Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy: results from a systematic literature review and modelling study

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Trials of add-on therapy for severe asthma do not include adequate assessment of adherence to maintenance therapy. As a result, they suffer from a significant loss of statistical power, leading to greatly increased sample sizes and associated costs. http://ow.ly/ZCyH30nSFHc

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ABSTRACT Adherence to inhaled maintenance therapy in severe asthma is rarely adequately assessed, and its influence on trial outcomes is unknown. We systematically determined how adherence to maintenance therapy is assessed in clinical trials of "add-on" therapy for severe asthma. We model the improvement in trial power that could be achieved by accurately assessing adherence.

A systematic search of six major databases identified randomised trials of add-on therapy for severe asthma. The relationship between measuring adherence and study outcomes was assessed. An estimate of potential improvements in statistical power and sample size was derived using digitally recorded adherence trial data.

87 randomised controlled trials enrolling 22 173 participants were included. Adherence assessment was not reported in 67 trials (n=13 931, 63%). Studies that reported adherence used a range of self-report and subjective methods. None of the studies employed an objective assessment of adherence. Studies that reported adherence had a significantly reduced pooled variance in forced expiratory volume in 1 s (FEV_1) compared to those that did not assess adherence: s^2=0.144 L^2 *versus* s^2=0.168 L^2, p<0.0001. Power to detect clinically relevant changes in FEV_1 was significantly higher in trials that reported adherence assessment (mean power achieved 59% *versus* 49%). Modelling suggests that up to 50% of variance in FEV_1 outcomes is attributable to undetected variations in adherence. Controlling for such variations could potentially halve the required sample size.

Few trials of add-on therapy monitor adherence to maintenance inhaled therapy, resulting in a greater variance in trial outcomes and inadequate power for determining efficacy.

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Introduction

Treatment with inhaled corticosteroids (ICS) alone or combined with a long-acting β_2-agonist (LABA) is usually adequate to control the symptoms of asthma. However, asthma in a significant minority of patients remains uncontrolled even on high dose ICS/LABA treatment, and may require "add-on" therapy. Because both adherence to inhaled therapy and inhaler technique are known to be poor among patients with severe asthma, Global Initiative for Asthma (GINA) guidelines recommend that patient adherence and inhaler technique should be optimised before additional therapy is prescribed, to avoid unnecessary treatment [1, 2]. In practice, because objective methods of assessing inhaler adherence are not yet widely used, this is rarely achieved.

Recently, several digital technologies have become available that objectively quantify adherence [3, 4] to inhaled therapy. Sulaiman *et al.* [5] used a digital recording technology to assess adherence to ICS/LABA therapy among patients with moderate to severe asthma (GINA stage 3–4). The patients were aware of active monitoring. The authors reported significantly lower baseline mean adherence rates than otherwise assumed (mean±SD 64±28%), with a remarkable level of variability on a participant level (mean month-to-month change in adherence rate of 30%). Variable adherence to inhaled therapy may therefore be a confounding factor in patients enrolled in add-on therapy trials, which may consequently affect study endpoints in several ways. Failure to objectively assess adherence to maintenance ICS/LABA therapy during both the run-in phase and throughout the study means that a significant source of variance in objective measures such as lung function is not appreciated.

We hypothesised that adherence to maintenance ICS/LABA therapy is under-assessed and poorly reported in clinical trials of add-on drug treatment for patients with severe, uncontrolled GINA stage 3/4 asthma. We thus conducted a systematic review of clinical trials of add-on therapy for severe asthma to determine the extent to which adherence to maintenance ICS/LABA was assessed, prior to and during the intervention in question. Based on the published results of trials included in this review, we modelled potential effects of variations in maintenance ICS/LABA adherence on study outcomes to determine the effects on study power that may be derived from improved monitoring of ICS/LABA adherence.

Methods

Systematic review

This systematic review was conducted using Cochrane methodology [6]. Pre-specified eligibility criteria were included in the international prospective register of systematic reviews in Prospero (CRD42015029611). The study flow diagram is shown in figure 1.

Briefly, parallel and crossover randomised controlled trials (RCTs) reported as full-text publications that were written in the English language were eligible for inclusion. Specifically, RCTs conducted to investigate add-on therapy in adolescents aged ⩾12 years or adult patients with severe asthma on treatment consistent with GINA step 3–4 therapy were included. Review articles, unpublished studies, case reports, audits, guidelines, editorials, conference abstracts, letters, unpublished studies, comments and studies where only the abstracts were available were excluded.

Search strategy

Two independent authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science and PsycINFO to identify studies published from January 1, 1995 to June 30, 2017. Details of search strategies for the relevant databases are shown in appendix 1. The electronic search was conducted on November 25, 2015 and updated on June 30, 2017.

Selection criteria and data extraction

Titles, abstracts and descriptors were reviewed by two independent authors to identify potentially relevant trials for the review. Texts and bibliographies were reviewed to identify additional studies. Two review authors independently screened full-text study publications and selected trials for inclusion. Disagreements

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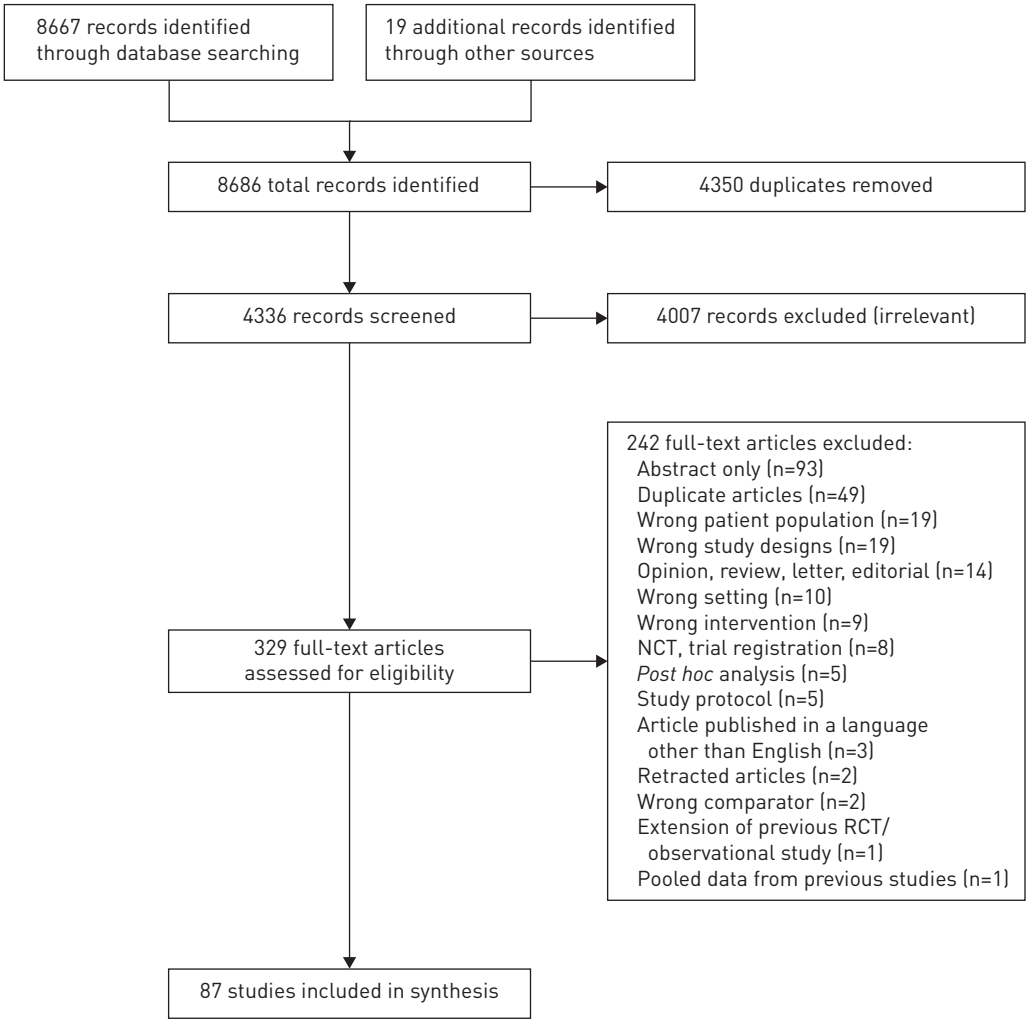


FIGURE 1 Systematic review flow diagram. NCT: national clinical trial; RCT: randomised controlled trial.

were resolved by consensus and discussion with a third author. The selection process was recorded with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [7] using the online systematic review software programme (www.covidence.org). Data extracted from the trials included study characteristics, study interventions and outcomes. Missing data were obtained by directly contacting the authors whenever possible and/or www.clinicaltrials.gov or other registries if the trial was registered.

Assessing the risk of bias in the included studies

Two authors independently assessed the risk of bias for each trial using the Cochrane Risk of Bias tool 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 and other bias.

Outcomes

The primary outcome was the assessment and reporting of adherence to ICS/LABA therapy and measures of adherence. Subjective measures were those that included self-reported adherence; semi-objective measures included the use of measures such as weighing the inhaler, pharmacy refill or if a participant filled in a daily diary; an objective measure was if a subject was required to use an enabled inhaler that digitally recorded when the inhaler was used.

Data analysis

Descriptive statistics were used for reporting the primary outcome. Random effect meta-analyses were conducted to compare study outcomes using RevMan5 software [6]. Pooled estimates of the mean difference in outcomes and 95% confidence intervals are reported.

Estimating the effects of assessing adherence to ICS/LABA therapy on clinical outcomes

We derived models of the potential effect of additional variance introduced by unmonitored changes in adherence to ICS/LABA on the outcomes of studies included in the systematic review. While the most common primary outcome in the included studies was the annualised exacerbation rate, large differences in the definition and reporting of exacerbations, as well as a lack of data on baseline exacerbation rates, made it impossible to accurately model the effect of adherence variations on exacerbation rates. Instead we focused on forced expiratory volume in 1 s (FEV_1), which was the second most commonly reported outcome, and usually measured at both baseline and at the end of studies, allowing for accurate modelling of the effects of variation in adherence over the study period. However, while we focused on FEV_1 in this modelling study, similar reasoning applies in the case of exacerbations, where changes in the baseline rate due to ICS/LABA adherence may affect the power of trials. This is discussed further in appendix 5.

Effects of adherence variations on FEV_1

Using published estimates of the distribution of adherence rates and of the effect of ICS/LABA treatment on FEV_1, we estimated the proportion of variance in study outcomes that could be attributed to variations in adherence to ICS/LABA.

Three likely scenarios in which failure to objectively assess adherence could influence clinical trials were modelled:

- *Scenario 1*: No objective adherence monitoring either during run-in or throughout the trial period. We model the effect of normal month-to-month adherence variations.
- *Scenario 2*: Screening for adherence was performed during the run-in but there was no objective monitoring throughout the study. We model the "regression to the mean" effect.
- *Scenario 3*: Adherence was monitored during the study period but not during run-in. We model a hypothetical "Hawthorne effect".

Estimates of the distribution of adherence and variations in adherence from month to month were taken from the control group of the study by Sulaiman *et al.* [5], in which adherence to ICS/LABA therapy was electronically monitored over 3 months in 100 patients with severe asthma [5]. Estimates of the effect of ICS/LABA on FEV_1 were taken from a study by Shapiro *et al.* [8] comparing inhaled fluticasone/salmeterol against placebo. Because Shapiro *et al.* [8] did not perform objective adherence assessment, adherence rates were assumed to be similar to those reported by Sulaiman *et al.* [5]. The reported effect size was adjusted to obtain the "true effect" that would be expected given perfect adherence (appendix 4).

Figure 2 shows a schematic of the three model scenarios. A brief description of these scenarios is given below. For details see appendix 4.

Scenario 1: month-to-month variation

Sulaiman *et al.* [5] found that while the mean change in adherence from month to month was negligible (0.8%), there was a large SD (31.3%), indicating large within-subject variability. In the absence of any objective monitoring of adherence, this variability can introduce a large additional variance component into physiological outcomes. The additional variance in FEV_1 can be estimated as:

$$\sigma^2_{\text{additional}} = \sigma^2_{\text{adh}}\sigma^2_{\text{ICSLABA}} + \mu^2_{\text{ICSLABA}}\sigma^2_{\text{adh}} + \mu^2_{\text{adh}}\sigma^2_{\text{ICSLABA}}$$

where μ_{ICSLABA} is the mean and σ_{ICSLABA} the SD of the effect of ICS/LABA treatment, and μ_{adh} is the mean and σ_{adh} the SD of the change in adherence.

Using the values reported by Sulaiman *et al.* [5], and the estimated ICS/LABA effect from Shapiro *et al.* [8], we estimated an expected additional variance in FEV_1 of 0.083 L^2.

Scenario 2: regression to the mean

A number of included studies screened participants for adherence to ICS/LABA during the run-in phase, but did not assess adherence during the study period. In this case, patients who had good adherence during the run-in phase were assumed to have had good adherence throughout the study. However, screening in this way creates the potential for a regression to the mean effect, whereby participants who had better-than-usual adherence are enrolled, and subsequently revert to their mean adherence rate.

The data from Sulaiman *et al.* [5] show that patients who had good adherence (>80%) at month 1 of the study displayed a significant drop in adherence over the study period (mean change from month 1 to month 3 of −8.5±21.2%). Using the same formula as in scenario 1, we estimate the additional variance in

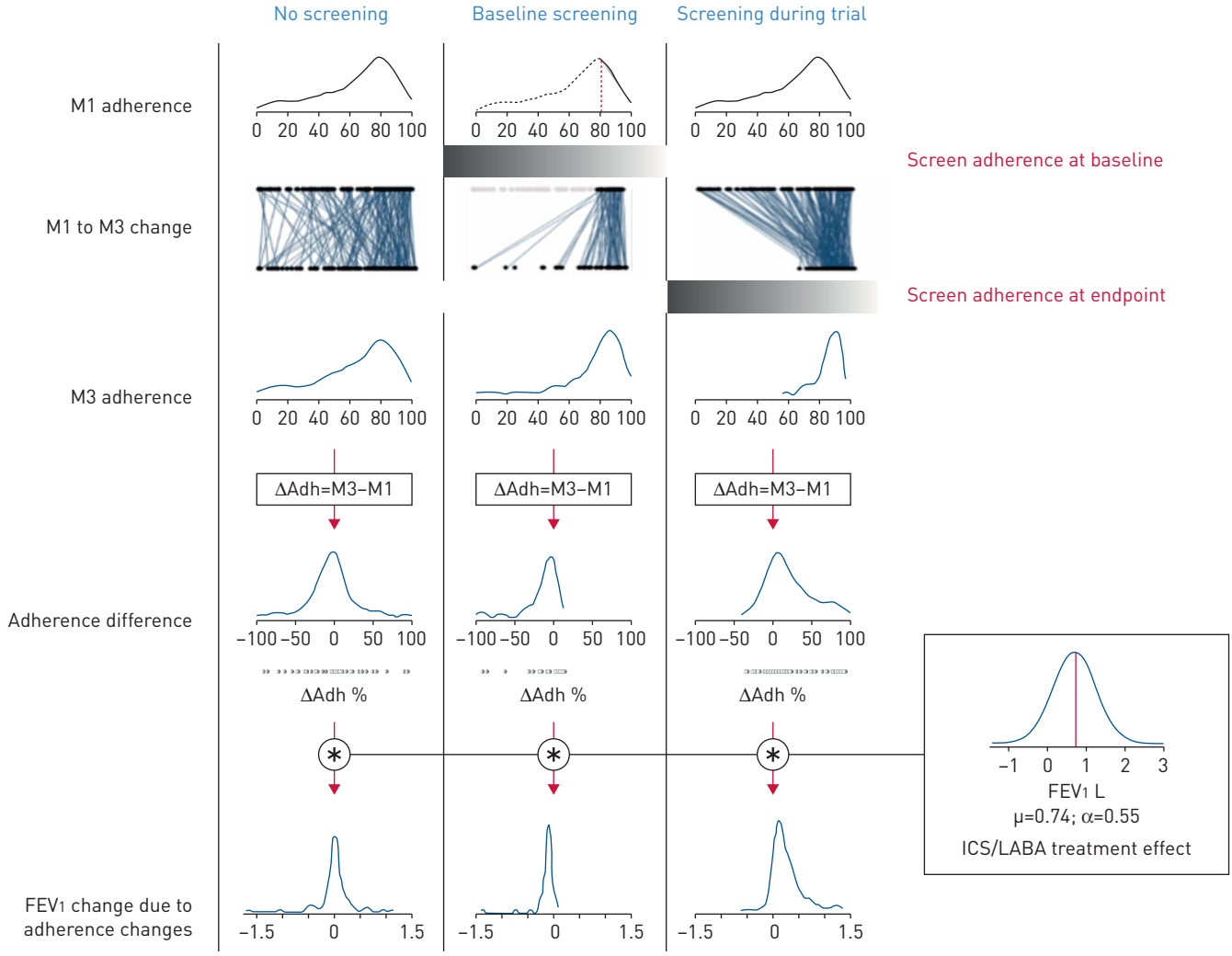


FIGURE 2 Schematic representation of three model scenarios. Data from Sulaiman *et al.* [5] is used to estimate the distribution of adherence change (ΔAdh) from month to month. The resulting distribution of changes in forced expiratory volume in 1 s (FEV_1) is estimated using the inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) treatment effect derived from Shapiro *et al.* [8]. The left column represents scenario 1, in which no adherence screening is performed. In scenario 2 (centre), screening is performed only at baseline. In scenario 3 (left), we simulate a Hawthorne effect, in which patients' adherence improves during the study and is screened during the trial. The central column clearly displays the regression to the mean effect due to screening at baseline. Although only patients with >80% adherence at month 1 are included, by month 3 their adherence distribution is not noticeably difference from that in scenario 1, where no screening is performed.

FEV_1 introduced by assessing adherence only at baseline as:

$$\sigma^2_{\text{additional}} = \sigma^2_{\text{adh}}\sigma^2_{\text{ICSLABA}} + \mu^2_{\text{ICSLABA}}\sigma^2_{\text{adh}} + \mu^2_{\text{adh}}\sigma^2_{\text{ICSLABA}} = 0.04\ \text{L}^2.$$

Scenario 3: the "Hawthorne effect"

In this scenario, we consider the case where adherence is monitored during a study, but not during the preceding run-in period. In this case there is the potential for a "Hawthorne effect", in which patients improve their adherence to maintenance therapy after enrolment in the study as a result of participating in the study. We model an effect whereby patients' prior adherence is similar to that shown by Sulaiman *et al.* [5], but subsequently improves to match standard study inclusion guidelines (typically >80% adherence). We derived an estimate of the mean (μ_{adh}) and variance (σ^2_{adh}) of this change (appendix 4).

Using the estimates of effect on FEV_1 as before, we get an estimate of the additional variance in FEV_1:

$$\sigma^2_{\text{additional}} = \sigma^2_{\text{adh}}\sigma^2_{\text{ICSLABA}} + \mu^2_{\text{ICSLABA}}\sigma^2_{\text{adh}} + \mu^2_{\text{adh}}\sigma^2_{\text{ICSLABA}} = 0.061$$

TABLE 1 Summary of findings: semi-objective methods of assessing and reporting adherence to ICS/LABA therapy

Study	Participants n	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique assessed/ reported
Nair (benralizumab) [71]	220	Screening/ run-in	Patients reported compliance with ICS/LABA daily on electronic diaries and were enrolled if they demonstrated compliance of ⩾70%	Electronic diary	No
Hanania (lebrikizumab) [48]	2148	Screening	Patients recorded inhaler use daily on an electronic diary	Electronic diary	No
FitzGerald (benralizumab) [38]	1306	Run-in	Daily asthma diaries were used by patients to record compliance with ICS/LABA therapy and patients were enrolled if they demonstrated compliance of ⩾70%	Electronic diary	No
Bleecker (benralizumab) [15]	1204	Run-in	Daily asthma diaries were used by patients to record compliance with ICS/LABA and patients were enrolled if they demonstrated compliance of ⩾70%	Electronic diary	No
Brightling (tralokinumab) [16]	452	Throughout the study	Patients were prompted to take their required dose of ICS/LABA through a trigger in the electronic patient-reported outcome device; patients were asked to return used inhalers to study sites to facilitate assessment of compliance	Electronic diary	No
Pavord (bronchial thermoplasty) [79]	27	Throughout the study	Patients recorded use of usual asthma medication daily on the electronic diary	Electronic diary	No
Marin (nedocromil sodium) [67]	26	Screening	Assessment of the difference between the observed canister weight and the expected weight	Weighing inhaler canister	No
Hodgson (ciclesonide) [50]	30	Screening	Assessment of primary and secondary care prescribing information	Review of prescription records	No
Brusselle (azithromycin) [18]	109	Run-in	Inhaler technique was reviewed and optimised before enrolment; patients were only included if a FeNO level was <50 ppb to ensure adherence to ICS	FeNO	Yes
Morjaria (etanercept) [68]	26	Methods	General practitioner prescription records were reviewed; bioassay for serum theophylline levels was collected	Review of prescription records	No
Berry (etanercept) [13]	30	Methods	Primary care records on the issuing and filling of prescriptions were reviewed; pharmacists consulted patients at their homes; measurement of serum prednisolone, cortisol and theophylline concentrations	Bioassays and review of primary care records on the issuing and filling of prescriptions	No

ICS: inhaled corticosteroids; LABA: long-acting β2 agonist; FeNO: fractional exhaled nitric oxide.

We extracted reported variances from all studies in the systematic review and obtained adjusted variance estimates by subtracting our estimate of the variance due to adherence changes. Forest plots and meta-analyses were constructed to compare the results with those using the uncorrected variance values.

Results

Description of studies

Of 8686 articles identified in the literature search, 329 full texts were assessed for eligibility with 87 RCTs involving 22 173 participants [9–95] fulfilling eligibility criteria (figure 1). A detailed review of the design, duration, inclusion and exclusion criteria, and data collected for the 87 trials is outlined in appendix 2. In the majority of trials (n=83), the study design was a parallel group design, with a crossover design in only four [13, 33, 49, 80]. There was a wide range in the duration of the trials from 2 to 52 weeks; mean study length was 27±16.1 weeks. There was considerable heterogeneity between studies. A summary of the risk of bias for all included studies is shown in supplementary table S1 of appendix 3.

Adherence to ICS and LABA combination therapy reporting in the included studies

Of the 87 RCTs included in the systematic review, 20 reported an assessment of adherence to ICS/LABA. Of these, 11 (5578 participants, 25%) reported semi-objective measures of adherence, while nine (2664 participants, 12%) used subjective, self-report methods only. 12 assessed adherence during the screening or run-in phase only, five assessed it during the trial period, and a further three provided no information on the timing of the assessment. None of the included studies performed objective assessment throughout the whole study period. The methods and timing of adherence assessment are shown in tables 1 and 2.

TABLE 2 Summary of findings: subjective methods of assessing adherence to ICS/LABA therapy reporting objective methods

Study	Participants n	Stage of study	Adherence reporting	Methods of monitoring adherence
Hanania (lebrikizumab) [47]	463	Screening	Patients who reported good adherence with background controller medication were randomised	Self-report
Cahill (imatinib) [23]	62	Throughout the study	Patients' used a diary to record their inhaler use	Self-report
Piper (tralokinumab) [95]	194	Throughout the study	Investigators had a discussion with patients about use of controller medication at each study visit	Self-report
Corren (lebrikizumab) [30]	218	Run-in	Response from author	Self-report
Tamaoki (Th2 antagonist, IL4/IL5 inhibitor) [88]	85	Throughout the study	Daily recording of all the medications taken throughout the study in a booklet	Self-report
Bjermer (reslizumab) [14]	314	Screening	Patients were asked to report compliance to ICS/LABA therapy and were asked to demonstrate inhaler technique	Inhaler technique
Humbert (omalizumab) [53]	419	Run-in and screening	During the run-in period inhaler technique was assessed	Inhaler technique
Hanania (omalizumab) [46]	850	Throughout the study	Adherence to ICS and LABA was assessed at clinic visits during run-in and treatment phase	Not documented
Dente (prednisolone) [35]	59	Screening	Compliance with treatment assessed when determining eligibility	Not documented

ICS: inhaled corticosteroids; LABA: long-acting β2 agonist; Th2: T-helper 2; IL: interleukin.

Secondary clinical outcomes

A meta-analysis limited to studies that conducted trials of biological therapy against placebo was conducted to compare outcomes in the 11 studies that assessed adherence to asthma maintenance therapy using semi-objective methods with studies that did not assess adherence. In the case of crossover studies in which multiple dosing regimens were employed, the results of each protocol were included as a separate study in the meta-analysis.

The meta-analysis of changes from baseline in control groups showed that subjective outcomes such as scores from the Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) displayed significant placebo effects; the weighted mean difference in AQLQ and ACQ was 0.48 (95% CI 0.28–0.68) and −0.57 (95% CI −0.63– −0.51), respectively. Physiological measures such as FEV_1 and peak expiratory flow did not change significantly from baseline in control groups. For this reason, pre-bronchodilator FEV_1 was used for further analyses.

Studies which assess adherence to ICS/LABA display reduced variance in FEV_1 and achieve higher statistical power

Further analyses were conducted for studies that reported FEV_1 as a study outcome. For consistency we considered only the 20 studies of biological therapies that reported the difference from baseline FEV_1 in litres. Studies which reported FEV_1 as per cent predicted or which did not report baseline FEV_1 were omitted. The overall pooled mean difference in FEV_1 for these 20 studies was 0.09 L (95% CI 0.06–0.11; n=6036) (figure 3). Of these, 10 reported adherence to ICS/LABA, using a mix of subjective and semi-objective methods, while the other 10 did not report adherence. Both sets of studies reported similar weighted mean differences in FEV_1 between active and control: change in FEV_1 of 0.09 L (95% CI 0.06–0.11; n=2938) for trials reporting adherence (figure 4a) and 0.09 L (95% CI 0.06–0.13; n=3094) for studies that did not report adherence (figure 4b).

By contrast, studies which reported adherence to ICS/LABA had a significantly reduced pooled variance in FEV_1 (s^2=0.144 L^2) compared to those which did not assess adherence (s^2=0.168 L^2; p<0.0001). As a result of this difference in variance, trials reporting adherence achieved a considerably higher power to detect expected differences in FEV_1, despite having slightly lower sample sizes. The power to detect a difference in FEV_1 of 0.1 L for each study was calculated. Trials which did not report adherence achieved power in the range 20%–70% (mean power 49%, mean sample size 309) compared to 25%–81% (mean power 59%, mean sample size 293) for those which reported adherence.

While both sets of studies were homogeneous, studies not assessing adherence displayed a higher, though nonsignificant, level of heterogeneity compared to those which did report adherence (I^2=26% *versus*

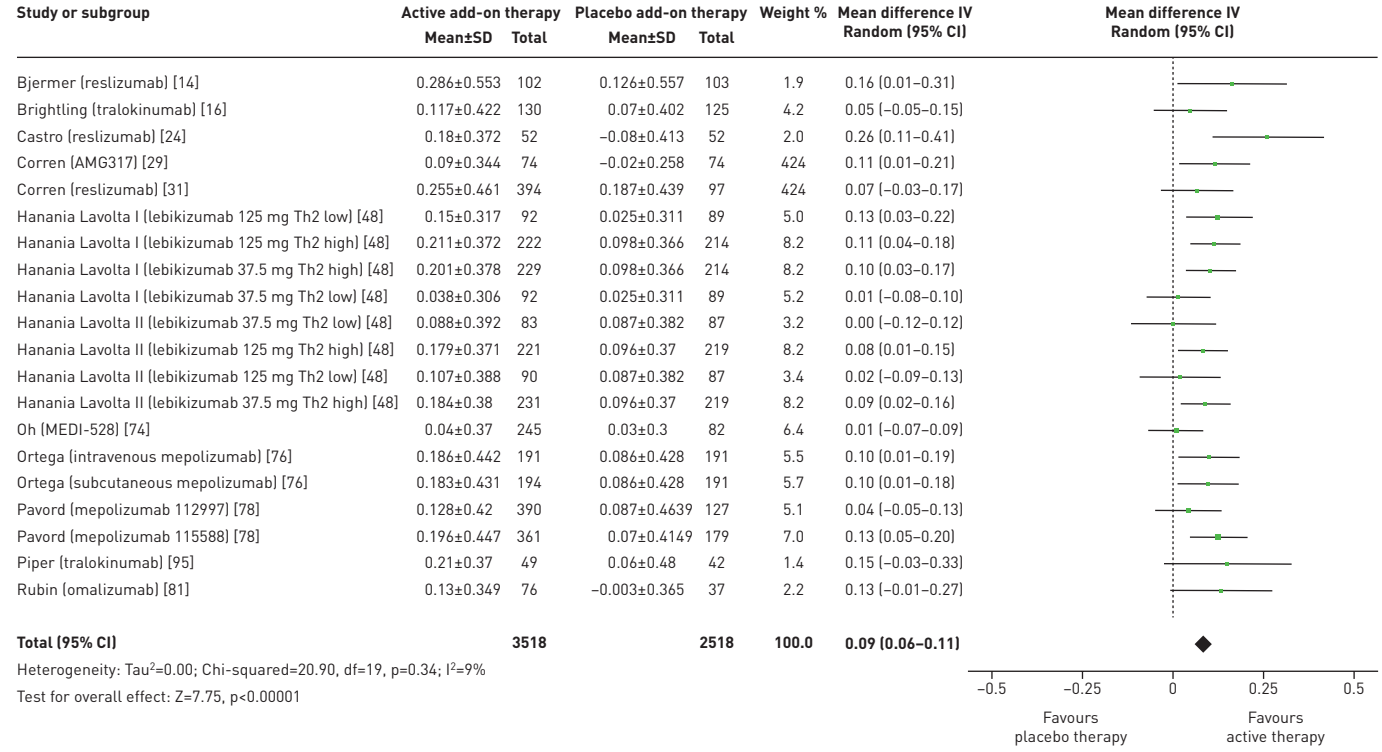


FIGURE 3 Meta-analysis and forest plot of treatment effect on forced expiratory volume in 1 s (FEV_1). Meta analysis is performed using the inverse variance (IV) method with random effects.

I^2=0%; p=0.21). As a result, while we consider the difference in FEV_1 variance between studies to be most likely attributable to adherence assessment, we cannot rule out the possibility of other systematic differences with the data available.

Modelling the effect of adherence variations on study outcomes

Three scenarios of adherence assessment were conceived, one in which there was no assessment of adherence to maintenance ICS/LABA at any stage, a second model estimating the effect of screening for adherent patients during the run-in period only, and a third model estimating the effect of only assessing adherence to maintenance ICS/LABA during the study period (figure 2). Each of these models suggests that a significant component of the variance in reported FEV_1 outcomes is attributable to variations in ICS/LABA adherence. In scenario 1, the estimated variance due to adherence variations was 0.083 L^2, compared to a total pooled variance in the trials which did not assess adherence of 0.168 L^2. This implies that accurate assessment of adherence could eliminate up to 50% of variance in these studies. Similarly, the estimated variance due to adherence changes in scenarios 2 and 3 was 0.04 L^2 and 0.06 L^2 respectively, implying that in each possible model, more than 20% of variance could be attributable to unmonitored adherence variations.

Figure 5 illustrates the potential benefits of adjusting for adherence to ICS/LABA both before and during the study. While the mean difference between groups was unaffected, the reduction in outcome variance due to correcting for adherence means that clinically important differences can be detected with greater confidence.

Figure 6 demonstrates the improvement that could be achieved in those trials in our review which did not assess adherence. Based on model scenario 1, we estimate the reduction in variance in FEV_1 which would be achieved if adherence was controlled for. This reduction was applied to the published results to produce a forest plot of corrected results. In this scenario, correcting for adherence led to fewer nonsignificant results (two nonsignificant findings compared to five in the original studies) and a considerable reduction in the pooled confidence interval.

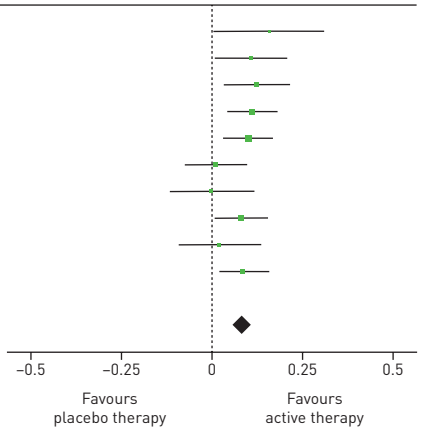
Although mean differences between groups did not change in our model, the reduction in SD due to adjusting for adherence resulted in an increased standardised mean difference in the meta-analysis of 0.34 (95% CI 0.16–0.3) in the corrected analysis, compared to 0.23 (95% CI 0.14–0.32) in the uncorrected, for those trials which did not report adherence.

a)

Study or subgroup	Active add-on therapy Mean±SD	Total	Placebo add-on therapy Mean±SD	Total	Weight %	Mean difference IV Fixed (95% CI)
Bjermer (reslizumab) [14]	0.286±0.553	102	0.126±0.557	103	3.2	0.16 (0.01–0.31)
Brightling (tralokinumab) [16]	0.117±0.422	130	0.007±0.402	125	7.1	0.11 (0.01–0.21)
Hanania Lavolta I (lebikizumab 125 mg Th2 low) [48]	0.15±0.317	92	0.025±0.311	89	8.7	0.13 (0.03–0.22)
Hanania Lavolta I (lebikizumab 125 mg Th2 high) [48]	0.211±0.372	222	0.098±0.366	214	15.2	0.11 (0.04–0.18)
Hanania Lavolta I (lebikizumab 37.5 mg Th2 high) [48]	0.201±0.378	229	0.098±0.366	214	15.2	0.10 (0.03–0.17)
Hanania Lavolta I (lebikizumab 37.5 mg Th2 low) [48]	0.038±0.306	92	0.025±0.311	89	9.0	0.01 (–0.08–0.10)
Hanania Lavolta II (lebikizumab 37.5 mg Th2 low) [48]	0.088±0.392	83	0.087±0.382	87	5.4	0.00 (–0.12–0.12)
Hanania Lavolta II (lebikizumab 125 mg Th2 high) [48]	0.179±0.371	221	0.096±0.37	219	15.2	0.08 (0.01–0.15)
Hanania Lavolta II (lebikizumab 125 mg Th2 low) [48]	0.107±0.388	90	0.087±0.382	87	5.7	0.02 (–0.09–0.13)
Hanania Lavolta II (lebikizumab 37.5 mg Th2 high) [48]	0.184±0.38	231	0.096±0.37	219	15.2	0.09 (0.02–0.16)
Total (95% CI)		**1492**		**1446**	**100.0**	**0.09 (0.06–0.11)**

Heterogeneity: Chi-squared=8.53, df=9, p=0.48; I^2=0%

Test for overall effect: Z=6.17, p<0.00001



b)

Study or subgroup	Active add-on therapy Mean±SD	Total	Placebo add-on therapy Mean±SD	Total	Weight %	Mean difference IV Random (95% CI)
Castro (reslizumab) [24]	0.18±0.372	52	–0.08±0.413	52	5.0	0.26 (0.11–0.41)
Corren (AMG317) [29]	0.09±0.344	74	–0.02±0.258	74	10.2	0.11 (0.01–0.21)
Corren (reslizumab) [31]	0.255±0.461	394	0.187±0.439	97	10.1	0.07 (–0.03–0.17)
Oh (MEDI-528) [74]	0.04±0.37	245	0.03±0.3	82	13.6	0.01 (–0.07–0.09)
Ortega (intravenous mepolizumab) [76]	0.186±0.442	191	0.086±0.428	191	12.1	0.10 (0.01–0.19)
Ortega (subcutaneous mepolizumab) [76]	0.183±0.431	194	0.086±0.428	191	12.3	0.10 (0.01–0.18)
Pavord (mepolizumab 112997) [78]	0.128±0.3899	387	0.087±0.4226	126	12.8	0.04 (–0.04–0.12)
Pavord (mepolizumab 115588) [78]	0.196±0.447	361	0.07±0.4145	179	14.4	0.13 (0.05–0.20)
Piper (tralokinumab) [95]	0.21±0.37	49	0.06±0.48	42	3.7	0.15 (–0.03–0.33)
Rubin (omalizumab) [81]	0.13±0.349	76	–0.003±0.365	37	5.7	0.13 (–0.01–0.27)
Total (95% CI)		**2023**		**1071**	**100.0**	**0.09 (0.06–0.13)**

Heterogeneity: Tau^2=0.00; Chi-squared=12.13, df=9, p=0.21; I^2=26%

Test for overall effect: Z=5.03, p<0.00001

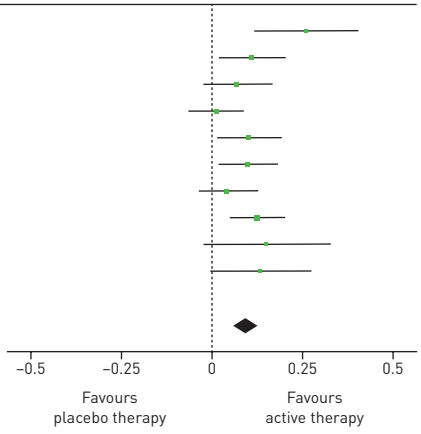


FIGURE 4 Forest plots of differences in forced expiratory volume in 1 s (FEV_1) for studies which a) did and b) did not report monitoring of adherence to inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) therapy. Meta analysis is performed using the inverse variance (IV) method, employing fixed or random effects as appropriate. The pooled mean difference is identical for both sets of studies; however, those reporting adherence assessment have notably lower variance both within studies and between studies.

The influence of adherence variations on the power to detect a clinically significant difference of 0.1 L in FEV_1 was estimated. SDs for the change in FEV_1 from baseline for the studies included in the systematic review ranged from 0.31 to 0.55 (figure 3). Using values for sample size and common SD representative of those found in the systematic review (n=250, pooled SD=0.37 L), we could expect a power of ~55%. Based on our model, assessing adherence throughout the study could lead to an increase in power to ~85% (figure 7). Similarly, the sample size required to detect a mean difference of 0.1 L with 80% power would be reduced from ~450 to 220 participants.

Discussion

There has been a proliferation of novel add-on therapies for severe asthma [96]. However, many of these medications are expensive and access may be limited in certain healthcare systems. One of the major drivers of the cost of these novel medicines is the high cost of drug development. Phase 3 studies typically must enrol several hundred participants in order to demonstrate important differences. These large sample sizes are required to compensate for large variances in outcome measures such as lung function. This study attempted to assess whether this large variance could be accounted for by variations in adherence to maintenance therapy.

In this systematic review involving 22 174 patients with unstable moderate to severe asthma despite GINA step 3–4 therapy, we identified that adherence to maintenance ICS/LABA therapy was assessed in only 20 trials, of which only 11 employed semi-objective methods, while none of the trials identified used an objective assessment of adherence (*e.g.* electronic monitoring). Furthermore, despite inhaler technique being

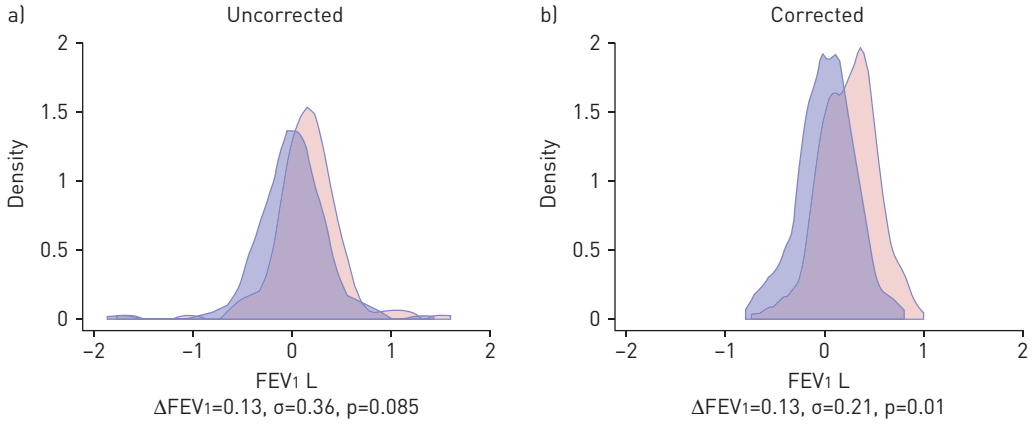


FIGURE 5 The benefit of removing variance due to adherence changes. Simulated data showing the potential improvements that can be achieved by correcting for adherence variations. a) The uncorrected plot shows simulated distributions of change in forced expiratory volume in 1 s (FEV_1) for placebo (blue) and treatment (red) groups generated using representative values from the studies in our review (mean difference±SD=0.13 ±0.36 L, n=200). b) The corrected plot shows the same estimated distributions where excess variance of 0.08 L^2 due to adherence changes has been removed. As a result of adherence variations, the mean difference in the uncorrected case does not reach the threshold for statistical significance, whereas in the corrected case the difference is highly significant (p=0.01).

a significant part of inhaler adherence, its assessment was documented and reported in only three studies (3%). This suggests that there is a potential for participants recruited to these studies to have shown suboptimal adherence or have poor inhaler technique prior to and during RCTs of asthma add-on therapy.

Failure to assess adherence to maintenance asthma therapy during screening risks including patients with "difficult to treat" asthma and may introduce a significant additional variance with subsequent higher SDs in clinical endpoints. Inadequate assessment of adherence to maintenance ICS/LABA therapy during trials of add-on treatment also risks adding greater variance in outcomes as patients' month-to-month adherence may change during the study. These patterns of adherence behaviour may have an appreciable effect on study power and may result in significant extra costs due to the larger sample sizes required to overcome additional variance arising from adherence variations.

Recent work by Sulaiman *et al.* [5] and others [97] has identified several methods to increase adherence to inhaled therapy in asthma. In reality, however, it may be undesirable, not to mention highly impractical, to completely exclude patients with suboptimal adherence from trials. Nonetheless, given the significant

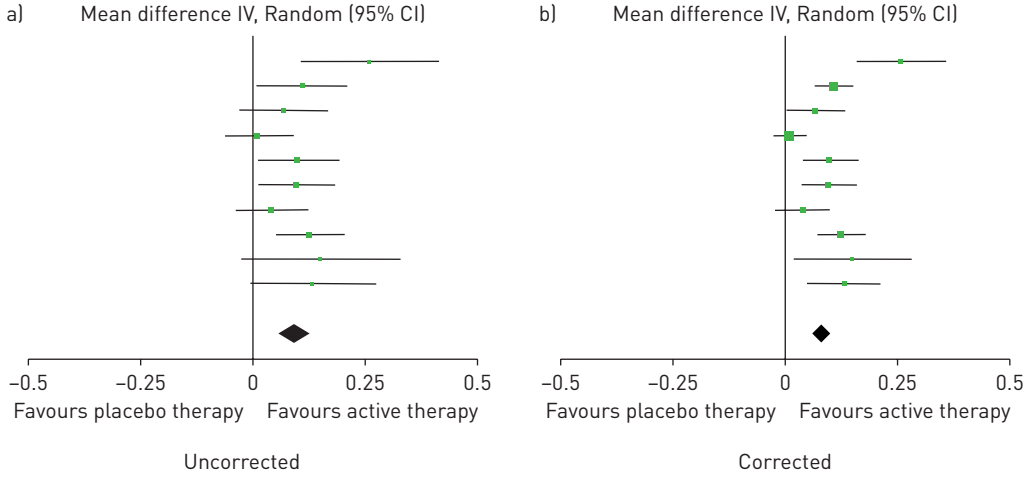


FIGURE 6 Potential improvements in study power with adherence monitoring. a) Reported differences in forced expiratory volume in 1 s (FEV_1) for those studies which did not assess adherence to maintenance therapy. b) The same forest plot where the estimated variance due to adherence variations has been removed. Three studies reporting negative results in fact achieve significant differences in FEV_1 under our model. Note that all effect sizes are unchanged in our model, because inhaled corticosteroid/long-acting β_2-agonist adherence variations are assumed to affect both placebo and active patients equally. IV: inverse variance method.

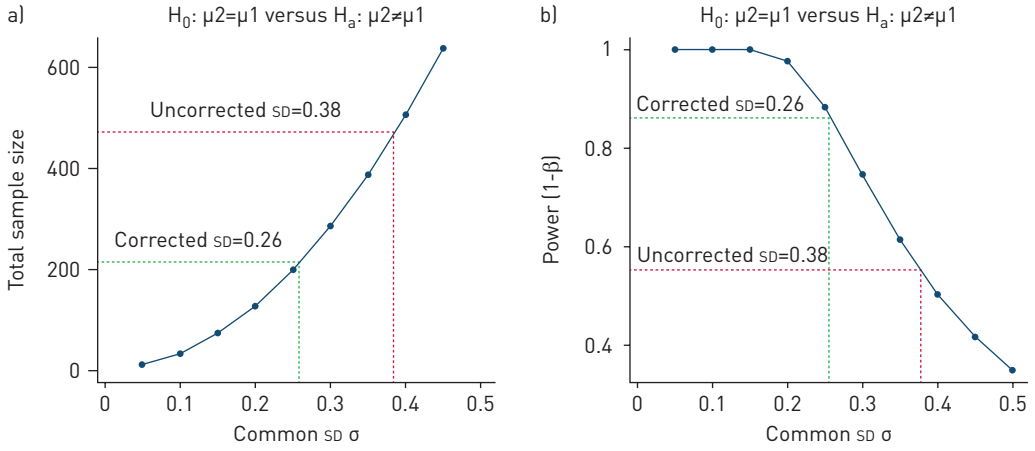


FIGURE 7 Improvements in sample size and study power due to adherence monitoring. a) Sample sizes required to detect a difference of 0.1 L in forced expiratory volume in 1 s (FEV_1) as a function of the common SD. The mean pooled SD for all studies in our review was 0.38, corresponding to a sample size of ~450. Correcting for adherence variations may potentially reduce the pooled SD to 0.26 L, resulting in a reduction in sample size of >50%. b) Power to detect an FEV_1 difference of 0.1 L as a function of pooled SD for a representative sample size (n=250). Correcting for adherence changes results in an increase in power from 55% to ~85%.

potential for confounding and loss of power, efforts should be made to control for adherence variations wherever possible throughout trials. A number of electronic monitors are now available for assessing adherence to inhaled therapy, such as the INCA [98] and Propeller [99] devices, which allow researchers to correct for the effect of adherence variations in trial outcomes. While the use of such devices throughout a lengthy trial may add to study costs, this additional expense is likely to be heavily outweighed by the potential reduction in sample sizes required.

Meta-analysis of FEV_1 outcomes shows that trials which assessed adherence to ICS/LABA displayed significantly lower variance in FEV_1 and achieved greater power to detect meaningful differences. Because these trials do not report data on the levels of adherence to maintenance ICS/LABA therapy, we performed modelling experiments on the impact of assessing adherence during the run-in phase and trial phase of the study. The results demonstrate that a significant proportion of variance in outcomes could be attributed to variation in ICS/LABA adherence. These data further suggest that study power may potentially be doubled and sample size halved, thereby lowering drug development costs, if adherence to current therapy is controlled for, both before and during trials of add-on asthma therapy.

Strengths and limitations

To our knowledge this is the first systematic review of clinical trials assessing asthma add-on therapies. Risk of bias assessment showed that the majority of studies are at low risk of selection, detection and biases associated with blinding. During the timescale of this review, incorporating trials published from 1995 through to 2017, changes in asthma guidelines, asthma study outcomes and guidelines of reporting RCTs have occurred, perhaps contributing to the limited information available to enable further meta-analysis. The review is also limited by inconsistencies in the reporting of outcomes. In particular, a wide range of definitions of asthma exacerbations and severe inconsistency in reporting make it difficult to meaningfully compare this outcome across studies. An effort to standardise asthma clinical outcomes for future clinical trials to enable comparison should be made internationally. For example, is it more useful to assess absolute changes in FEV_1 compared to changes in per cent predicted or should both values be reported to enable data transparency? Incorporating objective measures of adherence into the methodology of conducting clinical trials is challenging because most of the available methods of assessing adherence do not yet have the ability to assess inhaler technique. To overcome these limitations, the first crucial step is to develop validated, objective methods that assess the timing of inhaler use as well as inhaler technique.

Our modelling of the effect of adherence assessment on outcomes was also limited by the near total absence of actual adherence data in the included trials. As a result, while we attribute differences in variance and study power to the benefit of controlling for adherence, we cannot verify this assumption with reference to actual adherence data. Similarly, while we think it reasonable to attribute the reduction in FEV_1 variance to adherence assessment, we cannot rule out other systematic differences between trials that did and did not assess adherence which may account for this variation.

Conclusion

The results of this study indicate that less than a quarter of trials assessing asthma add-on therapy assessed adherence to ICS/LABA therapy prior to randomisation or monitored adherence throughout the trial. Furthermore, none of the studies which assessed adherence employed a truly objective method. Incorporating objective inhaler adherence assessment in the conduct of clinical trials of add-on therapy will allow researchers to control for variations in adherence to maintenance therapy, with a resultant significant decrease in variance of outcomes. This would ultimately enable smaller, more cost-effective studies to be conducted.

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