



Efficacy versus effectiveness trials: informing guidelines for asthma management

David Price^a, Elizabeth V. Hillyer^b, and Thys van der Molen^c

Purpose of review

Randomized controlled trials, known as efficacy trials and long considered the gold standard for evidence-based asthma guidelines, are designed to test whether interventions have a benefit for selective patient populations under ideal conditions. The goal of pragmatic trials and observational studies instead is to understand real-life efficacy, known as effectiveness. This review summarizes the strengths and limitations of efficacy and effectiveness trials, results of recent effectiveness trials in asthma and initiatives promoting effectiveness research.

Recent findings

Recent pragmatic trials and observational studies have examined outcomes of interventions for diverse real-life patient populations, including smokers and patients with variable adherence, inhaler technique and baseline asthma control. Study results challenge practice guidelines regarding relative effectiveness of leukotriene receptor antagonists and inhaled corticosteroids (ICS); supplement guidelines with regard to effectiveness of interventions in smokers; and begin to address gaps in guidelines regarding choice of ICS and inhaler device. Initiatives are ongoing to refine methods of observational research and to harmonize asthma outcomes for better integration of results from all types of trials.

Summary

Results of pragmatic trials and observational studies are an important component of the evidence needed to inform guideline recommendations and decision-making by healthcare providers, patients and policymakers.

Keywords

asthma, effectiveness, efficacy, pragmatic, real life

INTRODUCTION

Most asthma management guidelines use similar rankings for categorizing the evidence to support their recommendations, listing randomized controlled trials (RCTs) at the top as the gold standard for evidence of therapeutic efficacy, meta-analyses at or near the top, and nonrandomized and observational studies two or more rungs below [1–3]. Although classical RCTs, also known as explanatory or efficacy trials, may shed light on possible mechanisms in disease pathogenesis and are important to test the efficacy of therapies in ideal circumstances, their limitations are increasingly recognized with regard to characterizing real-life efficacy, known as effectiveness [4[•],5[•],6,7[•]]. Instead, effectiveness trials, including pragmatic trials and observational studies, aim to evaluate treatment outcomes for real-life patients in real-life clinical settings [5[•],8[•]].

Efficacy trial results may be overgraded by guideline reviewers when applied to make recommendations for everyday clinical practice, in which

conditions are less idealized and patient populations much more diverse than in RCTs [4[•],6,9,10[•]]. Moreover, cost-effectiveness determinations are best made using real-life data, as payors want to understand the true cost impact of utilizing interventions in real life [7[•],11].

This review summarizes the strengths and limitations of efficacy and effectiveness trials. Examples of current effectiveness trials in asthma

^aAcademic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, ^bResearch in Real Life Ltd, Cambridge, UK and ^cDepartment of General Practice, Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to David Price, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK. Tel: +44 1224 554588; fax: +44 1224 550683; e-mail: david@rirl.org

Curr Opin Allergy Clin Immunol 2013, 13:50–57

DOI:10.1097/ACI.0b013e32835ad059

KEY POINTS

- Long considered the gold standard for evidence-based asthma guidelines, the results of classical RCTs, also known as explanatory or efficacy trials, may be overgraded when applied to make broad recommendations for everyday clinical practice, in which conditions are less idealized and patient populations much more diverse than in RCTs.
- Pragmatic trials and observational studies provide important information characterizing real-life efficacy, known as effectiveness, that complements the results of RCTs and can answer practical clinical questions for healthcare providers, patients and policymakers.
- Results of recent pragmatic trials and observational studies of patients with asthma 1) challenge practice guidelines with regard to the relative effectiveness of LTRAs and ICS; 2) are beginning to address gaps in guidelines with regard to the choice of ICS and inhaler device; and 3) complement guideline recommendations with regard to understanding effectiveness of interventions in smokers.
- Several governmental and nongovernmental policy groups are actively promoting effectiveness research in Europe and the United States, and payors are increasingly looking at real-life research as an important component of the evidence base to guide decision-making.
- Guideline writers should take into account the strengths and weaknesses of data from both efficacy and effectiveness trials when formulating evidence reviews for guideline recommendations.

are reviewed to illustrate the importance of this work and how these trials differ from efficacy trials.

EFFICACY VERSUS EFFECTIVENESS TRIALS: STRENGTHS AND LIMITATIONS

‘Hierarchies place RCTs on an undeserved pedestal ... Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches’. – Sir Michael Rawlins, Harveian Oration, 2008 [12]

The ideal (pure) classical RCT lies on the opposite end of a continuum from the ideal (pure) pragmatic trial. Classical RCTs, or efficacy trials, are designed to maximize internal validity in order to test whether an intervention has a benefit under ideal circumstances, usually as compared with placebo. Instead, pragmatic trials are designed to compare interventions under usual clinical

circumstances, thereby to maximize applicability of findings to real-life issues and inform everyday clinical decision-making [13,14[■],15,16[■]]. Table 1 summarizes the features of RCTs as compared with pragmatic trials in asthma using the 10 domains of the pragmatic-explanatory continuum indicator summary (PRECIS) tool, developed to help trialists assess where trials lie on this continuum [17].

The major limitation of classical RCT design is the sacrifice of external validity (generalizability) in favor of maximizing internal validity. The design of asthma RCTs typically incorporates frequent patient monitoring, including lung function testing, and patient instruction in using treatment technologies such as inhalers, which cannot easily be duplicated in everyday practice, in which time and equipment limitations are operative, and clinic visit frequency, treatment adherence and inhaler technique are often suboptimal. Moreover, many clinically important patient populations are not studied in RCTs, including smokers and those with ‘insufficient’ bronchodilator reversibility, serious comorbidities and adherence or other psychosocial problems [5[■],18]. Only a small minority of patients with asthma are eligible for asthma RCTs, estimated at 3.3% in one study [19].

In short, the patients and procedures of efficacy trials occur outside the ecology of normal care, and many important issues that influence asthma control in real life, summarized in Fig. 1, are usually not captured in an RCT design [18,20,21[■],22,23]. Moreover, the usual 4-week to 8-week length of RCTs does not provide information to guide long-term asthma management strategies. These limitations may then be incorporated, and hidden, in meta-analyses of RCTs [24].

The goal of pragmatic trials is to assess treatment outcomes in the complete context of real-life clinical practice. Pragmatic trial design incorporates relevant practice settings, everyday (usual) clinical care, a heterogeneous patient population and outcomes relevant to interested parties, including patient-oriented measures, with a duration sufficient to answer practical clinical questions for healthcare providers, patients and policymakers.

By focusing on external validity (generalizability), the naturalistic design of pragmatic trials necessarily sacrifices internal validity. A challenge in conducting pragmatic trials is maintaining patient follow-up without the close monitoring that occurs in an RCT. Even the knowledge of being studied or observed can alter behavior, a phenomenon known as the Hawthorne effect [25]. Introducing more monitoring and engagement than usual care can eliminate differences between two interventions being tested, particularly with regard to

Table 1. Efficacy to effectiveness continuum for clinical trials in asthma

PRECIS domain	Explanatory (efficacy) trial	Pragmatic (effectiveness) trial
Patient eligibility criteria	Stepwise selection, excluding patients with <12% bronchodilator reversibility, PEF variability <20%, FEV ₁ <50% or ≥80%, poor adherence, suboptimal inhaler technique, >10 pack-years cigarette exposure, serious comorbidity	All patients with physician-diagnosed asthma, regardless of comorbidities or smoking status, with exclusions for reasons of safety, e.g. pregnancy, respiratory infection Specify important subgroups for study, e.g. smokers
Interventions and expertise		
Experimental intervention- flexibility	Inflexible: intervention to be administered according to strict study instructions	Highly flexible/naturalistic: intervention tailored according to symptoms, side effects, usual practice
Experimental intervention-practitioner expertise	Expert clinicians with special interest in asthma	All healthcare providers who see patients with asthma, full range of clinical settings
Comparison intervention-flexibility	Inflexible, often placebo	Best alternative comparator in current use or other usual practice
Comparison intervention-practitioner expertise	Expert clinicians with special interest in asthma	All healthcare providers who see patients with asthma, full range of clinical settings
Follow-up and outcomes		
Follow-up intensity	Scheduled study visits, more frequent and longer than possible in usual clinical practice	No formal predefined follow-up; use of information from EHRs and/or administrative databases
Primary trial outcome	Emphasis on objective measures, e.g. lung function	Clinically meaningful patient-oriented measure, e.g. quality of life, exacerbation rate
Compliance/adherence		
Patient adherence to intervention	Adherence closely monitored; good inhaler technique required	Unobtrusive or no monitoring
Practitioner adherence to study protocol	Close monitoring of trial conduct	Unobtrusive or no monitoring
Analysis		
Analysis of primary outcome	Intention-to-treat analysis supplemented by per-protocol analyses	All patients included (intention-to-treat analysis)

EHRs, electronic health records; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; PRECIS, pragmatic-explanatory continuum indicator summary. Adapted from [4[■], 17].

patient-reported measures, because the experience of receiving care can have beneficial effects on subjective outcomes [26[■], 27]. This fact can be used to advantage, however. For example, in a recent pragmatic trial comparing twice-daily mobile phone based or paper-based self-monitoring, with both groups receiving the same structured clinical and educational intervention, the changes in asthma control at 6 months were similar in the two treatment groups [26[■]]. The authors thus concluded that mobile technology did not improve asthma control or self-efficacy beyond the provision of clinical care to guidelines standards; moreover, the mobile technology was not cost-effective.

Another challenge of pragmatic trial design is detecting what is often a small difference in

treatment effect between two interventions under conditions of usual clinical care; this requires either a large study population or use of a validated survey instrument that is very sensitive to the treatment effect [16[■]]. In addition, the lack of blinding may introduce bias in patient self-assessments because of preconceived notions about intervention effectiveness; therefore, the concurrent use of objective outcome measures, such as test results and survival, is recommended [16[■]]. The increasing availability of routine electronic health records (EHRs) and the potential for cross-linking with anonymized medical databases may facilitate the implementation of pragmatic trials, an approach currently being tested in the UK in two randomized evaluations of accepted choices in treatment (REACT) trials [28[■]].

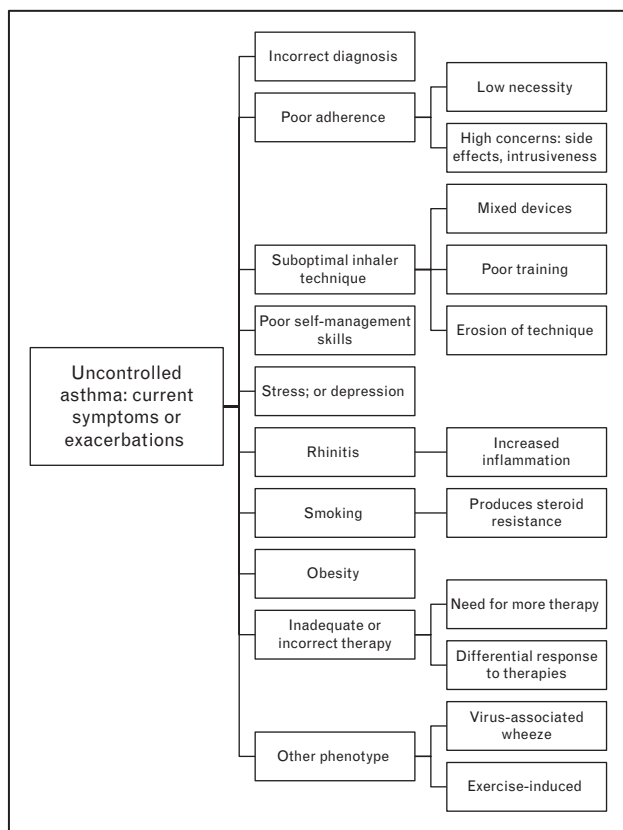


FIGURE 1. Reasons for poor asthma control in real-life clinical practice, few or none of which is accounted for in most classical randomized controlled (efficacy) trials. Adapted from [20].

OBSERVATIONAL STUDIES: STRENGTHS AND LIMITATIONS

Observational studies, including cohort, case-control and cross-sectional studies, can be used to study real-life effectiveness, safety and tolerability of interventions over long periods of time in large patient populations; data collection can be prospective or retrospective from sources, including EHRs and anonymized medical research, pharmacy and administrative claims databases. Studies comparing observational studies with RCTs on the same topic have concluded that well designed observational studies can provide answers similar to those of RCTs [29,30]. Moreover, results of observational studies can be obtained more quickly and often at a lower cost than RCTs, although rigorously conducted observational studies are not inexpensive.

The limitations of observational studies include the potential for bias, introduced if there is flawed information or patient selection, and for confounding [31]. Confounding occurs when an unidentified factor is responsible for an effect or outcome that is mistakenly attributed to another factor. Moreover,

missing data in observational studies can limit the interpretation of findings. Patients included in observational studies are not randomly assigned to interventions, and patients and healthcare providers are not blinded.

The validity of observational studies is strengthened by the *a priori* (namely, before observation or study) identification of patient characteristics and testing rules, as well as the *a priori* identification of potential confounding factors, based on knowledge of the condition and intervention under study; registration of observational studies as for RCTs is encouraged [32]. Analytic methods to reduce the possibility of bias or confounding include propensity score matching or matched cohort analyses using key patient and disease-related characteristics, and applying statistical adjustments for confounding factors.

For patients with asthma, clinically important indicators of asthma control and severity that can be used for matching include demographic characteristics (age and sex) and baseline frequency of exacerbations (hospitalizations or oral corticosteroid prescriptions), asthma consultations, use of short-acting β_2 -agonist and inhaled corticosteroid (ICS) dose [33]. The frequency of nonasthma general practitioner (GP) consultations is a factor predictive of future asthma control (specifically exacerbations), particularly among nonadherent patients [34]. Work is ongoing by several research groups to define and validate database indicators of asthma control and medication adherence [35[■],36[■],37].

Detailed information on the strengths and limitations of efficacy and effectiveness trials [5[■],12,24,31] and guidelines for reporting pragmatic trials and observational studies have been published [15,38].

RECENT EFFECTIVENESS TRIALS IN ASTHMA

Recent pragmatic trials and observational studies have examined outcomes of interventions for diverse real-life patient populations, including smokers and patients with variable adherence, inhaler technique and baseline asthma control.

Choice of controller therapy

Asthma management guidelines list ICS as the most 'effective' controller (preventer) therapy for adults and older children; leukotriene receptor antagonists (LTRAs) are listed as a secondary option for initiating controller therapy (at step 2) in the United States (US) and Global Initiative for Asthma (GINA) guidelines [1,3] and as a secondary option for add-on

therapy to ICS (at step 3) in US, UK and GINA guidelines [1–3]. The results of a recent meta-analysis of asthma RCTs support the superior efficacy of ICS monotherapy compared with antileukotrienes in adults and children [39[■]]. A second meta-analysis comparing long-acting β 2-agonist (LABA) with LTRA as an add-on therapy to ICS reports mostly modest differences for adults, and no conclusions were drawn for children [40[■]].

The results of recent pragmatic trials and observational studies provide a fuller picture of the effectiveness of LTRA in clinical practice and challenge asthma guideline recommendations. In two pragmatic trials conducted in the UK primary care setting, a patient-oriented measure of quality of life (QoL) was equivalent at 2 months for LTRAs compared with ICS as monotherapy and LABA as an add-on to ICS for adults with physician-diagnosed asthma [41[■]]. At 2 years, equivalence in QoL was not proven; however, asthma control scores and exacerbation rates were comparable. Adherence rates with LTRA were 65 and 74% as compared with 41 and 46% with ICS in the two trials, respectively. Similarly, better adherence with LTRA than ICS was observed in a matched cohort study [42[■]] of 227 children and adolescents (2–17 years old); outcomes were similar or better for patients prescribed LTRA, including a significantly lower rate of hospital admissions for asthma and rescue β 2-agonist use than in the ICS cohort.

The findings of these studies suggest that, in real-life clinical practice, better patient adherence with an oral (LTRA) than inhaled medication (ICS) may eliminate the efficacy advantage of ICS seen in the idealized settings of RCTs. Moreover, patients with rhinitis may benefit from systemic antileukotriene effects, and smokers may respond better to LTRAs than ICS [8[■], 41[■]]. In another larger database study [43[■]] of children ages 5–15 years ($n = 27\,355$), the risk of asthma exacerbations was significantly lower with LTRA than ICS for patients with no exacerbations at baseline but was similar for those with at least one exacerbation at baseline. Interestingly, there were no differences in patient adherence with LTRA and ICS, but the proportion of days covered with prescriptions' supply was higher for LTRA than ICS, suggesting that in practice ICS was being prescribed as an intermittent rather than daily controller.

Choice of inhaled corticosteroid and inhaler device

Asthma guidelines and results of systematic reviews and meta-analyses of RCTs comparing corticosteroids [44,45] and inhaler devices [46,47] provide

little guidance for clinicians faced with several choices when prescribing ICS for patients with asthma. In recent years, ICS have been developed with extrafine particles that show more uniform and deeper airways penetration than the larger particle ICS [48]. Whether distribution of ICS to the peripheral small airways provides additional clinical benefit in asthma is an area of active investigation for which observational studies are ideally suited because of the ability to study large patient populations over long timelines.

In a matched cohort study [33[■]] using a UK primary care database, the adjusted odds of achieving asthma control over 1 year were significantly greater for patients (ages 5–60 years) initiating ICS ($n = 11\,528$) or stepping up dose of ICS ($n = 774$) with extrafine particle beclomethasone rather than the larger particle chlorofluorocarbon-beclomethasone. These results supported those of an earlier, similarly designed study [49] comparing extrafine particle beclomethasone with fluticasone, a larger particle ICS.

Brusselle *et al.* [50[■]] used a prospective cohort study to evaluate the real-life effectiveness of extrafine particle beclomethasone in fixed-dose combination (FDC) with formoterol for adult patients, including those who smoked ($n = 123/619$). They recorded significant improvements in patient-reported and physician-evaluated measures of asthma control over 1 year for nonsmokers as well as for current or ex-smokers. In a small cross-sectional study ($n = 111$) [51[■]], the extrafine beclomethasone–formoterol combination delivered by pressurized metered-dose inhaler (pMDI) provided significantly better asthma control, and at a lower ICS dose, than two larger particle FDC ICS/LABA delivered by dry powder inhaler. Cumulatively, the results of these studies suggest better effectiveness of extrafine particle than larger particle ICS.

Inhaler mishandling and improper inhalation technique are common problems in clinical practice [52[■]]. Guidelines report no differences, based on RCT results, among inhaler types [1–3, 46, 47]; however, this may be because patients in RCTs are well trained to use their inhalers [53[■]]. In real-life studies, some differences begin to emerge, indicating that inhaler device selection likely has a bearing on clinical outcomes. For patients initiating ($n = 56\,347$) or stepping up dose ($n = 9169$) of ICS monotherapy, outcomes in a large cohort study [54] were better with BAIs and dry powder inhalers (DPIs) than pMDIs. Instead, for delivery of FDC fluticasone-salmeterol therapy, results of a matched cohort study [55[■]] of 3134 patients 4–80 years old indicate that patients using a pMDI had better odds of asthma control over 1 year than those using

a DPI. Differences in real-life effectiveness among these devices require closer evaluation in well designed prospective trials. Results of another observational study [56[¶]] indicate that outcomes for patients initiating ICS are better when inhaler device types are the same for both ICS and reliever therapy.

Safety of therapy

Observational studies are useful to track potential adverse effects of interventions. Two long-standing concerns about asthma therapy are whether ICS use in childhood reduces attained adult height and whether long-term use of LABAs is safe. In the observational follow-up study [57[¶]] to the Childhood Asthma Management Program, patients who had received budesonide as prepubertal children reached an adjusted mean adult height 1.2 cm lower than that in the placebo group, indicating that the decrease in attained height associated with ICS therapy was persistent but not progressive since the end of the trial. A larger daily dose during the first 2 years of therapy was associated with a lower height, suggesting that the lowest ICS dose that controls symptoms should be prescribed to children.

With regard to the safety of LABAs, the US Food and Drugs Administration (FDA) has required LABA manufacturers to conduct a total of five clinical trials [58]. These trials are intended to mimic a real-life scenario, and patient eligibility is indeed broad; however, ICS dose titrating is not allowed, and thus the future real-life applicability of the findings is uncertain.

CURRENT INITIATIVES PROMOTING AND SUPPORTING EFFECTIVENESS RESEARCH

Opinion pieces in major journals have called for incorporating effectiveness research into the evidence base [4^{¶¶}, 7[¶], 13, 16[¶]], and several governmental and nongovernmental policy groups are promoting and working to improve effectiveness research. In the United States, recent healthcare legislation has resulted in a new emphasis on comparative effectiveness research and use of patient-centered outcomes, with recent publication of a draft methodology report containing 60 standards to guide patient-centered outcomes research [59–63, 64[¶]]. A US public–private partnership called the Observational Medical Outcomes Partnership (OMOP; <http://omop.fnih.org/>) has been launched with the goal of identifying methods for analyzing observational data drawn from heterogeneous sources, and the Association of the British Pharmaceutical

Industry has published guidance on using real-world data [65].

Initiatives specific to asthma include the Brussels Declaration on Asthma, sponsored by The Asthma, Allergy and Inflammation Research Charity, which called for funding of more ‘real world’ studies [9]. In the United States, an expert working group was convened for the Asthma Outcomes Workshop to standardize clinical research outcomes to permit comparisons across asthma interventional or observational studies [66[¶]]. The Workshop proposals have recently been published [21[¶], 66[¶], 67^{¶¶}]. In a year-end summary of asthma research in 2011, Apter [68[¶]] noted that results of bench research, RCTs and real-world studies have an interwoven relationship in which each study type informs the others, similar to what Rawlins described in 2008 [12].

CONCLUSION

There are valid doubts about whether efficacy trial results are applicable to real-life patients in real-life clinical practice. The results of effectiveness trials provide parallel, and we would argue essential, strands of evidence that should be incorporated into the evaluation process for guideline recommendations. Payors are increasingly looking at real-life research as an important component of the evidence base to guide decision-making. Guideline writers should take into account the strengths and weaknesses of data from both efficacy and effectiveness trials when formulating evidence reviews for guideline recommendations.

Acknowledgements

None.

Conflicts of interest

D.P. has consultant arrangements with Almiral, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz and Teva. He or his research team have received grants and support for research in respiratory disease from the following organizations in the last 5 years: UK National Health Service, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Novartis, Nycomed, Orion, Pfizer and Teva. He has spoken for Almiral, AstraZeneca, Activaero, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Novartis, Merck, Mundipharma, Pfizer and Teva. He has shares in AKL Ltd, which produces phytopharmaceuticals. He is the sole owner of Research in Real Life Ltd and its subsidiary social enterprise Optimum Patient Care.

E.V.H. has served as a consultant for Research in Real Life Ltd. and received payment for manuscript preparation from Teva Sante and Merck & Co.
T.vdM. has served as a consultant for GlaxoSmithKline; received support for travel to meetings from Glaxo-SmithKline; served on boards for GlaxoSmithKline, MSD Pharma, AstraZeneca and Nycomed; and received grant support from AstraZeneca and MSD Pharma.

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