosteroids **Exclusion criteria:** diagnosis of a chronic lung disease other than asthma, congenital heart disease; living outside the Auckland catchment area; diagnosis of a severe chronic medical disorder that causes impaired immunity or increased morbidity

Chan 2015 (*Continued*)

	Percentage withdrawn: 2% from the intervention arm and 5% from the control arm **Other allowed medication:** other asthma drugs, including LABAs and theophylline
Interventions	**Intervention summary:** covert electronic monitoring device for use with preventive inhalers (SmartTrack) with the audiovisual function enabled **Control summary:** covert electronic monitoring device for use with preventive inhalers (SmartTrack) with the audiovisual function disabled **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence to preventive inhaled corticosteroids; number of days absent from school and whether or not parents or carers were absent from work for 1 day or longer; asthma control (cACT); asthma symptoms (Asthma Morbidity Score) ; exacerbations since previous visit; unscheduled doctor, emergency clinic or hospital visits; rescue medication use; lung function **Adherence calculation:** Adherence was defined as the proportion of preventer doses taken relative to the number of doses prescribed. This proportion was calculated by measuring the degree of deviation from the prescribed dose up to the prescribed dose (i. e. non-adherence, up to a maximum of 0% non-adherence) and subtracting from 1 (i. e. 100% adherence)
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** Health Research Council of New Zealand and Cure Kids

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Using a simple, unrestricted block randomisation with block sizes of 200, we randomly assigned patients"
Allocation concealment (selection bias)	Low risk	"The study statistician provided the randomisation group to investigators in opaque, sealed envelopes, which were opened by investigators and research assistants in consecutive order to allocate participants to their randomisation group. Envelopes were sealed to investigators, and research assistants did not know the next allocation group"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Participants were unaware of the adherence monitoring function of either device, but were informed that the reliever monitoring device was to be used with their reliever inhaler to enable investigators to know when the drug was running out" Primary outcome - adherence - was monitored covertly and objectively with an elec-

		tronic device. However, other outcomes such as cACT are subject to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Primary outcome - adherence - was monitored covertly and objectively with an electronic device. However, other outcomes such as cACT and parent-reported exacerbations are subject to risk of detection bias, as participant or parent is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low drop-out (< 5%) in both arms; all participants accounted for and ITT analysis performed
Selective reporting (reporting bias)	Low risk	Retrospectively registered trial. All planned outcome measures in trial registration and methods reported
Other bias	Low risk	None noted

Charles 2007

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 24 weeks **Setting:** participants recruited from research volunteer databases, newspaper advertisements and informal contacts. New Zealand **Trial registration:** not reported
Participants	**Population:** 110 people with asthma randomised to receive an audiovisual inhaler reminder (n = 55) or usual care (n = 55) **Age:** 12 to 65 years; median age (range) in audiovisual reminder group was 39 (13 to 65) years and in control group was 35 (15 to 64) years **Baseline asthma severity:** intervention group: baseline ICS dose: median (range) 500 (100 to 2000); PEF: mean (SD) 434 (99). Control group: baseline ICS dose: median (range) 500 (100 to 4000); PEF: mean (SD) 444 (128) **Inclusion criteria:** requirement to take regular ICS at a fixed dose, no exacerbation in previous month or run-in period, not pregnant or lactating;if of child-bearing potential, using contraception **Exclusion criteria:** diagnosis of chronic obstructive pulmonary disease, use of a long-acting beta-agonist, history of other clinically significant disease. Individuals were required to not be taking a long-acting beta-agonist to avoid the potential influence of such treatment on adherence to ICS therapy **Percentage withdrawn:** 20% from the intervention arm and 16% from the control arm **Other allowed medication:** not reported, apart from the criterion that participants could NOT be taking a long-acting beta-agonist

Charles 2007 (*Continued*)

Interventions	**Intervention summary:** covert electronic monitoring device for use with preventive inhalers (SmartInhaler) with the audiovisual function enabled **Control summary:** covert electronic monitoring device for use with preventive inhalers (SmartInhaler) with the audiovisual function disabled **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence to ICS, Asthma Control Questionnaire (ACQ), peak expiratory flow (PEF) **Adherence calculation:** adherence defined as the proportion of medication taken as prescribed over the latter half of the trial (expressed as a percentage)
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** supported by a research grant from GlaxoSmithKline, UK. The sponsor had no involvement in study design; collection, analysis or interpretation of data; writing of the report; or the decision to submit for publication

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization was by reference to a computer-generated random code"
Allocation concealment (selection bias)	Low risk	"The randomization was by reference to a computer-generated random code concealed from the researcher who opened an envelope at the time of randomization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Subjects were informed that the purpose of the study was to determine the outcome when patients with asthma on a wide range of ICS doses and inhaler devices were changed to standard treatment via the novel Smartinhaler MDI device. Subjects were not informed of the electronic adherence monitor placed within their FP MDI" Primary outcome - adherence - was monitored covertly and objectively with an electronic device. However, other outcomes such as ACQ are subject to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Primary outcome - adherence - was monitored covertly and objectively with an electronic device. However, other outcomes such as ACQ are subject to the risk of detection bias, as the participant is the

Charles 2007 (*Continued*)

		outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out moderately high (16% to 20%) , although quite balanced. All participants accounted for in flow diagram. 11 participants in the intervention group and 9 participants in the control group "did not provide data" in the final 12-week period of the study. It is not clear whether these participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, but all outcomes stated in methods clearly reported
Other bias	Low risk	None noted

Chatkin 2006

Methods	**Design:** open-label, parallel-group, multi-centre randomised controlled trial **Duration:** 13 weeks **Setting:** '15 states of the country'. Brazil **Trial registration:** not reported
Participants	**Population:** 271 people with asthma randomised to receive telephone calls to promote adherence (n = 140) or usual care (n = 131) **Age:** 12 years of age and older; mean age (SD) in the telephone call group was 43.3 (15) years and in the control group was 44.4 (16.6) years **Baseline asthma severity:** intervention group: proportion with severe persistent asthma 47.1%; proportion with history of asthma emergencies 30.7%; proportion with history of asthma hospitalisations 48.6%. Control group: proportion with severe persistent asthma 47.3%; proportion with history of asthma emergencies 38.9%; proportion with history of asthma hospitalisations 53.4% **Inclusion criteria:** 12 years of age or older with moderate to severe persistent asthma according to GINA criteria and the Third Brazilian Consensus on Asthma Management; residential phone number; ability to comprehend study procedures and to sign the relevant consent form **Exclusion criteria:** mild persistent asthma, pregnancy or breast feeding, intention to move during the study, regular use or recent past abuse of alcohol or illicit drugs, clinically significant active general medical conditions **Percentage withdrawn:** Report states that 293 participants were 'screened'; 4 were excluded for not fulfilling inclusion criteria, 8 for not responding to telephone calls and 10 for not returning the monitoring disk to the office. It is not clear whether these participants were excluded before or after randomisation, and if after randomisation, from which arm they were excluded. Baseline characteristics and results are given for only 271 participants **Other allowed medication:** not reported

Chatkin 2006 (*Continued*)

Interventions	**Intervention summary:** telephone calls every 2 weeks to reinforce asthma management and to promote adherence, delivered by a specially trained nursing student **Control summary:** usual care **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence **Adherence calculation:** percentage of patients taking 85% or more of prescribed doses as measured by electronic monitor
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** funded by GSK-Brazil

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding of participants or personnel described. However, the only outcome measured - adherence - was monitored objectively with an electronic device
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of participants or personnel described. However, the only outcome measured - adherence - was monitored objectively with an electronic device
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out not reported for each arm (22 dropped out in total); total numbers randomised at start of intervention not clear
Selective reporting (reporting bias)	High risk	No prospective trial registration identified. Adherence not reported in a way that can be included in a meta-analysis (percentages per group with no measure of variance, only an inexact P value
Other bias	Unclear risk	None noted

Foster 2014

Methods	**Design:** open-label, 4-arm cluster randomised trial **Duration:** 6 months **Setting:** 60 GPs. To minimise cross-contamination between intervention groups, only 1 GP from a practice could participate. Australia **Trial registration:** ACTRN12610000854033
Participants	**Population:** 60 GPs (of which 55 attended training, and 43 were available to enrol patients) were randomised to be trained in 1 of the following 4 interventions: personalised adherence discussion (PAD); inhaler reminders and feedback (IRF); PAD + IRF; or usual care. GP participants then enrolled 143 patient participants between them; PAD n = 24; IRF n = 35; PAD + IRF n = 41; usual care n = 43 **Age:** enrolled patients 14 to 65 years of age; mean age (SD) in PAD group 42.3 (15.6) years; in IRF group 40 (30.7) years; in PAD + IRF group 39.7 (17.1) years; in usual care group 40 (14.1) years **Baseline asthma severity:** FEV_1 % predicted mean (SD) in the PAD group 67.3 (21.3); in the IRF group 84.4 (19.4); in the PAD + IRF group 78.0 (15.2); in the usual care group 75.7 (22.0); percentage prescribed high-dose (> 500 mcg/d) inhaled steroids: PAD group 54%, IRF group 40%, PAD + IRF group 66%, usual care group 44% **Inclusion criteria:** 14 to 65 years of age; suboptimal asthma control; twice-daily ICS/LABA for at least 1 month **Exclusion criteria:** asthma exacerbation in the last month; use of combined inhaler as maintenance/reliever; major respiratory disease (e.g. COPD); serious uncontrolled medical conditions; clinically important visual or auditory impairment; shift workers with a variable roster; pregnant or lactating women **Percentage withdrawn:** 13% from the PAD arm, 0% from the IRF arm, 22% from the PAD + IRF arm, 5% from the usual care arm **Other allowed medication:** not reported
Interventions	**Intervention summary (1): PAD:** GPs asked participants to complete a short questionnaire about barriers to controller inhaler use. GPs were trained to carry out a personalised discussion about the participant's key barrier(s) to adherence and to help the participant set goals and goal-achievement strategies around an asthma issue that the participant wished to resolve, using patient-centered materials **Intervention summary (2): IRF:** Participants received twice-daily SmartTrack reminders for missed ICS/LABA doses. They could customise ringtones/ring times, cancel individual reminders or switch reminders off completely. Each month, GPs received an automated e-mail to view a website graph of their patients' daily ICS/LABA use; the participant could log in to view his or her own graph at any time. GPs were asked to discuss the ICS/LABA use graph with the participant at the study follow-up visit or at any subsequent appointments, at the GP's discretion. Only GPs in PAD groups were trained in specific communication strategies for discussing adherence **Intervention summary (3): PAD + IRF:** both PAD and IRF components as outlined above **Control summary:** All GPs in all groups received usual care training. This included advice on writing an asthma action plan (10 minutes), demonstration and review of inhaler technique (10 minutes) and recent changes to asthma guidelines (15 minutes) **Complex intervention:** yes

Foster 2014 (*Continued*)

Outcomes	**Outcomes measured:** ACT score; Mini-AQLQ; HADS; MARS-A; FEV_1; exacerbations **Adherence calculation:** monitored with SmartTrack device on inhaler. Calculation of adherence not described
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** National Health and Medical Research Council of Australia (ID571053)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each GP's patients represented 1 cluster. GPs were randomized separately 1:1 to active and control groups for the 2 interventions, using a 2 × 2 factorial design, allowing the effect of the 2 interventions (given in addition to UC) to be tested separately and together, in comparison with UC alone. Randomization of GPs was by a computer-generated program prepared by an independent statistician before study start, with an automated minimization algorithm to ensure a balance of randomization across 3 stratification factors"
Allocation concealment (selection bias)	Unclear risk	"Allocation concealment for GPs was maintained before study start, and revealed to each GP only during the training workshop" However, it is unclear whether allocation was concealed from investigators until randomisation had occurred
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants (GPs or their patients) described. Most of the outcomes measured are subjective and are susceptible to influence from knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcome - ACT - was collected via telephone by a researcher blinded to group allocation. However, for many outcomes, measures are subject to risk of detection bias, as the participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary analysis was by intention to treat. However, drop-out was somewhat unbalanced, with 5% dropping out from the

Foster 2014 (*Continued*)

		usual care group, 13% from the PAD group, 0% from IRF group and 21% from the IRF + PAD group
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, but all outcomes stated in methods clearly reported
Other bias	Low risk	None noted

Gallefoss 1999

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** 1 year **Setting:** recruited at outpatient chest clinic and followed up by GPs. Norway **Trial registration:** not reported
Participants	**Population:** 78 adults with asthma randomised to an asthma education intervention (n = 39) or usual care (n = 39) **Age:** 18 to 70 years; mean age (SD) in the intervention group 41 (12) years and in the control group 44 (12) years **Baseline asthma severity:** FEV_1 % predicted (SD) in the intervention group 93 (13) and in the control group 95 (17). 95% were using an ICS at baseline in the intervention group and 97% in the control group **Inclusion criteria:** asthma, defined as prebronchodilator $FEV_1 \geq 80\%$ of predicted value; positive reversibility test;documented 20% spontaneous variability (PEF or FEV_1) ; positive methacholine test **Exclusion criteria:** unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure **Percentage withdrawn:** 18% from the intervention group and 0% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** patient brochure; 2 × 2 hour group sessions (separate groups for asthma and COPD patients). First session delivered by doctor, second by pharmacist; 1 or 2 individual sessions with nurse or physiotherapist; individual treatment plan **Control summary:** standard treatment plan; GP follow-up for 1 year **Complex intervention:** yes
Outcomes	**Outcomes measured:** patient compliance, GP visits, absenteeism, days in hospital **Adherence calculation:** Medication compliance was coded to Daily Defined Doses (DDD). Dispensed medication reported from local pharmacies on monthly basis. Compliance calculated as prescribed DDD/dispensed DDD × 100. Defined a priori patients as compliant at 75%
Notes	**Type of publication:** 2 peer-reviewed full-text journal articles reporting different outcomes **Funding:** Norwegian Medical Association Fund for Quality Improvement

Gallefoss 1999 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"At inclusion they signed a written consent and were then randomized to an intervention group or a control group using random number tables"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Outcomes measured were relatively objective (e.g. exacerbations, hospitalisations, GP visits, absenteeism), but participant knowledge of group allocation may have affected health care-seeking behaviour
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described; although some outcomes measured were relatively objective and unlikely to be affected by assessors' knowledge of group allocation, patient-reported outcomes such as QOL may be at risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unbalanced drop-out: 0% in control group but 18% in intervention group
Selective reporting (reporting bias)	High risk	No prospective trial registration found; multiple publications, each including a different set of outcomes. Not clear if all measured outcomes have been reported
Other bias	Low risk	None noted

Gerald 2009

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** intervention delivered over 65 weeks **Setting:** school setting. USA **Trial registration:** NCT00110383
Participants	**Population:** 290 children with asthma randomised to supervised ICS therapy at school (n = 145) or usual care (n = 145) **Age:** 5 to 18 years; mean age (SD) in the intervention group 11.1 (2) years and in the control group 10.8 (2.1) years **Baseline asthma severity:** intervention group: 22 had mild asthma, 113 moderate

	asthma and 9 severe asthma; control group: 24 had mild asthma, 115 moderate asthma and 14 severe asthma **Inclusion criteria:** physician-diagnosed asthma, requiring daily controller medication **Exclusion criteria:** children not able to switch medications to budesonide **Percentage withdrawn:** 14% from the intervention group and 21% from the usual care group **Other allowed medication:** Children could take additional medications if their physician considered this necessary
Interventions	**Intervention summary:** Child took inhaler medication at a set time each schoolday under the supervision of staff members. Child was provided education in using the inhaler if he or she was observed to use the inhaler incorrectly. Daily monitoring **Control summary:** continued usual parent or self-supervised daily ICS treatment. Daily monitoring **Complex intervention:** no
Outcomes	**Outcomes measured:** episode of poor asthma control (EPAC); rescue medications; school absences; peak flow; rescue medication use at school **Adherence calculation:** not applicable
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** National Institutes of Health Grant R01HL075043; AstraZeneca provided the medications (Pulmicort Turbuhaler)

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A random sequence of treatment codes, stratified according to school system, was generated"
Allocation concealment (selection bias)	Low risk	"Allocation was concealed", although no details given regarding how this was achieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Patients, their parents, and study staff were not blinded to intervention condition; however, physicians were blinded to their patient's intervention condition" Main outcome (EPAC) measured might be subject to performance bias, as participant knowledge of group allocation may have affected behaviour
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Main outcome (EPAC) measured might be subject to detection bias, as par-

Gerald 2009 (*Continued*)

		ticipant knowledge of group allocation may have affected behaviour, such as decision to use rescue medication or absenteeism from school
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was somewhat higher in the control group (20.7%) than in the intervention group (13.8%), and data do not appear to have been imputed for those who did not complete the study. The length of the study explains the extent of drop-out, although the quantity of missing data and imbalance between groups may still have affected endpoint scores
Selective reporting (reporting bias)	High risk	Prospectively published protocol and main outcome measure - EPAC - clearly reported. However, some data not reported in a way that would allow inclusion in a meta-analysis (e.g. QOL)
Other bias	Low risk	None noted

Halterman 2004

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 9 weeks **Setting:** schools in the Rochester City School District. USA **Trial registration:** not reported
Participants	**Population:** 184 children with asthma randomised to school-based care (n = 93) or usual care (n = 91) **Age:** 3 to 7 years; mean age in each group not reported **Baseline asthma severity:** not reported **Inclusion criteria:** symptoms consistent with mild persistent or more severe asthma; 3 to 7 years of age; enrolled in the Rochester City School District; family had access to a working telephone for monthly follow-up telephone calls **Exclusion criteria:** children scheduled to move from the school district within 6 months; Spanish-speaking families enrolled in study year 2 only **Percentage withdrawn:** 4% from the intervention group and 0% from the usual care group **Other allowed medication:** Children using more than 1 preventive medication were instructed to continue with their other medications (in addition to the fluticasone given through school) at the discretion of their primary care provider
Interventions	**Intervention summary:** School nurse administered fluticasone once each day the child was in school **Control summary:** carers and parents notified of their child's asthma severity. No medications received in school through the programme

	Complex intervention: no
Outcomes	**Outcomes measured:** number of symptom-free days during the 2 weeks before the follow-up interview; asthma symptoms; night-time asthma symptoms; need for rescue inhaler use; absenteeism **Adherence calculation:** not applicable
Notes	**Type of publication:** peer-reviewed journal article **Funding:** Halcyon Hill Foundation, Webster, NY; Robert Wood Johnson Foundation's Generalist Physician Faculty Scholars Program. GlaxoSmithKline, Research Triangle Park, NC, donated fluticasone propionate and spacers used in this study

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by current use of preventive medications and was blocked in groups of 6. Pairs of siblings were assigned randomly to the same group. Randomization cards were made from a table of random numbers"
Allocation concealment (selection bias)	Low risk	"Randomization cards were made from a table of random numbers and were kept in sealed, opaque, sequentially numbered envelopes until after the baseline assessment was completed. Following randomization, families and primary care providers were notified of the child's group allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Some outcomes (e.g. PAQLQ, health care-seeking behaviour) may be subject to risk of performance bias from knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	"To ensure an unbiased assessment, an independent research group, blinded to each child's group allocation, conducted the follow-up interviews" However, for participant-reported outcomes, such as symptoms and PAQLQ, the unblinded participant is the outcome assessor; therefore, these outcomes are at risk of detection bias

Halterman 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All but 4 participants (for whom no data were available - all from the intervention group) were included in the primary analysis
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods reported
Other bias	Low risk	None noted

Hart 2002

Methods	**Design:** parallel-group randomised controlled trial; blinding not stated **Duration:** 13 weeks **Setting:** not reported. UK **Trial registration:** not reported
Participants	**Population:** 83 'pre-school' children with asthma randomised to an asthma education intervention or usual care (n for each group not given) **Age:** 'pre-school children'; no further details reported **Baseline asthma severity:** not reported **Inclusion criteria:** 'asthmatic pre-school children'; no further details reported **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Other allowed medication:** not reported
Interventions	**Intervention summary:** educational booklet about asthma and its treatment, and clinic consultation based on contents of booklet **Control summary:** usual care **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence; beliefs and anxieties about adherence **Adherence calculation:** medication electronically monitored; details of adherence calculation not given
Notes	**Type of publication:** conference abstract **Funding:** National Asthma Campaign, UK

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Children were "randomly allocated" - no further details
Allocation concealment (selection bias)	Unclear risk	No details

Hart 2002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of procedures to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No description of procedures to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out not reported, so unclear how many participants completed the study
Selective reporting (reporting bias)	High risk	Conference abstract, so minimal details given. No prospective trial registration identified
Other bias	Low risk	None noted

Kamps 2008

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 6 weeks, with follow-up to 52 weeks **Setting:** family home. USA **Trial registration:** not reported
Participants	**Population:** 15 children with asthma randomised to adherence improvement strategies (n = 7) or usual care plus education (n = 8) **Age:** 7 to 12 years; mean age (SD) in the intervention group 9 (1.16) years and in the control group 8.8 (1.67) years **Baseline asthma severity:** not reported **Inclusion criteria:** children 7 to 12 years of age with diagnosis of asthma **Exclusion criteria:** not reported **Percentage withdrawn:** 0% from the intervention group and 0% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** focused education, monitoring, contingency management, discipline techniques **Control summary:** comprehensive asthma education covering topics from the "Air Wise" programme **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence (MDILog); pulmonary function; PedsQL Asthma module; healthcare costs **Adherence calculation:** (number of actuations per day/number of actuations prescribed) × 100 (mean % dose per day per child)

Notes	**Type of publication:** single peer-reviewed journal article **Funding:** National Institute of Child Health & Human Development Grant number HD34784

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomisation table was developed by a statistics consultant before participant recruitment to assign children to a group; we assigned children to groups on the basis of this table
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of procedures to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No description of procedures to blind outcome assessors; in the case of VAS results and QOL results, the participant/career, who was aware of group allocation, is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Very small study; less than 50% in each arm completed the study
Selective reporting (reporting bias)	High risk	No prospective trial registration identified. Such small numbers make results difficult to interpret and combine in a meta-analysis; SDs small despite small sample sizes so will be falsely highly weighted in meta-analysis. Unable to extract adherence data owing to statistical method (pooled series time analysis) used to analyse and no raw data presented
Other bias	Low risk	None noted

Koufopoulos 2016

Methods	**Design:** open-label, parallel-group, proof-of-concept randomised controlled trial **Duration:** 9 weeks **Setting:** recruited through emails sent to 40 largest universities in the UK requesting that those with individuals managing their asthma with an ICS preventer should consider enrolling **Trial registration:** ISRCTN29399269
Participants	**Population:** 216 adults with asthma randomised to an online community intervention ("AsthmaVillage") (n = 99) or no online community intervention ("AsthmaDiary") (n = 117) **Age:** mean (SD) in the intervention group 27.2 (9.2) years and in the control group 28.8 (10.1) years **Baseline asthma severity:** not reported **Inclusion criteria:** individuals managing their asthma with an ICS preventer **Exclusion criteria:** failed to complete the eligibility questionnaire (n = 256) or baseline measures (n = 228), did not have asthma (n = 105), were not prescribed an ICS preventer inhaler for a weekly regimen of at least 1 dose per week (n = 87), failed to complete informed consent (n = 35), had previously participated in the pilot study (n = 9) **Percentage withdrawn:** 60.6% from the intervention group and 45.3% from the usual care group ('withdrawn' defined as insufficiently engaging in the intended intervention) **Other allowed medication:** not reported
Interventions	**Intervention summary:** an online community in which participants could report their preventer use and write posts, comments or questions. Questions and comments needed to be answered by community members themselves because no experimenter intervention was provided once the trial had begun. The only feedback participants could receive during the trial was that received from other participants because this intervention was optimised for implementation at scale and at low cost. This trial attempted to determine the value of an online community, implemented without the added support of a community manager to engage members **Control summary:** Control condition comprised an online diary, AsthmaDiary. This online diary was created with the use of Google Forms. A single-item survey was created: "How many times did you take your preventer?" Participants randomised to the control condition could report the number of puffs and, after entering their unique PIN, hit "submit". Because participants did not need to log in with a username to fill out the form, participants used a PIN that allowed their posts to be identified by the researcher. Participants in the control condition could not see the posts of other participants and could not otherwise know whether other participants were posting on their condition **Complex intervention:** no
Outcomes	**Outcomes measured:** medication adherence (SMAQ), website activity/'adherence' **Adherence calculation:** SMAQ was recalculated with dichotomous scoring of all variables (more than 2 missed uses was treated as non-adherent) and reverse scoring of item 4 of the SMAQ ("Thinking about the last week, how often have you not taken your asthma preventer medicine as prescribed?")
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** funded by a pilot grant from the University of Leeds School of Psychology. A Fulbright Scholarship from the US-UK Fulbright Commission supported the first study

	author	
Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization occurred through a random number generator, yielding two unequal groups"
Allocation concealment (selection bias)	Unclear risk	"The experimenters then manually separated the two lists and emailed both groups log-in instructions" It seems unlikely that allocation was not concealed given the nature of the study design (i.e. the participant is 'remote'), but this is not a standard description of an allocation procedure, so we cannot be sure exactly what the process entailed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded to group allocation and knowledge of group allocation, and adherence monitoring may have affected their self-reported adherence (e.g. those in the intervention arm systematically over-estimating adherence)
Blinding of outcome assessment (detection bias) All outcomes	High risk	The participant is the outcome assessor for the main outcome - self-reported adherence - and as participants were aware of group allocation, we consider this outcome to be at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high and unbalanced drop-out (60% in intervention arm and 45% in control arm). Although an ITT analysis was performed for the primary outcome - self-reported adherence - it is unclear how this high level of drop-out may have impacted the results
Selective reporting (reporting bias)	High risk	Trial retrospectively registered (ISRCTN 29399269), but not all outcomes reported in trial report, including AQLQ
Other bias	Low risk	None noted

Mann 1992

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 6 weeks, with follow-up to 6 weeks **Setting:** clinic and private practice. USA **Trial registration:** not reported.
Participants	**Population:** 16 adults with asthma randomised to twice-daily (bid) dosing (n = 8) or 4-times-daily (qid) dosing (n = 8) **Age:** over 18 years of age; mean age (SD) in the intervention group 46.9 (10) years and in the control group 42.3 (12.1) years **Baseline asthma severity:** intervention group: 2 on maintenance oral steroids; control group: 4 on maintenance oral steroids **Inclusion criteria:** clinical stable asthma, requiring regular ICS **Exclusion criteria:** not reported **Percentage withdrawn:** 0% from the intervention group and 0% from the usual care group **Other allowed medication:** "other asthma therapy continued throughout the study"
Interventions	**Intervention summary:** 4 inhalations flunisolide twice daily **Control summary:** 2 inhalations flunisolide, 4 times daily **Complex intervention:** no **Notes:** Participants changed to flunisolide at beginning of study if necessary. Both groups used bid dosing for a run-in period to establish a baseline
Outcomes	**Outcomes measured:** compliance; PEFR; symptom score **Adherence calculation:** % days with more or less than prescribed 8 inhalations; mean inhalations per day; frequency distribution of total daily inhalation; number inhaler responses per day
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** not reported

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After informed consent was obtained, patients were randomized into two groups of eight each. Randomization was stratified so each group contained four clinic and four private practice patients" - no further details given about how stratified random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of procedures to blind participants or personnel. However, primary outcome measure - adherence - objectively measured and unlikely to be prone to per-

Mann 1992 (*Continued*)

		formance or detection bias. Participants were unaware that the primary aim of the study was to assess compliance. Subjective nature of secondary outcomes, such as asthma symptoms, may result in higher risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of procedures to blind outcome assessors. However, primary outcome measure - adherence - objectively measured and unlikely to be prone to performance or detection bias. Subjective nature of secondary outcomes, such as asthma symptoms, may result in higher risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient did not use the NC at all for 39 of the 42 study days, but actuated the device 109 times on the day of the three-week visit, and 56 times on the day of the six-week visit. This patient was dropped and replaced in the study." No other withdrawals reported
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods reported in text
Other bias	Low risk	None noted

Mehuys 2008

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 6 months **Setting:** 66 community pharmacies in Belgium **Trial registration:** not reported
Participants	**Population:** 201 adults with asthma randomised to adherence education (n = 107) or control (n = 94) **Age:** 18 to 50 years of age; mean age (range) in the intervention group 32.5 (19 to 51) years and in the control group 36.3 (17 to 51) years **Baseline asthma severity:** intervention group: mean (range) ACT score: 19.3 (10 to 25) ; 89.5% on ICS at baseline; control group: 19.7 (11 to 25); 93.9% on ICS at baseline **Inclusion criteria:** required to carry a prescription for asthma medication; under treatment for asthma for at least 12 months; "using" controller medication; making regular visits to the pharmacy **Exclusion criteria:** smoking history of more than 10 pack-years, another severe disease (e. g. cancer) and an ACT score at screening < 15 (indicating seriously uncontrolled asthma; for ethical reasons, these patients were immediately referred to their GP or respiratory

	specialist) or = 25 (indicating complete asthma control; no room for improvement) **Percentage withdrawn:** 25% from the intervention group and 26% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** At the first visit, pharmacist delivered personal education about using an inhaler correctly; understanding asthma symptoms, triggers and early warnings; understanding asthma controller and reliever therapy; facilitating adherence to use of controller; and stopping smoking. At visits 2 and 3 (1 and 3 months), pharmacist gave advice based on participant's ACT score **Control summary:** usual pharmacy care. All participants filled in an asthma diary in the 2-week run-in period but had no further contact outside of usual pharmacy visits **Complex intervention:** yes
Outcomes	**Outcomes measured:** Asthma Control Test (Dutch), diary card data (nocturnal awakenings, rescue medication use, PEF), asthma-related ED visits and hospitalisations, AQLQ, Knowledge of Asthma and Asthma Medicine questionnaire (KAAM), inhalation technique checklist **Adherence calculation:** Adherence was measured using refill rates and self-reporting via an adherence scale
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The sequence of allocation to either control or intervention group was predetermined by the investigators based on a randomisation table"
Allocation concealment (selection bias)	Low risk	"Serially numbered, closed envelopes were made for each participating pharmacy. The envelope with the lowest number was opened by the pharmacist upon inclusion of a new patient"
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants, so although adherence is measured objectively using pharmacy data, many other outcomes such as ACT and AQLQ are subject to potential performance bias, as participants know to which group they were assigned

Mehuys 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors is not described, and although the primary outcome (adherence measured using pharmacy data) is not prone to detection bias, other patient-reported outcomes (such as ACT and AQLQ) are at risk because the participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximately 25% of participants dropped out of each arm of the trial. Although reasons were similar and baseline characteristics of those completing and not completing did not differ significantly, rate of drop-out is high, and we cannot be sure that this did not affect the results. Secondary outcomes were analysed per protocol rather than by ITT
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods reported in text/tables
Other bias	Low risk	None noted

NCT00115323

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** intervention delivered over 13 weeks; follow-up continued to 26 weeks **Setting:** primary care and asthma specialty practices serving low-income inner-city neighbourhoods with high prevalence of asthma morbidity. USA **Trial registration:** NCT00115323
Participants	**Population:** 333 adults with asthma randomised to a problem-solving (PS) intervention (n = 165) or an asthma education (AE) intervention (n = 168) **Age:** minimum age 18; mean age (SD) in PS group 49 years (13) and in AE group 49 (14) years **Baseline asthma severity:** sufficiently severe to require treatment with ICS. FEV_1% predicted (SD) in PS group 66 (19) and in AE group 64 (19) **Inclusion criteria:** English- or Spanish-speaking adults with moderate or severe persistent asthma according to National Heart, Lung, and Blood Institute Expert Panel Report 3 guidelines. Inclusion criteria were designed to identify patients with sufficiently severe and reversible asthma who were likely to benefit from ICS therapy. Specific criteria included the following: age ≥ 18 years; physician's diagnosis of asthma; prescription for an ICS-containing medication for asthma; and evidence of reversible airflow obstruction, that is, an increase ≥ 15% and 200 mL in FEV_1 with asthma treatment over the previous 3 years, or an increase in FEV_1 or FVC ≥ 12% and 200 mL in FEV_1 within 30 minutes of inhaled albuterol. Smokers were included

NCT00115323 (*Continued*)

	Exclusion criteria: severe psychiatric problems such as obvious mania or schizophrenia that would make it impossible for individuals to understand or carry out problem solving **Percentage withdrawn:** not specifically reported **Other allowed medication:** not specifically reported
Interventions	**Intervention summary:** four 30-minute sessions. Individualised intervention involved 4 interactive steps, usually 1 per research session, aimed at improving or maintaining adherence. Step 1: breaking problems into small achievable pieces; Step 2: brainstorming for alternative solutions; Step 3: choosing the best solution by weighing the consequences, both desirable and undesirable, of each candidate solution (between third and fourth meetings, the solution was tried); Step 4: evaluating and revising chosen solution. Intervention delivered to participants by a research co-ordinator (college graduates interested in health-related or education carers or further schooling, committed to working with patients and having a research experience. Co-ordinators were diverse in race/ethnicity, as were participants) **Control summary:** four 30-minute sessions, each focused on an asthma patient education topic unrelated to self-management, adherence or ICS therapy. Topics covered included proper technique for using an albuterol-rescue metered dose inhaler and a dry powder inhaler or spacer, depending on the patient's medications; use of peak flow meters; common asthma triggers; and pathophysiology of asthma. These sessions did not involve discussion of problem solving or adherence, only a didactic presentation of health information. Delivered to participants by a research co-ordinator (college graduates interested in health-related or education carers or further schooling, committed to working with patients and having a research experience. Co-ordinators were diverse in race/ethnicity, as were participants) **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence to ICS regimen prescribed by participant's physician assessed by an electronic monitor; Mini-AQLQ; ACQ; spirometry (FEV_1 and FVC); hospitalisations and ED visits for asthma or any cause; patient satisfaction **Adherence calculation:** Daily ICS adherence was calculated as (# actuations downloaded/# prescribed) × 100 (using an electronic adherence monitor attached to the inhaler)
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** supported by grants from the National Institutes of Health (HL070392, HL088469)

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomized according to a computer-generated algorithm in 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	No details

NCT00115323 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Main outcome - adherence - objectively measured, but other outcomes such as ACQ and AQLQ are subject to performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Main outcome - adherence - objectively measured, but other outcomes such as ACQ and AQLQ are subject to detection bias as the unblinded participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not reported
Selective reporting (reporting bias)	Low risk	Prospectively registered trial (NCT00115323). All outcomes reported
Other bias	Low risk	None noted

NCT00149487

Methods	**Design:** open-label, parallel-group, multi-centre randomised controlled trial **Duration:** 17 weeks, with follow-up continuing to 1 year **Setting:** recruitment from primary and subspecialty care, inpatient and emergency department settings at 1 large paediatric tertiary care centre. USA **Trial registration:** NCT00149487
Participants	**Population:** 141 children with asthma randomised to a problem-solving intervention or family-based education (n for each group not reported) **Age:** 5 to 17 years; mean age not reported **Baseline asthma severity:** not reported **Inclusion criteria:** African American, family income below the poverty line, physician-based diagnosis of asthma of at least 12 months, moderate to severe asthma (moderate asthma includes daily symptoms, daily use of inhaled short-acting beta-agonist, exacerbations more than 2 times per week that affect activity and night-time symptoms more often than once a week, FEV_1 or PEF between 60% and 80% predicted and PEF variability > 30%; severe asthma includes continual symptoms, limited physical activity, frequent exacerbations together with frequent night-time symptoms, FEV_1 or PEF < 60% predicted and PEF variability > 30%). Likely to be on a stable and daily medication (inhaled steroid) that can be modified electronically for the time period required to participate in the study **Exclusion criteria:** serious comorbid chronic condition, serious developmental disability, income exceeding poverty level **Percentage withdrawn:** not reported **Other allowed medication:** not reported

NCT00149487 (*Continued*)

Interventions	**Intervention summary:** intervention tailored to observed adherence behaviours and identified barriers to increasing adherence in African American children and adolescents with asthma and their families **Control summary:** family education **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence, frequency of asthma symptoms, utilisation of health-care services, use of reliever medication **Adherence calculation:** adherence defined as correspondence between medication doses taken each day and prescribed dose, tracked by electronic monitoring device during months 9 to 12 of the study
Notes	**Type of publication:** single peer-reviewed full-text journal article and NCT record with no study results provided. Full-text publication of RCT findings not found; above data extracted from a paper describing observational data related to trial participants **Funding:** National Heart, Lung, and Blood Institute (NHLBI)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" but no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out not reported for each arm; 49/141 dropped out overall (35%)
Selective reporting (reporting bias)	High risk	Unable to identify full-text report of the RCT. Observational study on same cohort reported. No study results posted on clinicalrials.gov. Not able to include any outcomes in meta-analysis
Other bias	Low risk	None noted

NCT00166582

Methods	**Design:** open-label, 3-arm, parallel-group randomised controlled trial **Duration:** 2 months **Setting:** recruited from asthma clinics at a rural, university-based hospital in northeastern United States and an urban-based children's hospital in the Midwest **Trial registration:** NCT00166582
Participants	**Population:** 55 children with asthma randomised to receive a team work intervention (n = 19), an asthma education intervention (n = 19) or usual care (n = 17) **Age:** 9 to 15 years; mean age (SD) 11.1 (1.9) years across the 3 groups (mean age not given for each group) **Baseline asthma severity:** team work intervention group: mild persistent asthma = 37.5%, moderate persistent asthma = 50.0%, severe persistent asthma = 12.5%; asthma education group: mild persistent asthma = 25.0%, moderate persistent asthma = 56.2%, severe persistent asthma = 18.8%; usual care group: mild persistent asthma = 18.8%, moderate persistent asthma = 62.5%, severe persistent asthma = 18.8% **Inclusion criteria:** child with diagnosis of persistent asthma for at least 6 months; fluticasone MDI taken daily; and no evidence of neurological or significant cognitive impairment (per parent report). Suspected history of medication non-adherence not required **Exclusion criteria:** not reported **Percentage withdrawn:** 16% from both teamwork intervention and asthma education intervention groups and 6% from usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary (1): teamwork:** emphasised the importance of parents and youth sharing responsibility for the patient's asthma management and learning methods for addressing conflicts associated with increased responsibility of youth. Involved handouts on adolescent development, promoting youth independence, appropriate parental medication supervision and problem solving around asthma management conflicts. MDI Log-II served as the primary source of adherence information for families. ICS adherence goals were set in consultation with physician (lowest 70%). Four sessions 2 to 3 weeks apart delivered by a 'therapist' **Intervention summary (2): asthma education:** similar to the teamwork group, families in this group received and reviewed written materials with the researcher during sessions. These materials covered topics often found in asthma education programmes. Time spent with families generally was equivalent to that of its parallel teamwork session, thereby creating an attention control condition. Four sessions 2 to 3 weeks apart delivered by a 'therapist' **Control summary:** Youth in the usual care group completed all assessments at the same time interval as other participants but did not receive guidance beyond usual care. On completion of follow-up, these families were provided feedback on their child's medication adherence and were offered an opportunity to receive either of the 2 interventions **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence to ICS using MDI Log-II; parent-adolescent conflict (CBQ-20); health outcomes (FSI); lung function; consumer satisfaction (CSQ) **Adherence calculation:** Mean daily adherence was defined as follows: total number of puffs inhaled divided by total number of puffs prescribed, multiplied by 100

Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** supported by the National Institute of Child Health and Human Development (R03-HD039767-02)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Initially, youth were randomly assigned (via computer-generated number sequence) to one of three parallel groups… subsequent participants were assigned using a randomized block design to maintain group balance across variables"
Allocation concealment (selection bias)	High risk	The sequence was available to the research assistant who recruited participants into the study, as participants were immediately randomised; thus, the research assistant might have been aware of group allocation before participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. The main outcome measured - adherence - was monitored objectively with an electronic device, but other outcomes such as functional severity index and satisfaction may have been affected by knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. The main outcome - adherence - was monitored objectively with an electronic device. However, other outcomes such as functional severity index are subject to risk of detection bias, as the participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out lower in the standard care group (6%) than in the 2 active groups (both 16%); all participants accounted for in the flow diagram, but uneven drop-out may have skewed results because these people were not included in the analyses
Selective reporting (reporting bias)	Unclear risk	Prospectively registered trial (NCT00166582), although details minimal in trial registration

NCT00166582 (*Continued*)

		and outcomes not specified. However, all outcome measures listed in methods of the paper are reported clearly
Other bias	Low risk	None noted

NCT00233181

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** 78 weeks **Setting:** Paediatric ED in Baltimore. USA **Trial registration:** NCT00233181
Participants	**Population:** 250 children with asthma randomised to adherence monitoring and education (n = 83), education (n = 84) or usual care (n = 83) **Age:** 2 to 12 years of age; mean (SD) age in the adherence group 6.5 (3.43) years, in the education group 7.1 (3.37) years and in the control group 7.4 (3.3) years **Baseline asthma severity:** not reported **Inclusion criteria:** eligible for randomisation when between 2 and 12 years of age, physician-diagnosed asthma, 2 ED visits or 1 hospitalisation for asthma in the preceding year, resided in Baltimore City, prescribed an asthma controller medication **Exclusion criteria:** not reported **Percentage withdrawn:** 8.4% from the adherence group, 3.5% from the education group and 8.4% from the control group **Other allowed medication:** not reported
Interventions	**Intervention summary (1):** Educational content in the education group PLUS electronic adherence monitoring with feedback, asthma control and adherence goal setting, reinforcement (praise and low-cost rewards), and strategies for self-monitoring medication use **Intervention summary (2):** five 30- to 45-minute home visits by trained asthma educators (AEs) 1, 2, 3, 4 and 8 weeks after randomization. ABC intervention is a home-based asthma education programme with 5 core components: review of prescribed asthma regimen and training in medication, spacer and peak flow technique; development of an asthma action plan; identification of barriers to accessing healthcare services and problem solving to reduce barriers; discussion of beliefs and concerns about asthma and medications; and provision of written asthma education materials **Control summary:** asthma education booklet and resource guide that provided information about low-cost asthma care providers, social services, legal services and other resources. Regardless of group assignment, participants were regularly encouraged to receive care from their primary care provider **Complex intervention:** yes
Outcomes	**Outcomes measured:** self-reported adherence; pharmacy-based adherence; career reports of symptoms, night-time awakenings, ED visits, hospitalisations and courses of OCS in the previous 6 months **Adherence calculation:** Pharmacy-based adherence was calculated as number of ICS refills per quarter, converted into equivalent values; rates were defined as number of ICS canisters dispensed quarterly (where 3 = 100% adherence). Self-reported adherence was

NCT00233181 (*Continued*)

	% use/prescribed dose × 100
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** National Heart, Lung, and Blood Institute grant HL063333

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"To mask staff to group assignment during recruitment, the statistician created block randomization schema and placed the randomization assignments into sealed envelopes, which were opened after families completed baseline surveys"
Allocation concealment (selection bias)	Low risk	"To mask staff to group assignment during recruitment, the statistician created block randomization schema and placed the randomization assignments into sealed envelopes, which were opened after families completed baseline surveys"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded to group allocation, and knowledge of group allocation and adherence monitoring may have affected healthcare utilisation behaviour, as well as adherence behaviour, beyond the effect intended by trialists
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Trained research assistants who were blinded to study assignments conducted surveys by telephone" However, all asthma morbidity measures were career reported, and therefore were at risk of detection bias, as the career is the outcome assessor for these self-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 80% of participants in all 3 arms completed all questionnaires and follow-up. Results analysed as ITT, and all randomised participants included in the ITT analysis
Selective reporting (reporting bias)	High risk	Prospectively registered trial (NCT00233181), but not all outcomes (e.g. QOL) reported in the published paper

NCT00233181 (*Continued*)

Other bias	Low risk	None noted

NCT00414817

Methods	**Design:** open-label, pragmatic, parallel-group randomised controlled trial **Duration:** 78 weeks **Setting:** conducted through 2 Kaiser Permanente research centres in Hawaii and Baltimore. USA **Trial registration:** NCT00414817
Participants	**Population:** 14,064 adults with asthma randomised to receive interactive voice response calls or usual care. Not all participants were previous ICS users. 3171 of the intervention group and 3260 of the usual care group described as the primary analysis sample - previous ICS users **Age:** 18 years of age and older; ages reported in categories rather than as mean (SD) **Baseline asthma severity:** 33.3% had comorbid COPD; other characteristics included recent ED visit, hospitalisation or OCS burst for asthma; current SABA usage; and number of medications used **Inclusion criteria:** Target population consisted of KPNW and KPH members 18 years of age and older who were members for the 12 months before randomisation, had been seen for asthma and received at least 1 dispensing of a respiratory medication during that time frame. For study of both primary and secondary ICS adherence, target population included individuals without evidence of prior ICS use. Present analysis focuses on the subset of 6903 individuals with ICS dispensing during baseline year **Exclusion criteria:** Individuals meeting the above criteria were included in the final analysis sample only if they had ever received (or for usual care participants would have qualified for) an intervention call **Percentage withdrawn:** of 6903 previous users qualifying for analysis, 3171 were included in the intervention analysis sample and 3260 in the usual care analysis sample **Other allowed medication:** not reported
Interventions	**Intervention summary:** interactive voice recognition (IVR) intervention including 3 basic IVR call types, each typically lasting 2 to 3 minutes: refill reminder call, for people whose last ICS dispensing was at least a month ago and who should have < 30 days supply left, reminded participants that they were due for a refill and offered a transfer to the automated pharmacy refill line and/or information about KP's online refill service; tardy refill call, for people > 1 month past refill date, reminded participants they were due for an ICS refill, assessed asthma control, explored ICS adherence barriers and provided tailored educational messages; and initiator/restart call, for participants who were starting ICS for the first time or were lapsed users, included probes for asthma control and adherence barriers and offered tailored educational messages **Control summary:** usual care **Complex intervention:** no
Outcomes	**Outcomes measured:** 8 alternative measures of pharmacy-based adherence, described as continuous multiple-interval measures of medication availability and gaps. Clinicaltrials.gov lists the primary outcome as days' supply of ICS available as documented in participants' pharmacy records at 19 months, and secondary outcomes as health status from

NCT00414817 (*Continued*)

	survey responses (subset), utilisation of acute healthcare services from medical record data and an economic analysis. Multiple post hoc analyses provided in published reports **Adherence calculation:** 8 alternative measures of pharmacy-based adherence (one of the resulting publications is a comparison of pharmacy-based measures of medication adherence)
Notes	**Type of publication:** multiple peer-reviewed journal articles **Funding:** NHLBI

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization stratified by region and the clinic facility to which each patient was paneled" - but no further details about how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although it was not possible to blind participants to group allocation, the primary outcome (adherence) was measured objectively using pharmacy data. However, as participants would have been aware that they were taking part in a trial of adherence and were being monitored, this may have affected their adherence behaviour beyond the effect intended by the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors is not described; however, the nature of the primary outcomes (adherence measured using pharmacy data) makes them not prone to detection bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Owing to the trial design, it was not possible to measure attrition in the usual way
Selective reporting (reporting bias)	High risk	Prospectively registered trial (NCT00414817), but many outcomes of interest not presented numerically, so unable to include it in the meta-analysis ("We also observed no significant intervention effects on reliever medication (SABA) use, quality of life, asthma control, or the rate of acute asthma health care utilization")

NCT00414817 (*Continued*)

Other bias	Low risk	None noted

NCT00459368

Methods	**Design:** single-blind, parallel-group, stratified cluster randomised trial **Duration:** 52 weeks **Setting:** primary care: 34 clusters ('practices' comprising 193 providers). USA **Trial registration:** NCT00459368
Participants	**Population:** 2698 adults and children with asthma from 34 clusters ('practices' comprising 193 providers) randomised to adherence education and individualised patient adherence information (17 practices, 88 providers, 1335 participants) or adherence education alone (17 practices, 105 providers, 1363 participants) **Age:** 5 to 56 years of age; mean age (SD) in the adherence education and individualised patient adherence information group 26.8 (17.4) years and in the adherence education alone group 28.8 (17.4) years **Baseline asthma severity:** physician diagnosis of asthma and prescription for ICS in the preceding 2 years; no other severity information given **Inclusion criteria:** Eligible primary care practices had to have access to electronic prescription writing. Eligible patients had to fulfil the following criteria: recent previous electronic prescription for an ICS; 5 to 56 years of age as of 30 April 2007; continuous enrolment in the affiliated health maintenance organisation (HMO) for at least 1 year before 30 April 2007; prescription drug coverage as of 30 April 2007; at least 1 physician diagnosis of asthma and no diagnosis of chronic obstructive pulmonary disease or congestive heart failure after 19 January 2005; and at least 1 visit to a primary care provider in the year before 30 April 2007 **Exclusion criteria:** ICS medication stopped and not restarted, left the HMO before start of the intervention **Percentage withdrawn:** 22% from the adherence education and individualised patient adherence information arm and 24% from the adherence education alone arm **Other allowed medication:** Participants continued their normal medication
Interventions	**Intervention summary:** Physicians assigned to both groups received an audio compact disc, a digital video disc and a booklet that contained information on the most recent national asthma guidelines and methods for discussing medication non-adherence with patients. Physicians in the intervention arm could also view their patients' individual adherence data generated by ePrescribing **Control summary:** as above, but physicians were not able to view their patients' individual adherence data **Complex intervention:** yes
Outcomes	**Outcomes measured:** patient adherence to ICS in last 3 months of intervention (i.e. an individual-level outcome accounting for practice clusters), time to and number of the following events during the intervention period: asthma-related emergency department visit, asthma-related hospitalisation and oral steroid use. Post hoc analysis revealed that the change in adherence between baseline and study end differed between participants in intervention and control arms **Adherence calculation:** Based on data from electronic prescribing, calculated days of

	supply was calculated to estimate adherence as a continuous measure of medication availability equal to the cumulative days of supply divided by the number of days of observation. This estimates the proportion of time that participants took their medication
Notes	**Type of publication:** multiple peer-reviewed full-text journal articles **Funding:** supported by grants from the National Heart, Lung, and Blood Institute (HL79055), the National Institute of Allergy and Infectious Diseases (AI61774, AI79139), the National Institute of Diabetes and Digestive and Kidney Diseases (DK64695), National Institutes of Health; the Fund for Henry Ford Hospital; and the Strategic Program for Asthma Research of the American Asthma Foundation

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Practices were randomised with stratification for whether the practice was a paediatric practice (i.e. paediatrics vs family medicine and internal medicine) to achieve approximately equal partitioning of children and adults in both study arms. One researcher (E.L.P.) generated the random allocation sequence within strata, and the identities of the practices were concealed at the time of randomisation
Allocation concealment (selection bias)	Low risk	The identities of practices were concealed at the time of randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Healthcare providers (rather than individual participants) were randomised and were aware of group allocation. It is unclear how their knowledge of group allocation may have impacted the adherence of their patients in ways unintended by the intervention itself
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study staff was masked to the individual practice treatment assignment, and the primary outcome - adherence as calculated from pharmacy data - is objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although > 20% of participants did not complete the trial (22% in the intervention arm and 24% in the control arm), we carried forward their last 3 months of adherence and analysed data in the primary analysis

NCT00459368 (*Continued*)

Selective reporting (reporting bias)	Low risk	Prospectively registered trial (NCT00459368). All outcomes reported in at least 1 of several associated publications
Other bias	Low risk	None noted

NCT00516633

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 26 weeks, with follow-up to 78 weeks **Setting:** children 'in our region' given diagnosis of asthma in previous 1 to 2 months. Sweden **Trial registration:** not reported
Participants	**Population:** 60 children with asthma and their parents randomised to group discussions plus basic education (n = 32) or basic education (n = 28) **Age:** 3 months to 6 years of age; mean age (SD) in the intervention group 28.1 months and in the control group 26.1 months **Baseline asthma severity:** not reported **Inclusion criteria:** moderate or severe asthma defined by SPT II Brazillian Consensus on Asthma Management **Exclusion criteria:** not reported **Percentage withdrawn:** 9% from the intervention group and 14% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** meetings in a group setting with both parents. Afternoon sessions of 1.5 hours' duration; 3 weekly meetings soon after asthma diagnosis and a follow-up meeting at 6 months. Session involved 3 paediatricians, 3 nurses and 2 psychologists. One nurse was present on all occasions. The method applied was based on the concept of concordance, meaning that we tried to "speak the same language" as the parents and to reach an alliance with them on how to look upon asthma and its management. Our goal was to reach their "main worry" and, apart from teaching about asthma, we asked the key question: "What is asthma to you?" Our intention was to use dialogue and peer education, whereby the group was encouraged to share personal experiences. In each group session, leaders had a list of subjects that were to be covered during the discussion. Attendees also received basic education **Control summary:** basic education about asthma and its treatment, including how to use the Nebunette, and information on environmental control at first visit to the clinic. Participants received a written treatment plan for which the principle was high dose initially, then, in association with URTI, stepping down therapy to the lowest possible dose according to the status of the child. Treatment was stopped if the child had no asthma symptoms for 6 months **Complex intervention:** yes

NCT00516633 (*Continued*)

Outcomes	**Outcomes measured:** presence of parents at group meetings; personal view on adherence at inclusion and after 6 and 18 months; how many days the child was hospitalised; how many times participants had to seek emergency help for asthma; exacerbations, as defined by the need for parents to stay at home to take care of their child because of asthma symptoms; objective measures of adherence; adherence according to parents **Adherence calculation:** diaries and weighing of MDIs used between 12 and 18 months after inclusion
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** Primary Care Unit in the county of Varmland. AstraZeneca provided the medicines

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The parents of the 60 children were randomized consecutively in groups of four to either the intervention or the control group" - but no further details about how this was achieved
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The nurses carried out the randomization and the three doctors that were involved in the group sessions also performed the follow-up visits. Therefore, a complete blinding procedure could not be established"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The nurses carried out the randomization and the three doctors that were involved in the group sessions also performed the follow-up visits. Therefore, a complete blinding procedure could not be established"
Incomplete outcome data (attrition bias) All outcomes	Low risk	High levels of follow-up in both arms (86% in control group, 91% in intervention group); all withdrawals accounted for in the publication
Selective reporting (reporting bias)	High risk	No prospective trial registration identified. Many outcomes reported narratively in text but with insufficient numerical detail for inclusion in the meta-analyses. Within-group or whole study population results sometimes presented rather than between-group differences. 'N.S.' frequently

NCT00516633 (*Continued*)

		reported rather than exact CIs, SDs or P values
Other bias	Low risk	None noted

NCT00958932

Methods	**Design:** open-label, pragmatic, parallel-group randomised controlled trial **Duration:** 2 years **Setting:** 18 primary care and 2 specialty care medical offices, 2 contract hospitals and more than 800 physicians. USA **Trial registration:** NCT00958932
Participants	**Population:** 1187 children with asthma randomised to speech recognition (SR) intervention (n = 590) or usual care (UC) (n = 597) **Age:** 3 to 12 years of age; mean age (SE) in SR group 8.2 (0.13) years and in the UC group 8.1 (0.13) years **Baseline asthma severity:** diagnosed persistent asthma for which daily inhaled corticosteroid treatment was prescribed. Children in the SR group had inpatient visits/person-year, mean (SE), number 0.04 (0.01); ED visits/person-year, mean (SE), number 0.09 (0.02); oral steroid bursts/person-year mean (SE), number 0.469 (0.04); primary care visits/person-year, mean (SE), number 2.3 (0.08); and children in the UC group had inpatient visits/person-year, mean (SE), number 0.04 (0.01); ED visits/person-year, mean (SE), number 0.09 (0.02); oral steroid bursts/person-year, mean (SE), number 0.383 (0.04); primary care visits/person-year, mean (SE), number 2.4 (0.10) **Inclusion criteria:** 3 to 12 years of age, diagnosis of persistent asthma, 1 or more ICS prescriptions filled in the prior 6 months. Participants were limited to those enrolled in KPCO (Kaiser Permanente Colorado; a group-model health maintenance organisation) for at least 1 year to ensure that patients were consistently given a diagnosis of persistent asthma and to establish a baseline ICS adherence rate **Exclusion criteria:** identified by physician as having a life-threatening comorbid condition; sibling already included in the study; parent who declined to participate; instructed to take an ICS only intermittently or as needed; obtained medication from a non-KPCO pharmacy **Percentage withdrawn:** 23% from the SR arm and 25% from the UC arm **Other allowed medication:** Participants continued their normal medication
Interventions	**Intervention summary:** Speech recognition telephone calls to parents in the intervention condition were triggered when an inhaled corticosteroid refill was due or overdue. Calls were automatically tailored with medical and demographic information from the electronic health record and from parent answers to questions during the call regarding recent refills or a desire to receive help refilling, to learn more about asthma control or to speak with an asthma nurse or a pharmacy staff member. All standard asthma resources remained available to both intervention groups throughout the duration of the study **Control summary:** All standard asthma resources remained available to the usual care group throughout the duration of the study **Complex intervention:** no

Outcomes	**Outcomes measured:** adherence to ICS, beta$_2$-agonist use, oral steroid use; asthma-related visits for primary healthcare services, ED visits, hospitalisations and after-hours visits on weekends or weekdays after 6 PM; participant satisfaction **Adherence calculation:** Adherence was expressed as proportion of days covered (PDC) over 24 months. PDC was calculated as total number of ICS days supplied divided by period for which medication was prescribed
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** supported by grant 1R01HL084067-01A2 from the National Institutes of Health. The National Institutes of Health had no role in design and conduct of the study; collection, management, analysis and interpretation of data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization will be at the level of individual patients" - but no further detail given in the study report or protocol
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel described. Main outcomes are related to usage of healthcare services and may be influenced by participants' knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessor described. However, main outcomes are related to usage of healthcare services, which was obtained from medical records and is unlikely to be influenced by knowledge of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although drop-out was relatively high (> 20%) owing to loss of insurance, it was balanced and trialists performed an intention-to-treat analysis; participants who lost insurance coverage during the 2-year study period were included in a secondary analysis for evaluation of potential sample attrition bias
Selective reporting (reporting bias)	Low risk	Prospectively registered trial (NCT00958932) and protocol available online. All main outcomes of interest reported; trialists state they will

NCT00958932 (*Continued*)

		report rescue medication use in the protocol, but this information does not appear in the main report
Other bias	Low risk	None noted

NCT01064869

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** intervention delivered over 12 weeks. Follow-up continued to 1 year **Setting:** Regional Difficult Asthma Service. Northern Ireland **Trial registration:** not reported
Participants	**Population:** 20 people with asthma attending a difficult asthma service facility randomised to individualised psychoeducational nurse-led intervention (n = 9) or usual care (n = 11) **Age:** age range not reported, but mean age (SD) in the intervention group was 50 (9.1) years and in the control group 45.2 (10) years **Baseline asthma severity:** All participants had 'difficult asthma' - defined as persistent symptoms, despite treatment at BTS/SIGN step 4/5. Baseline mean (SD) % predicted FEV_1 74.4 (20.5) **Inclusion criteria:** difficult asthma, defined as persistent symptoms, despite treatment at BTS/SIGN step 4/5; attendance at the Northern Ireland Regional Difficult Asthma Service; non-adherence after phase 1 of the study (received a patient concordance discussion); age over 18 years **Exclusion criteria:** current tobacco smoking or significant other comorbidity that contributed to persistent respiratory symptoms **Percentage withdrawn:** 22% from the intervention group and 0% from the usual care group **Other allowed medication:** ICS/LABA; prednisolone
Interventions	**Intervention summary:** individualised psychoeducational nurse-led intervention comprising 8 visits to a respiratory nurse, plus usual care **Control summary:** usual care **Complex intervention:** yes
Outcomes	**Outcomes measured:** change in adherence to inhaled combination therapy; daily prescribed dose of ICS; courses of rescue oral corticosteroids; total inhaled and nebulised beta-agonist doses; hospital admissions and lung function; ACQ; AQLQ; HADS; State Trait Anxiety Scale **Adherence calculation:** % of inhaled combination therapy prescriptions refilled and change in number of participants in each group filling ≤ 50% of prescription refills
Notes	**Type of publication:** single peer-reviewed full-text journal article **Funding:** Research and Development Office, Northern Ireland

Risk of bias		*Risk of bias*

NCT01064869 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated to either the intervention or control group" - no further details
Allocation concealment (selection bias)	Unclear risk	None noted
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as 'single blind' but blinding not further described. Seems unlikely that participants or personnel would have been masked, and many outcomes (e.g. ACQ, AQLQ) were subject to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as 'single blind' but blinding not further described. Seems unlikely that participants or personnel would have been masked, so likely outcome assessors were masked. However, many outcomes (e.g. ACQ, AQLQ) subject to risk of detection bias, as the unblinded participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out unbalanced, although small numbers in both arms (0% drop-out in control group, 22% in intervention group)
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods reported
Other bias	Low risk	None noted

NCT01132430

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** 6 weeks, with follow-up to 52 weeks **Setting:** Outpatient clinic. Single site. Canada **Trial registration:** not reported.
Participants	**Population:** 54 adults with asthma randomised to motivational interviewing (MI) (n = 26) or usual care (n = 28) **Age:** over 18 years of age; mean age (SD) in the intervention group was 52 (15) years and in the control group 49 (16) years **Baseline asthma severity:** intervention group: ACT score 17 (4); ACQ 1.7 (0.9); control group: ACT score 17 (4); ACQ score 2.1 (1.1) **Inclusion criteria:** age 18 years; primary diagnosis of moderate to severe persistent

NCT01132430 (*Continued*)

	asthma; prescribed stable dose of ICS for at least 12 months before enrolment; uncontrolled asthma according to ACQ; non-adherence (filling < 50% prescribed ICS in the past 12 months) **Exclusion criteria:** comorbid condition with greater risk than asthma (COPD, CVD, etc.), severe psychopathology; current substance abuse; cognitive or language difficulties; plan to become pregnant; plan to leave Quebec over course of the study **Percentage withdrawn:** 30.77% from the intervention group and 21.43% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** individual session based on an MI manual, with the overall goal of enhancing participant motivation to take ICS **Control summary:** Participants received whichever treatments were prescribed by their physician, which may include an action plan or referral to asthma education. Participants were given the opportunity to receive MI after study completion **Complex intervention:** yes
Outcomes	**Outcomes measured:** ICS adherence; self-reported adherence; asthma control; asthma-related quality of life; asthma-related self-efficacy **Adherence calculation:** number of treatment days/total number of days (6 months and 12 months)
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** unrestricted investigator-initiated grant from GSK, salary awards from Fonds del la Recherche Quebec (FRQS) and Canadian Institute of Health Research. Scholarship support from FRQS

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Following the completion of all baseline assessments, patients were randomized to MI or UC using a computer algorithm that generated a random code"
Allocation concealment (selection bias)	Low risk	"Patients were randomized to MI or UC using a computer algorithm that generated a random code that was kept in a concealed envelope until opened by the study coordinator at the time of randomization as per the CONSORT guidelines"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of procedures to blind participants or personnel. Subjective nature of many secondary outcomes results in high risk of bias

NCT01132430 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"With the exception of the visual analog scales assessing patients' impressions on the MI intervention (which were completed at baseline and immediately postintervention only), all postintervention assessments were completed in-hospital at 6 and 12 months postintervention by a research assistant who was blinded to patient group. To increase the success of blinding, patients were instructed not to disclose their group assignment to the research assistant" However, for some outcomes (such as AQLQ and ACT), participants the outcome assessor were unblinded; therefore, these outcomes are at risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 20% drop-out in both arms; however, ITT and per-protocol analyses were performed, and results were very similar overall
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods clearly reported
Other bias	Low risk	None noted

NCT01169883

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 10 weeks **Setting:** 3 primary care practices at Rush University Medical Center in Chicago, Illinois. USA **Trial registration:** not reported
Participants	**Population:** 68 adolescents with asthma randomised to adherence messaging and group sessions (n = 34) or an "attention control" (n = 34) **Age:** 11 to 16 years of age; mean age (range) in the intervention group was 13.3 (11 to 16) years and in the control group 13.6 (11 to 16) years **Baseline asthma severity:** intervention group: 85.3% of participants had uncontrolled asthma at baseline; control group: 76.5% had uncontrolled asthma at baseline **Inclusion criteria:** self-identified as African American or Hispanic, given diagnosis of persistent asthma, possessing an active prescription for a daily ICS for asthma. Persistent asthma was defined as asthma symptoms (e.g. cough, wheeze, shortness of breath, chest tightness) more than 2 days per week or night-time awakenings more often than twice a month; or taking a prescribed daily ICS for asthma **Exclusion criteria:** career or child unable to speak English, comorbidities that could interfere with study participation, ≥ 48% adherence over 2 weeks during the run-in

NCT01169883 (*Continued*)

	period. Participants with ≥ 48% adherence were excluded, as the aim of the study was to target children with poor adherence **Percentage withdrawn:** 15% from both intervention and control groups **Other allowed medication:** not reported
Interventions	**Intervention summary:** All participants received medical supervision, peak flow meters and an iPod during the run-in. Those in the intervention group received music tracks and attended coping peer group sessions led by social workers during weeks 1 to 4 and 6 to 9. Session leaders were trained to use a motivational interviewing approach and to follow the study guide. During the session, participants developed and recorded 2 to 4 messages from the discussion to encourage daily use of ICS, to be played at random between music tracks **Control summary:** All participants received medical supervision, peak flow meters and an iPod during the run-in. Those in the attention control group attended weekly individual sessions with a research assistant who did not promote adherence. They received the same number of iPod messages as those in the active intervention group, with content promoting adherence to ICS; also played at random between music tracks but recorded by an asthma doctor rather than by peers **Complex intervention:** yes
Outcomes	**Outcomes measured:** ICS adherence (measured at baseline and at 5 and 10 weeks), asthma knowledge (ZAP Caregiver Asthma Knowledge Instrument), ICS knowledge, ICS self-efficacy, social support, asthma exacerbations **Adherence calculation:** average daily adherence over previous 14 days, measured with the electronic medication monitor for ICS
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** National Heart, Lung, and Blood Institute grants K23 HL092292 and R21 HL098812. Support in the form of study drug was provided by a grant from GlaxoSmithKline (FLV114794)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Blocked group randomization, using a computer-generated allocation schedule"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants, although adherence, the only reported outcome of interest for this review, was measured objectively. However, awareness of intervention group and monitoring may have affected adherence behaviour beyond the effect intended by the intervention

NCT01169883 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcomes data were collected at baseline and at 5 and 10 weeks post-randomization (during the active treatment phase) by research assistants blinded to the participants' group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 80% in both arms attended at least 1 follow-up visit (at 5 or 10 weeks) and were included in the analysis; reasons for dropping out were similar between the 2 groups
Selective reporting (reporting bias)	Unclear risk	Prospectively registered trial (NCT01169883); outcomes listed on trial register clearly reported (although medians and IQR used, so unable to include it in the meta-analysis). Several outcomes of interest in this review were listed as measured in the methods section of the published report but were not reported in the results (e.g. unscheduled visits, exacerbations)
Other bias	Low risk	None noted

NCT01175434

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 6 to 8 months **Setting:** schools in the Rochester City School District. USA **Trial registration:** NCT01175434
Participants	**Population:** 100 children with asthma randomised to school-based care (n = 49) or usual care (n = 51) **Age:** 3 to 10 years of age; mean age (SD) in each intervention group 7.5 (1.7) years and in usual care group 7.0 (1.8) years **Baseline asthma severity:** baseline PAQLQ in the intervention group 6.25 (0.8) and baseline QOL 5.82 (1.2) **Inclusion criteria:** children with physician-diagnosed asthma with persistent symptoms based on NHLBI guidelines **Exclusion criteria:** career unable to speak and understand English, no access to a working phone for follow-up surveys, plan to leave the school district within 6 months;any other significant medical conditions, including congenital heart disease, cystic fibrosis or other chronic lung disease, that could interfere with assessment of asthma-related measures **Percentage withdrawn:** 2% from the intervention group and 0% from the usual care group **Other allowed medication:** not specifically reported; assumed children continued with usual medication

NCT01175434 (*Continued*)

Interventions	**Intervention summary:** systematic Web-based screening to assess children's asthma using guideline-based symptom questions along with an algorithm to compute NHLBI severity or control classification; report of generation and electronic communication with primary care provider for authorisation of directly observed therapy with preventive asthma medications through school; prescription of guideline-based preventive medications purchased through the child's health insurance and delivered to schools and children's homes by a local pharmacy; directly observed administration of medications at school by a school nurse or health aide; and systematic reassessment of symptoms using the same system, with guideline-based adjustments to therapy as needed **Control summary:** Similar to children receiving the intervention, children in the usual care group were screened for eligibility with the online screening tool at the beginning of the school year, but reports were not sent to their primary care provider and directly observed therapy was not implemented at school **Complex intervention:** yes
Outcomes	**Outcomes measured:** feasibility; mean symptom-free days over 2 weeks, averaged over the study period; numbers of days and nights with symptoms; activity limitations; rescue medication use; school absenteeism; parent sleep interruption; change in family plans due to the child's asthma over the prior 2 weeks; Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ); utilisation of healthcare services (office, ED visits, hospitalisations and non-urgent visits for asthma care); fractional exhaled nitric oxide **Adherence calculation:** recorded as part of feasibility assessment only in children randomised to the intervention arm
Notes	**Type of publication:** peer-reviewed journal article **Funding:** funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health (RC1HL099432)

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by use of a preventive asthma medication at baseline. A permutated block design was used to ensure an equal balance of children in each group over time. The randomisation scheme was independently developed by the Biostatistics Center
Allocation concealment (selection bias)	Low risk	The randomisation scheme was independently developed by the Biostatistics Center; the interviewer called the Study Co-ordinator, who provided the participant's ID number and treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants and personnel to group allocation. Although some outcomes may be more objective

NCT01175434 (*Continued*)

		(such as hospitalisations), other outcomes such as unscheduled visits and patient-reported outcomes (e.g. quality of life) may have been affected by participant (or career) knowledge of group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although the trial reports that "all follow up data were collected by a research group blinded to the child's group allocation" for outcomes such as quality of life, the unblinded participant or career is the outcome assessor; therefore, these outcomes are still at risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant from the intervention group was lost to follow-up before starting the intervention. The remainder were analysed in the groups to which they were randomised
Selective reporting (reporting bias)	High risk	Prospectively registered trial (NCT01175434); however, peer-reviewed publication reports outcomes not prespecified (e.g. quality of life). Unclear if other outcomes of interest (such as asthma control) may have been measured but not reported
Other bias	Low risk	None noted

NCT01714141

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 13 weeks **Setting:** an urban university and an affiliated medical centre, Detroit. USA **Trial registration:** not reported
Participants	**Population:** 49 young adults with asthma randomised to multi-component, technology-based intervention (n = 25) or asthma education (n = 24) **Age:** 18 to 29 years; mean age (SD) in the intervention group 21.8 (4) years and in the control group 23.1 (3.4) years **Baseline asthma severity:** intervention group: asthma exacerbations in last month mean (SD) 1.8 (2.0), ACT mean (SD) 14.0 (3.1), FEV_1 mean (SD) 80.0% (21.6). Control group: asthma exacerbations in last month mean (SD) 2.4 (4.6), ACT mean (SD) 14.4 (3.1), FEV_1 mean (SD) 80.4% (15.7) **Inclusion criteria:** 18 to 29 years old, African American with diagnosis of persistent asthma, prescribed a controller medication. Individuals also had to have access to a cell phone with texting capability and to report < 80% adherence in the past 30 days and score ≤ 19 on the ACT

	Exclusion criteria: pregnancy, inability to understand written or spoken English, another serious medical condition requiring regular medication, active psychiatric disorder that would interfere with study participation **Percentage withdrawn:** 8% from the intervention group and 4% from the usual care group **Other allowed medication:** not reported
Interventions	**Intervention summary:** Intervention consisted of 2 "Computerized Intervention Authoring Software" (CIAS)-delivered sessions with personalised, daily text messaged reminders to take medication delivered between these sessions. "Ecological Momentary Assessment" (EMA) via text messaging was conducted before the first intervention session to gather real-time data on participants' medication adherence and asthma symptoms. These data were used to tailor the intervention session for each participant **Control summary:** Control participants completed CIAS-delivered asthma education matched for length, location and method of delivery of the intervention session. Control session was delivered by the avatar "Peedy the parrot" and included interactive features such as quizzes and responses to poll questions. Content focused on facts and myths about asthma, control of environmental factors and pharmacological management. Control participants received text messages between sessions via CareSpeak, but message content was the same for all participants and contained general facts about asthma. Control participants also received 7 days of EMA before the first session, but data were not used to tailor the session **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence, asthma control (ACT), lung function (FEV_1), participant satisfaction **Adherence calculation:** calculated from self-reported number of doses missed compared with prescribed doses
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** supported by a grant from the National Institutes of Health (NHLBI, 1R34HL107664-01A1 (K.K.M.))

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After completing the questionnaires, the computer automatically randomized them to receive either the intervention (n =25) or control (n =24)" Of note is a baseline imbalance in males and females with fewer males in the control arm, but this is more likely to be the result of small numbers in the trial than failure of randomisation

NCT01714141 (*Continued*)

Allocation concealment (selection bias)	Low risk	"After completing the questionnaires, the computer automatically randomized them to receive either the intervention (n = 25) or control (n = 24)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors is not described. In addition, for many outcomes in this trial (self-reported adherence, ACT, etc.), the participant is the outcome assessor; therefore, we judge this study to be at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced drop-out (< 10%) in both arms
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, but all planned outcomes clearly reported
Other bias	Low risk	None noted

NCT02413528

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 12 weeks **Setting:** 1 university centre in New York. USA **Trial registration:** NCT02413528
Participants	**Population:** 12 adolescents with asthma planned to be randomised to adherence monitoring app and sensor or standard care with monitoring via sensor **Age:** 11 to 19 years **Baseline asthma severity:** not reported **Inclusion criteria:** asthma diagnosis, currently on a daily controller HFA medication for asthma, English-speaking, access to a smartphone or tablet **Exclusion criteria:** pregnancy, foster care, emancipated minor **Percentage withdrawn:** not applicable **Other allowed medication:** not reported
Interventions	**Intervention summary:** Participants would have been given an inhaler sensor to monitor medication use and a mobile phone application that would send them reminders and provide an opportunity to see their own medication use and win incentives for adherence **Control summary:** Participants would have been given an inhaler sensor to monitor medication use and a sham version of the mobile app that would not include reminders or incentives **Complex intervention:** no

NCT02413528 (*Continued*)

Outcomes	**Outcomes measured:** real-time medication adherence; asthma control (ACT) **Adherence calculation:** not reported
Notes	**Type of publication:** trial registration only **Funding:** CoheroHealth **NB:** Study terminated owing to "wireless connectivity challenges with device and mobile app"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomised" on NCT record - but no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label but minimal details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as open-label but minimal details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess as no study results posted; terminated owing to "wireless connectivity challenges with device and mobile app"
Selective reporting (reporting bias)	Unclear risk	Unable to assess as no study results posted
Other bias	Low risk	None noted

NCT02451709

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 1 year **Setting:** hospital clinics in Sheffield or Rotherham **Trial registration:** NCT02451709
Participants	**Population:** 90 children with asthma randomised to electronic adherence monitoring with reminders and feedback (n = 47) or monitoring with no reminders or feedback (n = 43) **Age:** 6 to16 years of age; mean age (SD) in the intervention group 10.4 (2.9) years and in the control group 10.2 (2.9) years **Baseline asthma severity:** poorly controlled asthma; BTS level 3 or above **Inclusion criteria:** Participants had to be taking regular inhaled steroids, with no change in their medication in the last month and an ACQ score $\geq$ 1.5, indicating poorly

	controlled asthma. Electronic monitoring devices available for this trial were compatible only with Seretide or Symbicort inhalers. Therefore, all participants were at BTS level 3 at the start of the trial **Exclusion criteria:** could not speak English, had another significant chronic condition **Percentage withdrawn:** 15% from the intervention group and 9% from the control group, but all randomised participants were included in the primary ITT analysis, with the exception of 1 control group participant who was withdrawn after randomisation for not meeting eligibility criteria **Other allowed medication:** not reported
Interventions	**Intervention summary:** Adherence was electronically monitored with regular feedback provided at clinic visits, during which the importance of adherence was emphasised and personalised strategies for improvement were devised. Devices also played medication reminder alarms. Alarms sounded for 5 seconds, every minute for 15 minutes (or until actuation), if the inhaler had not been actuated within the previous 6 hours of the specified time. Devices were locked to prevent tampering **Control summary:** Control participants had the same EMDs attached to their regular inhaler and were told that the devices monitored how often inhalers were taken, but that these data would not be reviewed. Participants were seen in their standard asthma clinic, and data were downloaded but were not reviewed. Alarms were disabled, and the devices locked **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence, change in ACQ, FEV_1%, number of unplanned attendances at general practitioner (GP)/emergency department (ED) for asthma since last visit (as reported by parents), number of courses of oral steroids required, number of days off school due to asthma, use of beta-agonists in the past week, BTS level of asthma therapy, mini PAQLQ **Adherence calculation:** calculated for each 3-month period, both morning and afternoon doses, and recorded as a percentage. This was calculated as number of doses actually taken/number of doses prescribed × 100
Notes	**Type of publication:** peer-reviewed journal article **Funding:** Sheffield Children's Hospital Charity

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised via permuted block randomisation, with allocation of 1:1 created from a computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Allocation of participants involved phoning the independent holder of the randomisation code

NCT02451709 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Owing to the nature of the intervention, neither participants nor study team members were blinded. Although adherence, lung function and oral steroid use might be considered objective outcomes, potential for performance bias remains for outcomes such as AQLQ and ACQ
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors is not described; although some outcomes are relatively objective and are not prone to detection bias (adherence, lung function and oral corticosteroid use), others such as ACQ and AQLQ involve the unblinded participant as the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 15% drop-out in both arms; all but 1 participant included in the intention-to-treat primary analysis
Selective reporting (reporting bias)	High risk	Prospectively registered trial (NCT02451709); all outcomes specified in the methods are mentioned in the paper, although some non-numerically (e.g. mini-PAQLQ, BMQ, SABA use, IPQ), so could not be included in the meta-analysis
Other bias	Low risk	None noted

Onyirimba 2003

Methods	**Design:** single-blind, parallel-group randomised controlled trial **Duration:** 10 weeks **Setting:** 1 asthma centre at Saint Francis Hospital, Connecticut. USA **Trial registration:** not reported
Participants	**Population:** 30 adults with asthma randomised to adherence monitoring and education or monitoring without feedback (n randomised to each arm not reported) **Age:** over 18 years of age; mean (SD) age in the intervention group 45 (11) years and in the control group 53 (14) years **Baseline asthma severity:** intervention group: mean FEV_1 78% predicted; mean (SD) ED visits in the past year 2.3 (2.4); 80% on LABA; mean (SD) AQLQ score 4.34 (1.62). Control group: mean FEV_1 63% predicted; mean (SD) ED visits in the past year 1.0 (0.8); 100% on LABA; mean (SD) AQLQ score 3.75 (1.39) **Inclusion criteria:** Adults with moderate to severe asthma were considered for the study if they met all of the following inclusion criteria: referral to the Asthma Center at Saint Francis Hospital and Medical Center; 1 or more markers of low socioeconomic status

	(Medicaid or no insurance, family income < $20,000, less than a high school education) ; prebronchodilator FEV_1 < 80% of predicted and 15% predicted greater reversibility after bronchodilator administration; and regular use of inhaled steroids and willingness to change the schedule, if necessary, to twice-daily dosing **Exclusion criteria:** not reported **Percentage withdrawn:** 10 participants in the intervention group and 9 in the control groups completed the trial. Numbers randomised to each arm not reported **Other allowed medication:** Use of long-acting oral or inhaled bronchodilators, theophylline and oral corticosteroid was permissible
Interventions	**Intervention summary:** Intensive asthma education and management was provided by a nurse and/or respiratory therapist over approximately a 3-week period, with follow-up for 7 additional weeks. Content was based on NAEPP guidelines covering goals of therapy, signs of worsening asthma, types of medications, importance of prophylactic medication, proper MDI technique, use of PEF meter, patient satisfaction and QOL and environmental evaluation and education. Data from MDI Chronologs were downloaded at each visit and were reviewed with the clinician, who emphasised techniques or strategies to improve adherence when necessary, according to type and timing of non-adherence **Control summary:** Control group visited to complete outcome measures, and data were downloaded from Chronologs, but no education or adherence advice was given **Complex intervention:** yes
Outcomes	**Outcomes measured:** adherence to ICS, albuterol use (mean actuations per 24 hours for each week), AQLQ, FEV_1 **Adherence calculation:** overall mean weekly adherence and percentage of days with overuse
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** in part by an award from the University of Connecticut Health Center Research Advisory Committee

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients were randomized into 1 of 2 groups" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Patients were told that these instruments recorded the time and date of each MDI actuation but were blinded to the study hypothesis" Although participants were blinded to the study hypothesis, knowledge of group allocation and the fact that adherence was being monitored may have altered adherence behaviour beyond the effect intended by

Onyirimba 2003 (*Continued*)

		trialists
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although trialists went to some lengths to blind outcome assessors ("For the initial period, patients met at the first visit and three subsequent visits with a nurse and/or respiratory therapist blinded to the patients' group"), for AQLQ the participant is the outcome assessor; therefore, such outcomes are presented at risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	10/30 participants did not complete the study; it is not clear how many were randomised to each group or whether reasons for dropping out were similar between groups
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods were reported in text/tables
Other bias	Low risk	None noted

Price 2010

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 12 weeks **Setting:** 143 sites in the UK **Trial registration:** not reported
Participants	**Population:** 1233 participants with asthma randomised to intervention (once-daily ICS) (n = 611) or control (twice-daily ICS) (n = 622) **Age:** 12 years of age and older; mean (SD not reported) age in the adherence group 50.9 years and in the control group 50.9 years **Baseline asthma severity:** intervention group: mean duration of asthma 16.4 years; control group: mean duration of asthma 16.2 years **Inclusion criteria:** treated with beclomethasone dipropionate (BDP) hydrofluoroalkane ($\leq$ 500 μg/d) or BDP chlorofluorocarbon ($\leq$ 1000 μg/d) for $\geq$ 12 weeks, with stable BDP dosing regimen for $\geq$ 4 weeks immediately before study entry. Inclusion of patients who used BDP as their prior ICS therapy was justified because BDP was the ICS prescribed most commonly in the UK at the time the study was conducted, thereby providing a patient population as large and as homogeneously treated as possible. Eligible patients had no clinically significant disease that would interfere with study evaluation, and female patients of childbearing potential were required to use medically accepted birth control **Exclusion criteria:** ventilator support required for respiratory failure due to asthma within the previous 5 years, hospitalisation within the previous 3 months due to asthma **Percentage withdrawn:** 16.5% from the adherence group and 15.3% from the control

Price 2010 (*Continued*)

	group **Other allowed medication:** not reported
Interventions	**Intervention summary:** mometasone furoate (MF) DPI 400 μg once daily in the evening. Participants were instructed in inhaler use and peak flow measurement to demonstrate proficiency and received salbutamol for rescue medication. They were also given diary cards and were instructed to follow an asthma action plan formulated at their first visit **Control summary:** mometasone furoate DPI 200 μg twice daily. Participants were instructed in inhaler use and peak flow measurement to demonstrate proficiency and received salbutamol for rescue medication. They were given diary cards and were instructed to follow an asthma action plan formulated at their first visit **Complex intervention:** no
Outcomes	**Outcomes measured:** Primary outcome was adherence measured by the counter. Secondary outcomes included self-report adherence, physician's assessment of response, quality of life on the Integrated Therapeutics Group Asthma Short Form (ITG-ASF) (week 12), utilisation of healthcare resources and number of days missed from work or school. Adverse events were recorded at all visits, and an abbreviated physical exam was performed at visits 1 and 4. Evaluation of asthma worsening was performed at all visits, defined as increased use of rescue medication (> 12 inhalations on 2 consecutive days) , a decrease in peak flow > 25% on 2 consecutive days or clinical asthma exacerbations (unscheduled doctor's visit, hospitalisation, ER visit and/or use of additional asthma medications other than short-acting beta-agonists) **Adherence calculation:** Adherence was calculated as the number of administered doses (as determined by device counter number) times 100 divided by the number of scheduled doses. Data were not included for analysis if invalid (e.g. gross misuse of device, missing treatment end dates, device malfunction)
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** Schering Corp., a division of Merck & Co.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized to receive either MF-DPI 400 μg once-daily in the evening or MF DPI 200 μg twice-daily from inhalers measuring 220 μg/actuation and delivering 200 μg/inhalation"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial is described as open-label; although adherence was measured objectively with a device counter, knowledge of group allocation and monitoring may have affected adherence behaviour. In addition, patient-

Price 2010 (*Continued*)

		reported outcomes, such as HRQOL, are susceptible to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial is described as open-label; although adherence was measured objectively with a device counter, knowledge of group allocation may have affected patient-reported outcomes, such as HRQOL, for which the participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out < 20% in both groups, and reasons for discontinuation appear similar between groups. All participants included in the safety analysis
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods were reported in text/tables. Asthma worsening was not reported as planned
Other bias	Low risk	None noted

Strandbygaard 2010

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 12 weeks **Setting:** 1 university hospital. Denmark **Trial registration:** not reported
Participants	**Population:** 26 adults with asthma randomised to SMS adherence reminders (n = 12) or usual care (no reminders) (n = 14) **Age:** 18 to 45 years of age; mean (SD not reported) age in the intervention group 34.4 years and in the control group 30.7 years **Baseline asthma severity:** among the randomised participants: 8 (30.8%) were categorised as mild persistent (GINA 2), 16 (61.5%) as moderate persistent (GINA 3) and 2 (7.7%) as severe persistent (GINA 4). Before enrolment into the study, 9 participants (34.6%) had used SABA as monotherapy, 9 (34.6%) had used ICS (alone or in combination with LABA and/or SABA) and the remaining 8 (30.8%) had not used any treatment at all over the last 3 months **Inclusion criteria:** diagnosis of asthma based on clinical history and daily symptoms, age between 18 and 45 years, positive methacholine challenge test with PD20 $\leq$ 4 mmol **Exclusion criteria:** other medical comorbidities, smoking history of more than 10 pack-years **Percentage withdrawn:** 17% from the intervention group and 14% from the control group **Other allowed medication:** not reported

Interventions	**Intervention summary:** 4-week run-in on LABA/ICS, then 12 weeks of daily SMS reminders. SMS reminder was sent daily at 10 AM on cell phone over the following 8 weeks. All enrolled participants received a thorough education concerning the necessity of ICS treatment in asthma, and all were provided with knowledge of disease mechanisms and correct inhaler technique **Control summary:** 4-week run-in on LABA/ICS and no reminders. All enrolled participants received a thorough education concerning the necessity of ICS treatment in asthma, and all were provided with knowledge of disease mechanisms and correct inhaler technique **Complex intervention:** no
Outcomes	**Outcomes measured:** mean rate of adherence to asthma treatment, reimbursement for asthma medication, change in exhaled nitric oxide levels, lung function, airway responsiveness **Adherence calculation:** Adherence rate was registered as the percentage of medicine actually taken by participants, calculated from medicine dose count on the Discos Seretide and number of days between clinical examinations: (60 dose-count)/2 × days × 100%
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** GlaxoSmithKline provided a financial contribution to the service on the Internet including the short message service provided by CIM mobility **NB:** Only 34.6% of people had taken ICS in the last 3 months, and 30.8% no treatment at all, but everyone was put on Seretide at the start of the study

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done by means of automatic computer generation of randomisation numbers in blocks of six"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial is not described as blinded; although adherence was measured objectively with a device counter, knowledge of group allocation and monitoring may have affected adherence behaviour. In addition, patient-reported outcomes, such as ACQ and AQLQ, are susceptible to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial is not described as blinded; although adherence was measured objectively with a device counter, knowledge of group allocation affected patient-reported outcomes, such as ACQ and AQLQ, for which the

Strandbygaard 2010 (*Continued*)

		participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out < 20% in both groups, but reasons for discontinuation not given and no participant flow diagram presented. Also unclear how many participants are included in the primary analysis, as this is presented in the text and not in a table
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified, although all outcomes listed in methods reported in text/tables
Other bias	Low risk	None noted

Ulrik 2009

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 12 weeks **Setting:** 29 GSK investigational sites in Denmark and Switzerland **Trial registration:** NCT00351143; EudraCT no. 2005-0003374-48; ACE104325
Participants	**Population:** 274 adults with asthma randomised to adherence education and study medication (n = 140) or study medication only (n = 134) **Age:** over 18 years of age; mean (SD) age in the intervention group 40.5 (13.9) years and in the control group 38.7 (14.6) years **Baseline asthma severity:** Across the 2 groups, most randomised participants had mild persistent (51%) or moderate persistent (34%) asthma **Inclusion criteria:** ≥ 18 years of age; diagnosis of persistent asthma; treatment with at least 250 mg fluticasone propionate bid (or equivalent for other ICS) 4 weeks before the study and/or LABA bid or monotherapy with a short-acting beta$_2$-agonist; ability to comply with use of the Asthma Monitor 2 (AM2) and the Asthma Quality of Life Questionnaire (AQLQ). Participants who had an exacerbation during the study period were allowed to remain in the study **Exclusion criteria:** known or suspected chronic obstructive pulmonary disease (COPD) ; pregnancy or lactation; smoking history > 10 pack-years; clinical or laboratory evidence of serious uncontrolled systemic disease; microbiologically verified upper or lower respiratory tract infection within 1 month before screening visit; acute asthma exacerbation requiring hospitalisation/emergency department treatment/treatment with systemic corticosteroids within 3 months before screening visit; furthermore, for entry into treatment period 1 and treatment period 2: changes in asthma medication, including treatment with systemic corticosteroid, during the preceding period; more than 1 week of guideline-defined asthma control before baseline visit/during treatment period 1; achieving total control in treatment period 1 (participants randomised at end of treatment period 1 and before entry into treatment period 2) **Percentage withdrawn:** not reported **Other allowed medication:** Those who had been treated with oral corticosteroids in the preceding 3 months were excluded from enrolling, and those who needed a change

	in asthma medication during period 1 were excluded from period 2
Interventions	**Intervention summary:** given salmeterol/fluticasone propionate 50/250 mg (Diskus®) bid and salbutamol prn for 12 weeks before randomisation (period 1). Then for 12 weeks (period 2), those who did not achieve total control were randomised and were given 5 patient-centred teaching modules that included education about asthma, risk factors, prognosis, expectations of treatment, correct ways of taking controller and rescue medication and mnemonics as an aid for optimal dosing/timing of medication. Based on both written and oral information. Coaches were trained to use the standardised material at all centres **Control summary:** given salmeterol/fluticasone propionate 50/250 mg (Diskus®) bid and salbutamol prn for 12 weeks before randomisation (period 1). Then for 12 weeks (period 2), those who did not achieve total control were randomised and continued with the same study medication **Complex intervention:** yes
Outcomes	**Outcomes measured:** total asthma control; PEF; symptom scores; rescue medication use; number of nights awakenings due to asthma; adverse events; quality of life (AQLQ); medication compliance; asthma severity; adverse events (including exacerbations, emergency visits and hospitalisations); vital signs. The asthma monitor AM2 medical device was used to collect the following data on a daily basis: FEV_1; pre-dose morning PEF; symptoms; use of rescue medication; night-time awakenings; exacerbations; change of medication due to side effects and emergency doctor visits **Adherence calculation:** Treatment compliance was assessed by counting the number of doses in the returned investigational product
Notes	**Type of publication:** single peer-reviewed journal article **Funding:** GlaxoSmithKline **NB:** Period 2 of interest. During study period 1, all participants were treated with salmeterol/fluticasone 50/250. Those who did not achieve total asthma control in treatment period 1 were randomised to continued treatment with or without adherence education concomitantly for a further 12 weeks (period 2)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"subjects who did not achieve total asthma control in treatment period 1 were randomised to continued treatment with or without compliance enhancement training concomitantly for a further 12 weeks" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial is described as open-label; although adherence was measured objectively with a device counter, knowledge of group allo-

Ulrik 2009 (*Continued*)

		cation and monitoring may have affected adherence behaviour. In addition, patient-reported outcomes, such as quality of life, are susceptible to risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial is described as open-label; although adherence was measured objectively with a device counter, knowledge of group allocation and monitoring may have affected patient-reported outcomes, such as quality of life, for which the participant is the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All efficacy analyses were performed by intent-to-treat (ITT) analysis on all participants with data entered into the database, who had received at least 1 single dose of trial medication in treatment period 2 (randomised portion of the trial); therefore, this was the population for analysis of the primary endpoint. Sensitivity analyses were performed for the per-protocol population for treatment period 2, which comprised all participants in the ITT-2 population who did not have major protocol violations. The safety population comprised all participants who had received at least 1 single dose of study medication. However, no flow diagram was presented and drop-out was not clearly reported
Selective reporting (reporting bias)	High risk	Prospectively registered trial (NCT00351143; EudraCT no. 2005-0003374-48). However, many outcomes of interest were not reported numerically, so could not used in the meta-analysis
Other bias	Low risk	None noted

Vasbinder 2015 E-MATIC

Methods	**Design:** open-label, parallel-group randomised controlled trial **Duration:** 52 weeks **Setting:** 5 outpatient clinics. The Netherlands **Trial registration:** Netherlands Trial Register NTR2583

Participants	**Population:** 219 children with asthma randomised to receive SMS adherence reminders (n = 108) or no reminders (n = 111) **Age:** 4 to 11 years of age; mean (SD) age in the intervention group 7.8 (2.2) years and in the control group 7.7 (2.1) years **Baseline asthma severity:** intervention group: 39.8% had poorly controlled asthma (ACT); control group: 36.5% **Inclusion criteria:** 4 to 11 years of age at the start of the study; doctor-diagnosed asthma for at least 6 months; ICS use for at least 3 months; use of a pMDI; use of fluticasone, fluticasone/salmeterol or beclomethasone; at least 1 parent/career with a mobile phone **Exclusion criteria:** refusal to participate in the study **Percentage withdrawn:** not reported **Other allowed medication:** not reported
Interventions	**Intervention summary:** All children received an RTMM-device that registers time and date of administered ICS doses. Children in the intervention group received "time-tailored" text messages that were sent only when a dose was at risk of omission **Control summary:** All children received an RTMM-device that registers time and date of administered ICS doses. Those in the control group do not receive such text messages **Complex intervention:** no
Outcomes	**Outcomes measured:** adherence to ICS; asthma control (ACT); frequency of asthma exacerbations and use of healthcare services (pharmacy data checked for OCS use and health records); disease-specific quality of life; school/work absence; paediatric AQLQ; acceptance of e-monitoring; economic evaluation **Adherence calculation:** proportion of all prescribed dosages taken by the child within a 6-hour time frame around planned time of inhalation (i.e. from 3 hours before until 3 hours after) calculated from RTMM data on ICS use, attached to the inhaler
Notes	**Type of publication:** multiple peer-reviewed journal articles **Funding:** supported by a non-conditional grant from The Netherlands Organisation for Health Research and Development (ZonMw, grand registration number 171101005). The study is also partially sponsored by the pharmaceutical company GlaxoSmithKline. The manufacturer of the RTMM devices, Evalan BV, partially sponsors the study by providing devices at cost price

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated block randomisation was used per hospital with block size of 16 patients"
Allocation concealment (selection bias)	Low risk	"At registration at the RTMM software interface, children were automatically assigned to the intervention or control group" - suggests that allocation was concealed, as this was performed at an IT in-

		terface
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Although physicians, researchers and patients were initially blinded for randomisation, patients were generally unblinded shortly after the start of the study period, when they found out whether they received SMS reminders or not" Knowledge about group allocation may have affected performance, especially in subjective measures such as PAQLQ and cACT
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors described. Primary outcome - adherence - measured objectively and not likely to be at risk of detection bias, but for other outcomes (such as PAQLQ and cACT), the unblinded participant/career is the outcome assessor; therefore, these outcomes are at risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	"Reasons why patients left the study prematurely were not systematically registered", and the total number of people who did not complete the study and hence had to have their data imputed is not reported. The numbers in Figure 2 suggest very low retention of around 50% in each arm
Selective reporting (reporting bias)	Low risk	Prospectively published protocol and all outcomes clearly reported in main publication
Other bias	Low risk	None noted

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AE: asthma education; AQLQ: Asthma Quality of Life Questionnaire; BDP: beclomethasone dipropionate; BMQ: Beliefs about Medication Questionnaire; BTS/SIGN: British Thoracic Society/ Scottish Intercollegiate Guidelines Network; cACT: Childhood Asthma Control Test; CBQ-20: Conflict Behaviour Questionnaire-20; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSQ: Consumer Satisfaction Questionnaire; CVD: cardiovascular disease; DDD: Daily Defined Doses; DPI: dry powder inhaler; ED: emergency department; EMA: Ecological Momentary Assessment; EMD: electronic monitoring device; EPAC: episode of poor asthma control; FEV_1: forced expiratory volume in one second; FP: fluticasone propionate; FSI: Functional Severity Index; FVC: forced vital capacity; GINA: Global Initiative for Asthma; GP: general practitioner; GSK: GlaxoSmithKline; HADS: Hospital Anxiety and Depression Scale; HFA inhaler: hydrofluoroalkane inhaler; HMO: health maintenance organisation; HRQOL: health-related quality of life; ICS: inhaled corticosteroids; IPQ: Illness Perceptions Questionnaire; IQR: interquartile ratio; IRF: inhaler reminders and feedback; IT: information technology; ITT: intention-to-treat; IVR: interactive voice response; KAAM: Knowledge of Asthma and Asthma Medicine Questionnaire; KP: Kaiser Permanente; KPCO: Kaiser Permanente Colorado; KPH: Kaiser Permanente Hawaii; KPNW: Kaiser Permanente Northwest; LABA: long-acting $beta_2$-agonists; MARS-A: Medication Adherence Report Scale; MD: mean difference; MDI: metered dose in-

haler; MI: motivational interviewing; NAEPP: National Asthma Education and Prevention Program; NHLBI: National Heart, Lung, and Blood Institute; NS: not statistically significant; OCS: oral corticosteroid; PAD: personalised adherence discussion; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; PDC: proportion of days covered; PedsQL: Paediatric Quality of Life Inventory; PEF: peak expiratory flow; pMDI: pressurised metered dose inhaler; PS: problem solving; QOL: quality of life; RTMM: real-time medication monitoring; SABA: short-acting beta$_2$-agonists; SD: standard deviation; SF-36: Short Form-36; SMAQ: Simplified Medication Adherence Questionnaire; SMS: short message service/text message; SR: speech recognition; UC: usual care; URTI: upper respiratory tract infection; VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Armour 2007	Adherence not primary focus
Canino 2016	Adherence not primary focus
Coté 1997	Adherence not primary focus
Dal Negro 2002	Drug trial observing adherence
Delaronde 2005	Adherence not primary focus
Demiralay 2002	Adherence not primary focus
Demiralay 2004	Adherence not primary focus
Fiks 2015	Adherence not primary focus
Fujita 2002	Drug trial observing adherence
Gallefoss 2002	Adherence not primary focus
Garcia-Cardenas 2013	Adherence not primary focus
Gerald 2012	Drug trial observing adherence
Goeman 2013	Trial of tailored asthma education in older adults; adherence not primary focus
Guenette 2015	Wrong study design
Holt 2004	Wrong study design
Iqbal 2004	Wrong study design
Janson 2003	Adherence not primary focus
Janson 2009	Adherence not primary focus

(*Continued*)

Jonasson 1999	Drug trial observing adherence
Jonasson 2000	Drug trial observing adherence
Krishnan 2012	Drug trial observing adherence
Kuna 2006	Trial of once-daily vs twice-daily dosing designed to demonstrate equivalent efficacy. Simplification of treatment regimen postulated to improve adherence in a real-life setting, but this was a double-blind, double-dummy trial, and participants in the trial were not aware of which regimen they had been prescribed. Judged not to be an intervention to improve adherence per se
Martin 2015	< 50% taking ICS at baseline
Mishra 2005	Wrong study design
Munks-Lederer 2001	Adherence not primary focus
NCT00181194	Wrong study design
NCT00201188	Adherence not primary focus
NCT00381355	Written action plan (WAP) vs unformatted prescription post exacerbation. WAP was multi-faceted and was intended to modify physician ICS prescribing behaviour as well as participant adherence, follow-up and asthma management more generally. Adherence to ICS not primary focus of the intervention
NCT01106326	Wrong study design
NCT01128348	Adherence not primary focus
NCT01644357	Adherence not primary focus
NCT02093013	Wrong study design
NCT02363192	Adherence not primary focus
NCT02426801	Wrong study design
Nikander 1998	Drug trial observing adherence
Nikander 2003	Drug trial observing adherence
Patel 2013	Drug trial observing adherence
Petitto 2012	Drug trial observing adherence
Pongchaidecha 2005	Not asthma, or mixed population

(*Continued*)

Sajadi 2016	Intervention to improve adherence to asthma therapy generally. Number using ICS not reported, and ICS not mentioned anywhere in trial report. Therefore assumed not to be an intervention aimed at improving adherence to ICS
Schacher 2006	Adherence not primary focus
Schultz 2012	Drug trial observing adherence
Sovani 2008	SMART therapy (single LABA/ICS inhaler for maintenance and reliever) vs separate inhalers for ICS and SABA, so groups received different medications. This means the effect on measures of asthma control might be a result of LABA therapy, or of improved adherence to ICS, but it is not a clear enough comparison to judge
Wilson 2010	Shared decision making vs clinician decision making and usual care. Interventions led to different medication usage, which meant this is not a clear comparison by which to assess ICS adherence, and that and was not primarily aimed at improving adherence to ICS. Adherence to ICS therefore not a primary focus of intervention
Wolthers 2002	Wrong study design

ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonists; SABA: short-acting beta$_2$-agonists; WAP: written action plan

Characteristics of studies awaiting assessment *[ordered by study ID]*

ISRCTN83334596

Methods	Randomised controlled trial. Title: Is Compliance With Inhaled Therapy in Asthma Increased by the Use of Small-Volume Spacers?
Participants	Asthma. No other details
Interventions	Patients are randomised to use: • Small-volume spacer • Large-volume spacer
Outcomes	Not provided at time of registration
Notes	Trial end date 01/10/2003. Listed as completed and no longer recruiting. No publications identified and no results posted

NCT00269282

Methods	Open-label randomised controlled trial with parallel assignment. Title: Increasing Adherence to Asthma Medication in Urban Teens
Participants	Inclusion criteria: 10 to 15 years of age; resident of Baltimore City; diagnosis of asthma or reactive airway disease; current emergency department visit or hospitalisation for asthma; prescribed a daily asthma controller medication Exclusion criteria: plans to move outside of the Baltimore City area within 1 year from study entry; current participation in another asthma education study; families unwilling or unable to participate; families who were enrolled and participated in the pilot study
Interventions	Self-management (standard care group) vs motivational interviewing plus self-management
Outcomes	Adherence to controller therapy measured by electronic medication monitoring at baseline, 3 months and 6 months. Number of symptom-free days, emergency department utilisation and hospitalisation, career/adolescent quality of life - all measured at the same time points
Notes	Planned enrolment 207. Primary completion date January 2012. Listed as completed, but no publications identified and no results posted

NCT01253330

Methods	Open-label randomised controlled trial with cross-over assignment. Title: Usage, Usability & Effect on Adherence and Clinical Outcomes of Text Message Reminders for Adolescents With Asthma
Participants	Inclusion criteria: between the ages of 12 and 22; diagnosis of persistent asthma; receiving care at Cincinnati Children's Hospital Medical Center or affiliate; prescription of a controller medication; must have a cell phone that receives text messages; asthma not well controlled based on Asthma Control Test (ACT) score; English speaking Exclusion criteria: no diagnosis of persistent asthma; receiving asthma care other than at a Cincinnati Children's Hospital Medical Center or affiliate; asthma well controlled based on ACT score; does not have a cell phone that receives text messages or plans to change phones within the next 6 months; not taking a daily asthma controller medication; currently receiving asthma appointment or medication reminder text messages from another source
Interventions	Text message reminders vs no intervention
Outcomes	Asthma Control Test (ACT), Pediatric Quality of Life Scale (PedsQL), adherence change from baseline
Notes	Planned enrolment 61. Primary completion date December 2012. Listed as completed but no publications identified and no results posted

NCT02045875

Methods	Open-label randomised controlled trial with parallel assignment. Title: Improving Asthma Control in the Real World: A Systematic Approach to Improving Dulera Adherence
Participants	Inclusion criteria: physician diagnosis of asthma of moderate severity; ≥ 18 years of age; currently receiving an inhaled corticosteroid medication and prescribed Dulera 100/5 as part of standard of care based on asthma severity and dosing guidelines; Asthma Control Questionnaire (ACQ) result > 1.0 at entry; demonstration of correct inhalation technique for use of meter dosed inhalers (MDIs); history of reversible airway obstruction documented by treating physician

NCT02045875 (*Continued*)

	Exclusion criteria: Intermittent asthma (asthma exacerbations or symptoms < 3 days/wk); diagnosis of emphysema in prior year; diagnosis at any time of chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, bronchiectasis, Churg Strauss, Wegener's, sarcoidosis, pulmonary hypertension or lung cancer; taking any medication documented to have a drug interaction with Dulera
Interventions	Dulera adherence monitoring with motivational interviewing vs standard asthma care
Outcomes	ACQ, adherence to Dulera, validation of an adult asthma adherence questionnaire (AAAQ)
Notes	Planned enrolment 40. Estimated study completion date December 2015. Note from clinicaltrials.gov: "The recruitment status of this study is unknown because the information has not been verified recently"

NCT02176694

Methods	Open-label randomised controlled trial with parallel assignment. Title: Adolescent Controlled Text Messaging to Improve Asthma Medication Adherence in Primary Care (ACT Me)
Participants	Inclusion criteria: provider-diagnosed persistent asthma; prescription of an inhaled corticosteroid (ICS) in accordance with National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 guidelines for at least 30 days before enrolment; Asthma Control Test (ACT) score < 20 (indicating lack of current control); no provider-diagnosed exacerbation in the 30 days before enrolment; possession of a text-enabled cell phone and plan to keep it throughout the study period; agreement by parents (or participants over 18 years old) to any charges levied by their cell phone carrier for text messages associated with the study if they do not have an unlimited texting plan; ability to speak and read English Exclusion criteria: another chronic lung disease (which would complicate measurement of asthma control); cognitive or psychiatric disorder that the treating clinician judges would impair study participation; use of Advair Diskus for ICS (for which no reliable electronic monitor exists); current enrolment in another asthma intervention study
Interventions	Technology-based system that allows adolescents to compose, schedule and send 1-time or recurring text messages to their own cell phones. Control group receives usual care
Outcomes	Adherence each month, feasibility, acceptability and useability of the website, asthma control (ACT), quality of life (Pediatric Quality of Life Scale (PedsQL))
Notes	Planned enrolment 29. Primary completion date December 2015. Listed as completed, but no publications identified and no results posted

Characteristics of ongoing studies *[ordered by study ID]*

NCT01381159

Trial name or title	Motivational Intervention for Asthma (MI-ACT)
Methods	Double-blind, parallel-group randomised controlled trial

NCT01381159 (*Continued*)

Participants	• Patients 18 years of age and older • Primary diagnosis of moderate to severe persistent asthma (as per GINA) • Prescribed inhaled corticosteroid medication (minimum dose of 250 µg fluticasone equivalent per day) for at least 12 consecutive months • Uncontrolled asthma (≥ 1.25 on the Asthma Control Questionnaire) • Coverage by a drug insurance plan • Non-adherence to ICS medication (based on having filled < 50% of their prescriptions over the past year) • Ability to speak English or French
Interventions	Motivational communication or control
Outcomes	Primary outcome measure: inhaled corticosteroid adherence
Starting date	January 2011
Contact information	
Notes	Link to study registration: https://clinicaltrials.gov/ct2/show/NCT01381159

NCT02170883

Trial name or title	EmPhAsIS: Empowering Pharmacists in Asthma Management Through Interactive SMS
Methods	Open-label, parallel-group randomised controlled trial
Participants	• Filling a (incident or prevalent) prescription for inhaled corticosteroids (monotherapy or in combination inhaler with long-acting beta-agonists) who have received a diagnosis of asthma from a doctor • Possessing a cell phone with ability to send/receive text messages • Residing in British Columbia (BC), Canada, and planning to reside in BC for the next 12 months • Registered with the medical services plan (MSP, the provincial insure of medically required services) in the past 12 months, and planning to remain registered for the next 12 months • Designated pharmacy being main drugstore for patient • Not participating in another interventional study • Providing consent to participate in the study
Interventions	Interactive SMS or usual care
Outcomes	Adherence to inhaled corticosteroid medication
Starting date	May 2015
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02170883

NCT02203266

Trial name or title	Teaching Inhaler Use With the INCA Device in a Community Pharmacy Setting
Methods	Open-label, parallel-group randomised controlled trial
Participants	• 18 years old or above • Capable of understanding and willing to provide voluntary informed consent before any protocol-specific procedures are performed • Capable of understanding and complying with requirements of the protocol, and demonstrating willingness to attend for all required visits • Capable of taking and willing to take inhaled medication • Valid prescription for use of a Seretide Diskus inhaler or already using a Seretide Diskus inhaler • History of regular attendance at the pharmacy in which they are recruited, which will be demonstrated by patient having collected 3 prescriptions for any medication in that pharmacy in the 6 months preceding their recruitment into the study
Interventions	Feedback on inhaler use, education or control
Outcomes	Rate of adherence
Starting date	February 2014
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02203266

NCT02307669

Trial name or title	Inhaler Adherence in Severe Unstable Asthma (INCA-SUN)
Methods	Double-blind, parallel-group randomised controlled trial
Participants	• Willing to give voluntary informed consent • Having a clinical diagnosis of asthma- • Having a bronchodilator FEV_1 > 40% and < 80% in the past 1 year • Having current unstable asthma (i.e. ACT score < 19) at enrolment • Taking 2 or more courses of oral corticosteroids in the prior year, or hospitalisation or ED attendance with an asthma exacerbation in the past year • 18 years of age or older at time of consent • Capable of understanding and complying with requirements of the protocol, including ability to attend for all required visits • Ability and willingness to take inhaled medication via a Diskus • In the opinion of the investigator, suitable for use of a salmeterol/fluticasone Diskus inhaler or already using a salmeterol/fluticasone inhaler
Interventions	Feedback on inhaler use or routine care
Outcomes	Adherence to preventer medication; cost and effectiveness of medication

NCT02307669 (*Continued*)

Starting date	December 2015
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02307669

NCT02386722

Trial name or title	Intervention to Improve Inhalative Adherence
Methods	Single-blind, parallel-group randomised controlled trial
Participants	• Inpatients and outpatients older than 18 years with a clinical diagnosis of asthma or COPD • At least 1 exacerbation in the past year • Ability to give informed consent. • Good knowledge of the German language by themselves • Use of a metered dose Inhaler (e.g. Ventolin®), Diskus (e.g.Seretide®), Turbohaler (e.g.Symbicort®), Aerolizer/Breezhaler (e.g. Onbrez®) or HandiHaler (e.g. Spiriva®)
Interventions	Audio reminders and support calls or control
Outcomes	Time to next asthma or COPD exacerbation; number of exacerbations; adherence
Starting date	January 2014
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02386722

NCT02426814

Trial name or title	Assessment of a Mobile Intervention to Increase Adherence to Asthma Medication Among Adolescents
Methods	Open-label, parallel-group randomised
Participants	• Age 11 to 19 years • Asthma diagnosis • Current prescription for a hydrofluoroalkane (HFA) asthma controller medication • Ability to speak English • Having a smartphone or access to a smartphone or tablet
Interventions	Medication Monitoring and Mobile App or sham comparator
Outcomes	Real-time medication adherence
Starting date	August 2015

NCT02426814 (*Continued*)

Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02426814

NCT02556073

Trial name or title	ICS/LABA Combination With Integrated Dose Counter and Smartphone App to Improve Asthma Control
Methods	Open-label, parallel-group randomised
Participants	• Symptomatic asthmatic individuals free of controller medication for at least 3 months • 20 to 70 years of age • Life-long smoking index < 10 pack-years
Interventions	Smartphone self management or routine care
Outcomes	Changes in airway inflammation profile; changes in scores of Asthma Control Questionnaire; changes in lung function parameters; numbers of rescue medications used
Starting date	August 2014
Contact information	
Notes	Link to study registration: https://clinicaltrials.gov/ct2/show/NCT02556073

NCT02615743

Trial name or title	Asthma Controller Adherence After Hospitalization
Methods	Open-label, parallel-group randomised
Participants	• Unlimited text messaging plan • Prescription for 1 of the following metered dose inhalers for daily use: Flovent (fluticasone), QVAR (budesonide), Seretide (fluticasone-salmeterol), Advair MDI (fluticasone-salmeterol) or Dulera (mometasone-formoterol) • Primary care received at 1 of 3 urban CHOP primary care practices (Karabots, South Philadelphia or Cobbs Creek)
Interventions	Daily text message reminders or control
Outcomes	Feasibility; acceptability; adherence
Starting date	December 2015
Contact information	

NCT02615743 (*Continued*)

Notes	https://clinicaltrials.gov/ct2/show/NCT02615743

NCT02715219

Trial name or title	Effectiveness of an AEP on Patient's Knowledge, Medication Adherence and Inhaler Technique
Methods	Single-blind, parallel-group randomised controlled trial
Participants	• Confirmed diagnosis of bronchial asthma in the medical record • Use of inhaler medication for past 1 year
Interventions	Asthma Education Programme (AEP) or routine care
Outcomes	Participant knowledge status regarding asthma; participant medication adherence status; participant inhaler technique
Starting date	June 2015
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02715219

NCT02768623

Trial name or title	Evaluation of a Community Pharmacist Managed Asthma Consultation Service
Methods	Open-label, parallel-group randomised controlled trial
Participants	• Provided written consent • Intended to refill all asthma-related prescriptions at the study pharmacy • Given a diagnosis of asthma by a physician or a nurse practitioner • Taking inhaled corticosteroids for which dose and/or medication has remained unchanged for at least 2 months • 18 years of age or older • Having uncontrolled asthma (defined as in the past 4 weeks, patient has used rescue medication 4 or more times in a given week and/or patient has woken up in the night because of asthma during a given week)
Interventions	Comprehensive disease management programme for asthma or control
Outcomes	Peak expiratory flow rate; medication adherence; asthma control
Starting date	May 2016
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT02768623

NCT02787174

Trial name or title	A Computer-Based ED Intervention to Improve Pediatric Asthma Medicine Adherence (ED-AMAP)
Methods	Single-blind, parallel-group randomised controlled trial
Participants	• Asthma diagnosis by physician or parent report • Age 2 to 12 • Inhaled corticosteroid asthma controller medicine prescribed
Interventions	Interactive tailored asthma medication adherence education on an iPad or routine care
Outcomes	Asthma controller medication adherence
Starting date	February 2016
Contact information	
Notes	https://www.clinicaltrials.gov/ct2/show/NCT02787174

NTR5061

Trial name or title	Development and Testing of an Adolescent Adherence Patient Tool for Asthma
Methods	Open-label, parallel-group randomised controlled trial
Participants	Adolescent patients using ICS registered at 1 of the pharmacies in the UPPER-network • Age between 12 and 18 years • Use of ICS: filling of ≥ 2 prescriptions for ICS or ICS/LABA combination during previous 12 months • Diagnosis of (persistent) asthma (verified by GP) • Access to a smartphone
Interventions	Smartphone application for patients combined with a computer management system for healthcare providers (pharmacists)
Outcomes	Adherence
Starting date	April 2015
Contact information	
Notes	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5061

Sulaiman 2016

Trial name or title	Prospective Study of the Feedback From an Adherence Monitor on Asthma Control (INCA)
Methods	Single-blind, parallel-group randomised controlled trial
Participants	• Patients prescribed therapy equivalent to step 3 or higher on the Asthma Management Guidelines for at least 3 months • At least 1 exacerbation in the previous year with systemic glucocorticoids • Uncontrolled/Partially controlled asthma by GINA guidelines
Interventions	Feedback from a computer log of inhaler use or control
Outcomes	Adherence rate
Starting date	February 2012
Contact information	
Notes	https://clinicaltrials.gov/ct2/show/NCT01529697

ACT: Asthma Control Test; COPD: chronic obstructive pulmonary disease; ED: emergency department; FEV_1: forced expiratory volume in one second; GINA: Global Initiative for Asthma; GP: general practitioner; HFA: hydrofluoroalkane; ICS: inhaled corticosteroids; INCA: Inhaler Compliance Assessment device; LABA: long-acting $beta_2$-agonist; MDI: metered dose inhaler; SMS: short message service/text message

DATA AND ANALYSES

Comparison 1. Adherence education versus controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % Adherence (objective measures)	5	280	Mean Difference (IV, Random, 95% CI)	20.13 [7.52, 32.74]
1.1 Complex	4	230	Mean Difference (IV, Random, 95% CI)	21.55 [4.71, 38.39]
1.2 Simple education	1	50	Mean Difference (IV, Random, 95% CI)	15.40 [5.98, 24.82]
2 % Adherence (all measures)	10	1693	Mean Difference (IV, Random, 95% CI)	11.59 [3.72, 19.46]
2.1 Complex	8	744	Mean Difference (IV, Random, 95% CI)	12.21 [1.26, 23.17]
2.2 Simple education	2	949	Mean Difference (IV, Random, 95% CI)	10.60 [5.17, 16.03]
3 > 85% adherence	1	271	Odds Ratio (M-H, Random, 95% CI)	2.68 [1.61, 4.46]
4 Exacerbations requiring OCS (people with 1 or more)	3	349	Odds Ratio (M-H, Random, 95% CI)	1.82 [0.99, 3.36]
5 Asthma control	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 ACQ	4	455	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.49, 0.43]
5.2 ACT	3	333	Mean Difference (IV, Random, 95% CI)	0.30 [-0.82, 1.43]
6 Unsheduled visits to a healthcare provider (people with 1 or more)	4	688	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.19, 1.19]
6.1 Hospital	1	250	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.56, 2.70]
6.2 ED	2	367	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.06, 0.83]
6.3 GP	1	71	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.07, 0.54]
7 Quality of life (AQLQ)	6	734	Mean Difference (IV, Random, 95% CI)	0.01 [-0.20, 0.23]

Comparison 2. Electronic trackers or reminders (± feedback) versus controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % Adherence (objective measures)	6	555	Mean Difference (IV, Random, 95% CI)	19.86 [14.47, 25.26]
1.1 Reminders/trackers	3	321	Mean Difference (IV, Random, 95% CI)	16.29 [9.53, 23.04]
1.2 With feedback	3	234	Mean Difference (IV, Random, 95% CI)	24.98 [17.53, 32.44]
2 % Adherence (all measures)	8	762	Mean Difference (IV, Random, 95% CI)	18.41 [11.82, 25.00]
2.1 Reminders/trackers	4	361	Mean Difference (IV, Random, 95% CI)	16.92 [10.82, 23.02]
2.2 With feedback	4	401	Mean Difference (IV, Random, 95% CI)	20.06 [7.27, 32.85]
3 Exacerbations requiring OCS (people with at least 1)	4	3063	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.37, 1.39]
4 Asthma control	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 ACQ	2	109	Mean Difference (IV, Random, 95% CI)	0.24 [-0.29, 0.78]
4.2 ACT	4	596	Mean Difference (IV, Random, 95% CI)	0.74 [-0.20, 1.69]
5 Unscheduled visits to a healthcare provider	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

5.1 ED	2	2918	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.88, 1.47]
5.2 Hospital	2	2865	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.53, 1.78]
6 Unscheduled visits to a healthcare provider	1		Rate Ratio (Random, 95% CI)	Totals not selected
6.1 GP/ED visits	1		Rate Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Hospitalisations	1		Rate Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
7 Absenteeism	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
8 Absenteeism	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
9 Quality of life (AQLQ)	4	369	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.13]

Comparison 3. Simplified versus usual regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % Adherence	3	1310	Mean Difference (IV, Random, 95% CI)	4.02 [1.88, 6.16]
2 Exacerbations requiring OCS	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
3 Asthma control (ACQ)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Unscheduled visits	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 Absence from work/school	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6 Quality of life (ITG-ASF % change from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 All adverse events	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. School-based ICS therapy versus controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Unscheduled visits (1 or more hospitalisations for any cause)	2	279	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.16, 2.05]
2 Quality of life (PAQLQ)	2	279	Mean Difference (IV, Random, 95% CI)	0.25 [0.01, 0.49]

Comparison 5. Subgroup analyses for % adherence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparison 1. Children vs adults	10	1693	Mean Difference (IV, Random, 95% CI)	11.59 [3.72, 19.46]
1.1 Children	4	1241	Mean Difference (IV, Random, 95% CI)	8.01 [-4.77, 20.79]
1.2 Adults/adolescents and adults	6	452	Mean Difference (IV, Random, 95% CI)	14.43 [5.49, 23.36]

2 Comparison 2. Complex vs simple interventions	6	555	Mean Difference (IV, Random, 95% CI)	19.86 [14.47, 25.26]
2.1 Complex	3	234	Mean Difference (IV, Random, 95% CI)	24.98 [17.53, 32.44]
2.2 Simple	3	321	Mean Difference (IV, Random, 95% CI)	16.29 [9.53, 23.04]
3 Comparison 2. Children vs adults	6	555	Mean Difference (IV, Random, 95% CI)	19.86 [14.47, 25.26]
3.1 Children	3	314	Mean Difference (IV, Random, 95% CI)	17.29 [8.32, 26.26]
3.2 Adults/adolescents and adults	3	241	Mean Difference (IV, Random, 95% CI)	22.84 [16.66, 29.02]

ADDITIONAL TABLES

Table 1. Comparison 1 study characteristics: adherence education

Study ID ("first received" date for clinical trials registries)	Total n	Duration of intervention/ follow-up	Age	Country	Intervention	Control	Adherence measure	Outcomes
NCT0011532 (2005)	333	13/26 weeks	Adults	USA	Problem-solving intervention	Asthma education	Electronic inhaler monitor	Adherence, AQLQ, ACQ, LFTs, hospitalisation, ED visits, participant satisfaction
Bender 2010	50	10 weeks	Adults	USA	Interactive voice response intervention	Usual care	Electronic inhaler monitor or canister weight	Adherence, AQLQ, ACT, Beliefs about Medication Questionnaire
NCT0095893 (2009)	1187	2 years	Children	USA	Telephone speech recognition intervention	Usual care	Total ICS supplied/total prescribed	Adherence, beta-agonist use, OCS use, primary care, ED and out of hours visits, hospitalisations, participant satisfaction

Table 1. Comparison 1 study characteristics: adherence education (*Continued*)

Chatkin 2006	271	13 weeks	Adolescents and adults	Brazil	Telephone counselling	Ususal care	"Number of inhalations recorded on the disks"	Adherence
NCT0014948 (2005)	141	17 weeks/1 year	Children	USA	Problem-solving intervention	Family-based intervention	Electronic inhaler monitor	Adherence, symptoms, use of healthcare services, reliever medication use
NCT0016658 (2009)	55	2 months	Children	USA	Team work intervention	Asthma education	Electronic inhaler monitor	Adherence, Parent-Adolescent Conflict Questionnaire, Functional Severity Index, LFTs, Consumer Satisfaction Survey
Foster 2014	60 GPs, 143 patients	6 months	Adolescents and adults	Australia	Personalised adherence discussion (PAD) PAD + inhaler reminder feedback (IRF)	Usual care	Electronic inhaler monitor	ACT, AQLQ, Hospital Anxiety and Depression Scale, Medication Adherence Report Scale, LFTs, exacerbations
Gallefoss 1999	78	1 year	Adults	Norway	Asthma education	Usual care	Prescribed doses/dispensed doses	Adherence, GP visits, absenteeism, days in hospital
NCT0106486 (2010)	20	12 weeks/1 year	Not reported, but mean age suggests	Northern Ireland	Nurse-led psychoeducation	Ususal care (difficult asthma service)	Percent of prescriptions refilled	Adherence, OCS, beta-agonist use,

Table 1. Comparison 1 study characteristics: adherence education (*Continued*)

			adults					hospital admissions, LFTs, ACQ, AQLQ, Hospital Anxiety and Despression Scale
ADERE PEDIATRIC 1 (2008)	298	90 weeks	Children	Brazil	Telephone follow-up intervention	Usual care	Percentage of actual doses/number expected	Adherence, disease control, quality of life (SF-36)
Hart 2002	83	13 weeks	Children	UK	Asthma education	Usual care	Electronic inhaler monitor	Adherence, beliefs and anxieties about adherence
NCT0051663 (2007)	60	26 weeks/78 weeks	Children	Sweden	Group discussion plus basic education	Basic education	Diaries and canister weight	Adherence, views on adherence, days hospitalised, ED visits, exacerbations
Kamps 2008	15	6 weeks/52 weeks	Children	USA	Specific adherence improvement strategies (education, monitoring, etc.)	Usual care plus education	Electronic inhaler monitor	Adherence, LFTs, PedsQL, healthcare costs
NCT0113243 (2010)	54	6 weeks/52 weeks	Adults	Canada	Motivational interviewing	Usual care	Prescribed treatment days/number of days	Adherence, asthma control, quality of life, asthma-related self-efficacy
Mehuys 2008	201	6 months	Adults	Belgium	Adherence education	Usual care	Prescription refill rates, self-reporting	ACT, diary card, rescue medication use, ED

Table 1. Comparison 1 study characteristics: adherence education (*Continued*)

								visits, hospitalisations, AQLQ, Knowledge of Asthma and Asthma Medicine Questionnaire, inhalation technique
NCT0116988 (2010)	68	10 weeks	Adolescents	USA	Adherence messaging and group sessions	"Attention control"	Electronic inhaler monitor	Adherence, asthma knowledge, ICS knowledge, ICS self-efficacy, social support, exacerbations
NCT0241352 (2015)	12	12 weeks	Adolescents	USA	Adherence monitoring and incentivisation via app and sensor	Usual care	Electronic inhaler monitor	Adherence, ACT **NB:** study terminated
Onyirimba 2003	30	10 weeks	Adults	USA	Adherence monitoring and education	Monitoring without feedback	Electronic inhaler monitor	Adherence, rescue medication use, AQLQ, LFTs
NCT0023318 (2005)	250	78 weeks	Children	USA	Adherence education	Usual care	Prescription refill rates, self-reporting	Adherence, symptoms, nighttime awakenings, ED visits, hospitalisation, OCS courses
Ulrik 2009	274	12 weeks	Adults	Denmark and Switzerland	Adherence education and study medi-	Study medication alone	Dose counting in returned investigational	Adherence, asthma control, LFTs, symp-

Table 1. Comparison 1 study characteristics: adherence education (*Continued*)

					cation		product	toms, rescue medication use, nighttime awakenings, adverse events, AQLQ, asthma severity, adverse events, vital signs
NCT00414811 (2006)	14,064 (6903 previous ICS users)	78 weeks	Adults	USA	Telephone interactive voice recognition intervention	Usual care	Pharmacy-based adherence measures	Adherence, use of healthcare services, economic evaluation

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; GP: general practitioner; ICS: inhaled corticosteroid; IRF: inhaler reminder feedback; LFTs: lung function tests; OCS: oral corticosteroid; PAD: personalised adherence discussion; PedsQL: Paediatric Quality of Life Inventory; SF-36: Short-Form Health Survey

Table 2. Comparison 2 study characteristics: electronic trackers or reminders

Study ID	Total n	Duration of intervention/ follow-up	Age	Country	Intervention	Control	Adherence measure	Outcomes
Black 2008	40	2 months	Children	New Zealand	Inhaler alarm	Usual care	Electronic inhaler monitor	Adherence, AQLQ, LFTs, beta-agonist use
ACTRN12607000 (2007)	26	4 months	Children	Australia	Adherence feedback during consultations	Usual care	Electronic inhaler monitor	Adherence, symptoms, LFTs
Chan 2015	220	6 months	Children	New Zealand	Audiovisual inhaler reminder	Usual care	Electronic inhaler monitor	Adherence, school/work absences, ACT, Asthma Mor-

Table 2. Comparison 2 study characteristics: electronic trackers or reminders (*Continued*)

								bidity Score, exacerbations, unscheduled visits, beta-agonist use, LFTs
Charles 2007	110	24 weeks	Adolescents and adults	New Zealand	Audiovisual inhaler reminder	Usual care	Electronic inhaler monitor	Adherence, ACQ, LFTs
Foster 2014	60 GPs, 143 patients	6 months	Adolescents and adults	Australia	Inhaler reminder and feedback (IRF)	Usual care	Electronic inhaler monitor	ACT, AQLQ, Hospital Anxiety and Depression Scale, Medication Adherence Report Scale, LFTs, exacerbations
NCT0171414 (2012)	49	13 weeks	Young adults	USA	Computer sessions and tailored text reminders	Asthma education	Self-reported missed doses	Adherence, ACT, LFTs, participant satisfaction
NCT0245170 (2015)	90	1 year	Children	UK	Adherence monitoring with feedback	Adherence monitoring but no feedback	Electronic inhaler monitor	"Clinical outcomes", adherence, LFTs, exacerbations
NCT0023318 (2005)	250	78 weeks	Children	USA	Adherence monitoring and education	Adherence education	Prescription refill rates, self-reporting	Adherence, symptoms, nighttime awakenings, ED visits, hospitalisation, OCS courses
Strandbygaard 2010	26	12 weeks	Adults	Denmark	SMS (text message) adherence reminders	Usual care	"Dose-count" on the Seretide was diskus	Adherence, change in FeNO,

Table 2. Comparison 2 study characteristics: electronic trackers or reminders (*Continued*)

								LFTs, airway responsiveness
Vasbinder 2015 E-MATIC	219	52 weeks	Children	The Netherlands	SMS (text message) adherence reminders	Usual care	Electronic inhaler monitor	Adherence, ACT, exacerbations, use of healthcare services, AQLQ, school/work absence, acceptance of e-monitoring, economic evaluation
NCT0045936 (2007)	2698 (34 clusters)	52 weeks	Children and adults	USA	Adherence education with adherence feedback	Adherence education alone	Electronic prescribing data/refill rate	Adherence, ED visits, hospitalisation, OCS use

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; LFTs: lung function tests; OCS: oral corticosteroid

Table 3. Comparison 3 study characteristics: simplified regimens

Study ID	Total n	Duration of intervention/ follow-up	Age	Country	Intervention	Control	Adherence measure	Outcomes
Bosley 1994	102	12 weeks	Adults	UK	Combined inhaler	Separate inhalers	Electronic inhaler monitor	Adherence, LFTs
Mann 1992	16	6 weeks/12 weeks	Adults	USA	Twice-daily dosing	Four-times-daily dosing	Electronic inhaler monitor	Adherence, LFTs, symptoms
AC-TRN1260600 (2007)	111	24 weeks	Children	New Zealand	Combined inhaler	Separate inhalers	Electronic inhaler monitor	Adherence, LFTs, ACQ, OCS, unscheduled visits

Table 3. Comparison 3 study characteristics: simplified regimens (*Continued*)

Price 2010	1233	12 weeks	Adolescents and adults	UK	Once-daily ICS	Twice-daily ICS	"Device counter number"	Adherence, physician assessment of response, quality of life, use of healthcare services, days of school/work missed, adverse events, worsening asthma

ACQ: Asthma Control Questionnaire; ICS: inhaled corticosteroid; LFTs: lung function tests; OCS: oral corticosteroid

Table 4. Comparison 4 study characteristics: school-based ICS therapy

Study ID	Total n	Duration of intervention/ follow-up	Age	Country	Intervention	Control	Adherence measure	Outcomes
Gerald 2009	290	65 weeks	Children	USA	Supervised ICS therapy at school	Usual care	N/A	Episodes of poor asthma control, school absences, rescue medication use at school
Halterman 2004	184	9 weeks	Children	USA	Supervised ICS therapy at school	Usual care	N/A	Symptom-free days, daytime and nighttime symptoms, rescue medication use, school absences
NCT01175423 (2010)	100	6 to 8 months	Children	USA	Supervised ICS therapy at school	Usual care	N/A	Feasibility, symptom-free days, numbers of days and nights with symptoms, activity limitation, rescue medication

Table 4. Comparison 4 study characteristics: school-based ICS therapy (*Continued*)

								use, school absenteeism, parent sleep interruption, change in family plans due to the child's asthma, PAQLQ, utilisation of healthcare services, FeNO

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; PAQLQ: Pediatric Asthma Quality of Life Questionnaire

CONTRIBUTIONS OF AUTHORS

RN drafted the Background and Methods section according to the Cochrane Airways Group template, with input and revisions from KK and ES. ES ran the electronic searches. All three review authors contributed to sifting of search results, data extraction and assessment of risk of bias in duplicate. RN and KK ran the data analyses and graded the evidence. All review authors contributed to the write-up.

DECLARATIONS OF INTEREST

RN is the Deputy Co-ordinating Editor of the Cochrane Airways Group and is a qualified general practitioner.

ES is the Information Specialist for the Cochrane Airways Group.

KK is a systematic review author who was employed by a Cochrane Airways Programme Grant at the time of writing of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not use Covidence to extract data from the included studies because we found the process too time consuming, and we were unable to capture different types of data using the software. Instead, we used an Excel template commonly used by the Cochrane Airways Group to capture study characteristics, outcome data and risk of bias information.

In the protocol, we listed various factors that may alter the treatment effect; we intended to present these factors in an additional table. We anticipated that the factors listed (type, delivery, dose and schedule of ICS; whether treatment was given in a combination inhaler with a long-acting beta-agonist (LABA), baseline severity of asthma) would document differences between studies, but in practice, studies generally were not designed to assess adherence to a particular type of ICS, dose or regimen, with or without a LABA, so we did not design the table in this way. We have described these factors in the description of studies, and we have presented important clinical and intervention characteristics in Tables 1 to 3.

We had to define post hoc as what constituted an 'objective' measure of adherence. Studies used a variety of measures including self-report scales, pharmacy refill data, canister weight and electronic monitors. We decided that only electronic monitors could be considered truly objective. In a post hoc change to our analysis plan, we presented studies using objective measures (i.e. electronic inhaler monitors) as the primary analysis for % adherence, as we deemed this a more useful analysis. An analysis including studies that used all measures then follows.