

Asthma Cost-Effectiveness Analyses: Are We Using the Recommended Outcomes in Estimating Value?



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What is already known about this topic? In 2012, the National Institutes of Health convened a panel of experts to propose standardized measurement, collection, analysis, and reporting of health care utilization and cost outcomes in future asthma studies.

What does this article add to our knowledge? This article provides information regarding the use of National Institutes of Health—recommended outcomes and issues that prevent robust cross-study comparison in asthma cost-effectiveness analyses.

How does this study impact current management guidelines? This study provides recommendation to improve the quality of asthma cost-effectiveness analyses that will lead to better estimates of the cost-effectiveness of interventions, allowing for practitioners to be confident in prescribing cost-effective medications/therapies.

BACKGROUND: Asthma medication cost-effectiveness analyses (CEAs) lack the qualitative assessment regarding whether they capture the National Institutes for Health (NIH) 2012 recommended outcomes necessary to allow robust cross-study comparisons.

OBJECTIVE: We aimed to assess the current asthma outcomes used in CEAs and recommend a direction for improvement.

METHODS: We performed a systematic search using electronic databases including PubMed, EMBASE, Tufts CEA registry, Cochrane, and NHSEED from January 2010 through December 2015. Key words included (1) cost-effectiveness, cost-utility, economic evaluation, health economics, or cost-benefit AND (2) asthma. All CEA studies evaluating 1 or more asthma medication were included. Authors assessed each CEA study with respect to

asthma-specific NIH outcome recommendations including core (hospitalizations, emergency department visits, outpatient visits, medication, interventions costs), supplemental (visit categories and work/school absence), and emerging (academic/job-related) asthma outcomes. Besides outcomes of each CEA, issues that could prevent robust cross-study comparison were identified and thematically summarized.

RESULTS: A total of 12 pre-NIH and 14 post-NIH recommendation CEAs were included. Eleven (91.7%) and 14 (100%) of the pre-/post-NIH studies included at least 1 core outcome, respectively. Of the 26 total studies, 7 (26.9%) included asthma-specific outpatient visit categories, 6 (23.1%) included asthma school or work absences, 5 (19.2%) included respiratory health care use, and none of the studies included emerging outcomes. Other issues that hamper cross-study comparison include lack of standardized cost data, time frames, quality-of-life measures, and incorporation of adherence.

CONCLUSIONS: Although the use of NIH-recommended asthma core outcomes has improved, there is still room for improvement in using supplemental and emerging outcomes. To allow robust cross-study comparisons, future work should focus on further standardizing of data sources and methods. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:619-32)

Key words: Asthma; Cost; Effectiveness; Cost-effectiveness; Cost-benefit; Review

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The Global Initiative for Asthma estimates that 1% to 18% of the world's population has asthma. Consequently, the economic burden of asthma is considerable, with latest numbers for the United States ranging from \$18 million to \$37 billion.^{1,2} In the treatment of asthma, medications play a pivotal role. Medications are responsible for most of the financial impact of asthma, especially in Western countries. Therefore, in the current era with continuous rises in health care expenses, the cost-effectiveness of

Abbreviations used

CEA- Cost-effectiveness analysis

ED- Emergency department

GDP- Gross domestic product

HRQOL- Health-related quality of life

NIH- National Institutes for Health

WTP- Willingness to pay

new asthma treatments becomes increasingly important. Cost-effectiveness analyses (CEAs) help to assist decision makers in how to spend their limited budgets in the most efficient way, that is, with maximized health gains (Table I).

Systematic reviews may aid to provide a helpful overview of the cost-effectiveness of all existing treatments. Indeed, previous reviews have systematically assessed and summarized the existing economic evaluations of pharmacological and nonpharmacological asthma treatments.⁴⁻⁷ In general, the quality of the studies seems to be evolving,^{8,9} but even in the latest reviews several shortcomings were identified.^{4,5} To align future asthma cost-effectiveness studies, in 2012 the National Institute of Health (NIH) commissioned a position paper specifying which outcomes had to be included for optimal informative decision making and comparisons, with the goal of standardizing measurement, collection, analysis, and reporting of health care utilization, and cost outcomes in future asthma studies.¹⁰ Ultimately, this standardization will lead to enhanced cross-study comparisons and systematic interpretation of asthma treatment cost-effectiveness data.

In the upcoming years, several innovative, but also highly priced, biological asthma treatments are expected to enter the health care markets for which CEAs are yet to be performed.¹¹ Therefore, it is timely to systematically assess the current state-of-the-art of recent economic evaluations of pharmacologic asthma treatments. In recent years, several new CEAs of asthma medications have been reported.¹²⁻¹⁴ In particular, we were interested in knowing whether recommendations from the asthma NIH workshop¹⁰ have been implemented. The primary objective of this study was to evaluate the literature regarding the use of (NIH workshop—recommended) asthma-specific outcome measures through cross-study comparison of asthma CEAs. The secondary objective was to identify other issues (besides the inclusion of NIH-recommended outcomes) within asthma medication CEAs that prevent robust cross-study

comparison through a thematic analysis and to provide recommendations for future economic analyses.

METHODS**Study design and search strategy**

We performed a systematic search of multiple databases including PubMed, EMBASE, Tufts CEA Registry, Cochrane CENTRAL, and NHSEED from January 2010 through December 2015 using the MeSH terms “asthma” AND “cost-effectiveness analysis,” “cost utility,” “economic evaluation,” “health economics,” or “cost benefit.”

Inclusion and exclusion criteria

We limited the search to articles that were published in English. Only those studies comparing medications for asthma were included. All full CEAs that incorporated decision analytic models were included; models including transition probabilities, simulations, and/or a decision tree were included. Review articles, editorials, study protocols, and letters were excluded. Duplicate studies were identified and removed. A full CEA study was defined as a study that reported both cost and clinical outcomes with at least 1 comparison group.

Outcome assessment strategy. We evaluated the outcomes used in asthma health economic studies in a systematic and transparent way by using the asthma-specific health outcomes recommendations adopted from the “Recommendations for classifying outcome measures for asthma health care utilization and costs for NIH-initiated clinical research: Adult and children populations” set forth by an expert group convened by the NIH and other federal agencies.¹⁰ Among the studies meeting our inclusion criteria, 3 health economists (P.D., C.H.K., and J.F.M.B.) evaluated whether each study was considered to be of sufficient quality using the asthma-specific health outcomes recommendations. A study was considered to be of sufficient quality in terms of health care utilization and cost if at least 1 NIH-recommended core outcome was reported and all 3 evaluators were in agreement regarding the satisfaction of the core outcome reporting. The assessment also included supplemental and emerging outcomes that were used to highlight potential areas that may provide useful insight and future direction for asthma CEAs. Below, we further describe the various categories of outcomes (ie, core, supplemental, and emerging) to focus the discussion surrounding the level of quality regarding asthma CEAs.

Core outcomes. The core outcomes¹⁰ include asthma-specific hospital admissions, emergency department (ED) visits, outpatient visits, medications, and intervention-specific resources. Inclusion of at least 1 of these core outcomes indicates the study to have sufficient quality in terms of using NIH-recommended core outcomes relevant to health care utilization and cost.

Asthma-specific hospital admissions as a core outcome was included if the length of stay, intensive care unit days, and/or alternatively, the average length of stay was reported.¹⁰ ED visits as a core outcome was considered to be included if the ED visit costs are reported. Outpatient visits as a core outcome was included if the count of scheduled, unscheduled, subspecialty, and/or remote visits was reported. Medications were considered to be included if the medication name, dose duration, and utilization by class of medication per person per year were reported. Last, intervention-specific resources as a core outcome were included if supplies (purchase cost), patient costs (time invested for treatment and travel), and/or

TABLE I. Cost-effectiveness analysis basics and definitions

Cost-effectiveness analysis is a formal method for comparing the benefits and costs of clinical intervention to its next best alternative to determine whether it is of sufficient value to adopt or reimburse.³ The main output from a cost-effectiveness study is the incremental cost-effectiveness ratio (ICER), which compares 2 alternative interventions' average cost and effects, which is used to inform decision makers with regard to the intervention's cost-effectiveness relative to the comparator. Typically, cost-effectiveness analysis expresses the denominator (effectiveness) of the ICER as a gain in health from measures such as “years of life,” “death averted,” and “quality-adjusted life-years (QALYs) gained” while the numerator of the ICER may be expressed in terms of the cost associated with the health gain. A special case of cost-effectiveness analysis is cost-utility analysis, in which the effects are measured in terms of years full of health lived (ie, utility), which is expressed using measures such as QALY or “disability-adjusted life-years.”

personnel time (using time-and-motion studies or work sampling) were reported.

Supplemental outcomes. Asthma-specific outpatient visit categories as a supplemental outcome was considered to be included if the outpatient visits reported were categorized as scheduled (comprehensive scheduled health visits, preventive visits, and visits scheduled at least 72 hours in advance), unscheduled (patient-initiated visits resulting from worsening symptoms), subspecialty, or remote visits (e-mail or telephone consults).¹⁰ Respiratory health care use as a supplemental outcome was reported if respiratory visit and admission diagnostic categories match respiratory health care usage (ie, *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 422, 427-428, 460-466, 470-474, 480-487, and 490-519). Asthma school or work absences as a supplemental outcome were considered to be included if the school or work absenteeism (School: days missed from school; Work: work absence days using Work Productivity and Activity Impairment instrument) or presenteeism (School: Teacher Report Form of Child Behavior Checklist; Work: reduced effectiveness while working using Work Productivity and Activity Impairment) was reported.

Emerging outcomes. Asthma-specific remote visits as emerging outcome¹⁰ was considered to be included if the count of e-mail and telephone consults was reported and/or cost of clinical/staff time to handle e-mail/telephone consults was established. Academic outcome measures were considered to be included if studies used teacher ratings of student achievement and/or standardized test scores.

Pre-NIH versus post-NIH CEA comparison. Given that the NIH guidelines were published in 2012, studies that were published pre-NIH (studies published before 2013) and post-NIH (studies published during or after 2013) were compared through descriptive analysis. In addition, pre-NIH and post-NIH CEA studies were compared with regard to having at least 1 core outcome included in the studies.

Thematic qualitative analysis of other issues that prevent robust cross-study comparison. To identify other issues (besides the inclusion of NIH-recommended outcomes) that prevent robust cross-study comparison, we focused on identifying domains within the asthma CEAs article discussion sections, combined with authors' expert opinion. This qualitative approach to identifying other issues preventing robust cross-study comparison provides researchers with scope for further investigation of asthma CEA standardization and recommendations for future CEAs. The thematic analysis process informed by Boyatzis¹⁵ and Attride-Stirling¹⁶ was used to identify initial domains to which issues could be ascribed. This was achieved by an iterative process of reading and re-reading the studies, with particular attention to asthma outcomes, extracted by the authors and inputting them into the Microsoft Excel program to facilitate the mapping of the domains. The authors then considered various options before reaching consensus on broad or organizing domains to which finer-level issues could be allocated.

RESULTS

Literature search results

Two thousand one hundred thirty-seven articles were identified and screened during the primary literature search. Of the 2137 articles, a total of 1398 articles were reviewed. The exclusion of the rest was based on studies that were duplicate studies within each database. A total of 26 articles of the 1398 were comprehensively reviewed and included in our review. The most common reason for excluding studies during the first round of screening was the studies not being asthma-specific studies. The flow diagram of the study selection process is shown in [Figure 1](#). A summary of studies and articles reviewed for asthma CEAs is listed in [Table II](#).

Asthma-specific outcomes

Core outcomes. Overall, the proportion of studies incorporating asthma-specific hospital admissions as core outcomes in pre-NIH (83.3%) and post-NIH (85.7%) CEA studies is high (see [Figure 2](#) for summary and [Appendix](#) for individual

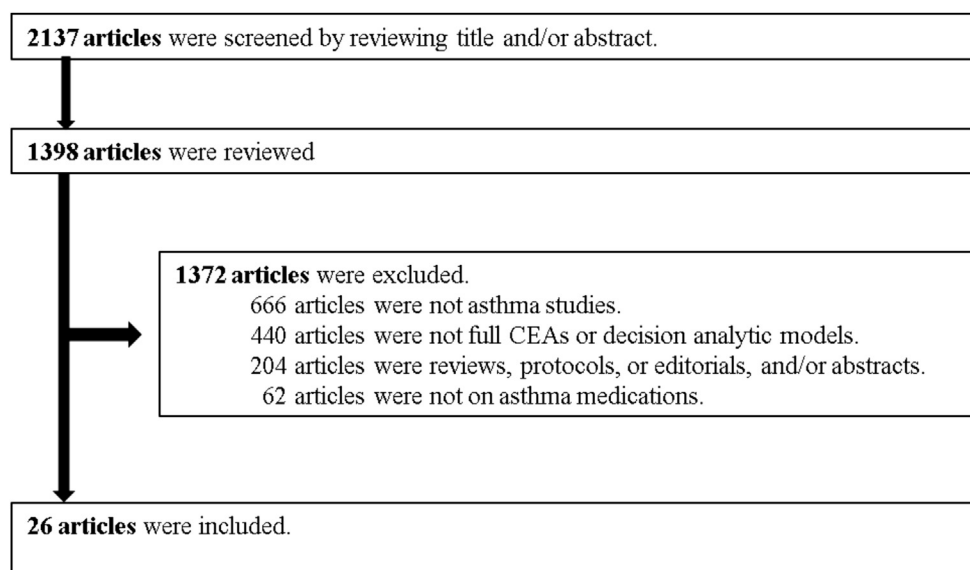


FIGURE 1. Flow diagram of the study selection process.

TABLE II. Studies analyzing the cost-effectiveness of asthma medications

Author (year), country	Model type, perspective, currency	Comparators	Primary effectiveness outcomes	Results	Stated conclusion	Sponsor
Bruggenjurgen et al ¹⁷ (2007), Germany	Model- based CMA and CEA, payer, €	1. BFo fixed 2. BFo 2 single inhalers	1. Days free of asthma	BFo-fixed ICER was € −9.77 per additional day free of asthma	BFo fixed is superior	Chiesi Farmaceutici Spa, Parma, Italy
Campbell et al ¹⁸ (2010), the United States	Model- based CEA, payer, US \$	1. Omalizumab 2. Usual care	1. Hospitalizations 2. ER visits 3. Corticosteroid bursts 4. QALY	Omalizumab has an ICER of \$172,300/QALY compared with usual care	Cost-effectiveness of omalizumab similar to that of other biologics	Novartis Pharmaceuticals Corporation
Kemp et al ¹⁹ (2010), the United Kingdom	Retrospective data—based CEA, payer, £	1. ICS-MDI 2. ICS-BAI 3. ICS-DPI	1. Asthma control measure	DPIs were consistently effective and more costly with an ICER of £1711 per additional controlled patient per year vs MDIs	Real-world ICS effectiveness may vary	Merck & Co. and Teva Pharmaceuticals Ltd.
Dal Negro et al ²⁰ (2011), Italy	Model- based CEA, regional health system, €	1. Omalizumab 2. Usual care	1. QALY 2. Hospitalization 3. Emergency unit/GP/ specialist visit 4. Exacerbations	Adding omalizumab corresponds to €26,000/QALY	Omalizumab cost-effective in difficult-to-treat, persistent allergic asthma	Centro Nazionale Studi Farmacoconomia e Farmacoepidemiologia Respiratoria (CESFAR)
Doan et al ²¹ (2011), Canada	Model- based CEA, hospital, Can\$	1. MDI 2. Nebulizers for albuterol delivery	1. Hospitalization averted	MDIs are dominant in the 90% iterations of Monte-Carlo simulation with −Can\$ 2226.98 admission-averted ICER value	MDI use in ED instead of nebulizers for albuterol delivery yields significant cost savings	None or not reported
Price et al ²² (2011), the United Kingdom	Trial-based CEA, societal, £	1. LTRA 2. ICS as initial control therapy 3. ICS-LABA	1. MiniAQLQ	ICER at 2-mo LTRA is dominant while ICER at 2-y ICS is dominant	LTRA unlikely to be a cost-effective alternative to ICSs	Clement-Clarke International, Merck Sharp & Dohme Ltd, AstraZeneca Ltd, and Respiratory Research Ltd
Wang et al ²³ (2011), the United States	Trial-based CEA, payer and societal, US \$	1. Low-dose fluticasone propionate 2. Montelukast	1. Asthma control days (ACDs) 2. Improvement in FEV ₁ 3. Exacerbations avoided	Fluticasone propionate cost less and was more effective at least 95% of the time	Low-dose fluticasone propionate cost-effective compared with montelukast	National Heart, Lung, and Blood Institute, National Jewish Health, University of Colorado Denver SOM, University of Washington SOM

Andrews et al ²⁴ (2012), the United States	Model- based CEA, health system, US \$	3 ED-based ICS delivery 1. Usual care (recom- mend outpatient follow-up) 2. Uniform ICS prescription 3. Uniform ICS dispensing	1. Follow-up rate after ED visit 2. ICS prescription rate 3. ICS/ED visit/admis- sion cost 4. Prescription fill rate	Total cost saving/100 patients comparing the usual care to the medication-dispensing arm was \$7000	Uniform prescribing or dispensing at time of the ED visit is cost- effective	Supported by the National Research Service Award (HRSAT32HP10255)
Andrews et al ²⁵ (2012), the United States	Model- based CEA, health system, US \$	1. Oral prednisone 2. Oral dexamethasone (prescription) 3. Oral dexamethasone (dispense at discharge)	1. Follow-up rate after ED visit 2. ICS prescription rate 3. ICS/ED visit/admis- sion cost 4. Prescription fill rate	Total cost savings per 100 patients for the dexamethasone prescription arm and the dispensing arm compared with the prednisone arm was \$3500 and \$7000	Use of oral dexamethasone is cost- effective	None or not reported
Dal Negro et al ²⁶ (2012), Italy	Trial-based CUA, payer, €	1. Omalizumab 2. Usual care	1. QALY 2. Hospitalization 3. Emergency unit/GP/ specialist visit 4. Exacerbations	Adding omalizumab translates into incremental cost-utility ratio of €23,880/ QALY gained	Omalizumab cost- effective in difficult-to- treat, atopic asthma	AdRes and Novartis S.p.A.
Gerzeli et al ¹³ (2012), Italy	Trial-based CUA, Italian NHS, €	1. BDP/F 2. Fluticasone propio- nate/salmeterol	1. Weeks lived in SC state 2. Cost for disease management 3. QALW and QALY	BDP/F was cost saving compared with fluticasone propionate/ salmeterol in 63% and 59% of the simulations shown by CUA and CEA	Overall, BDP/F is cost- effective	Chiesi Farmaceutici Spa, Parma, Italy
Stanciole et al ²⁷ (2012), sub-Saharan Africa and South East Asia	Model- based CUA, societal, \$Int	1. Low-dose ICS 2. Low-dose ICS + LABA 3. Medium- dose ICS 4. Medium- dose ICS + LTRA	1. DALY 2. Disease incidence 3. Primary care visit and follow-up costs	Low-dose ICS most cost- effective intervention with average cost per DALY averted of \$2500	Low-dose ICS for mild persistent asthma considered most cost- effective	None or not reported
Norman et al ²⁸ (2013), the United Kingdom	Model-based CEA, UK NHS, £	1. SOC + omalizumab 2. SOC	1. QALY 2. Exacerbation 3. Mortality 4. Adverse effects	ICER for adults and adolescents and children are £83,822 and £78,009, respectively, per QALY gained	ICER values above conventional thresholds	National Institute for Health Research Health Technology Assessment Programme (HTA 10/ 128/01)

(continued)

TABLE II. (Continued)

Author (year), country	Model type, perspective, currency	Comparators	Primary effectiveness outcomes	Results	Stated conclusion	Sponsor
Paggiaro et al ²⁹ (2013), Spain, the Netherlands, and the United Kingdom	Trial-based CEA, payer, € and £	1. High-dose fluticasone propionate/salmeterol 2. Medium-dose fluticasone propionate/salmeterol 3. Extrafine beclomethasone/formoterol	1. QALY 2. GINA-defined control levels 3. Cost for concomitant and rescue medications	High-dose and low-dose fluticasone propionate/salmeterol compared with BDP/F's ICERs are £72,441/QALY and £29,826/QALY in the United Kingdom	Maintaining controlled patients on high-dose fluticasone propionate/salmeterol is not cost-effective in the Netherlands, Spain, and the United Kingdom	Chiesi Farmaceutici Spa, Parma, Italy
Powell et al ³⁰ (2013), the United Kingdom	Trial-based CEA, societal, £	1. MgSO ₄ adjuvant with salbutamol and ipratropium bromide 2. Placebo with salbutamol and ipratropium bromide	1. Asthma Severity Score (ASS) 2. Length of stay in hospital 3. Pediatric QOL	Probability of MgSO ₄ being cost-effective is over 60% at cost-effectiveness threshold of £1000 per unit decrement in ASS and £20,000 per QALY gained	MgSO ₄ is cost-effective in the first hour of treatment as adjuvant therapy to acute episode of severe asthma	National Institute for Health Research Health Technology Assessment Programme (ISRCTN81456894)
Price et al ³¹ (2013), the United Kingdom	Model-based CEA, UK NHS, £	1. efBDP-FOR 2. Fluticasone propionate/salmeterol	1. Asthma exacerbations 2. Asthma control measures 3. Hospitalization 4. Adherence to ICS	Using exacerbation prevention as treatment effective, efBDP-FOR has 75% probability of cost-effectiveness	Switching from fluticasone propionate/salmeterol to efBDP-FOR at equivalent or lower ICS dose is cost-effective	Chiesi UK Ltd
Rodriguez-Martinez et al ³² (2013), Colombia	Model-based CUA, Colombian NHS, COP and £	1. Budesonide 2. Fluticasone propionate 3. Ciclesonide 4. Beclomethasone dipropionate	1. QALY 2. Adherence 3. Asthma exacerbations	The ICER of fluticasone propionate compared with that of BDP was £19,835.28 per QALY	Beclomethasone dipropionate is most cost-effective when the WTP is less than £21,129.22/QALY, otherwise fluticasone propionate is most cost-effective	None or not reported
van Nooten et al ³³ (2013), the Netherlands	Model-based CEA, payer, €	1. Omalizumab 2. Usual care	1. QALY 2. Asthma exacerbations 3. Work loss	The ICER for omalizumab in the observational data and INNOVATE clinical trial was €38,371/QALY and €34,911/QALY	Omalizumab found to continue to have attractive cost-effectiveness ratio	Novartis Pharmaceuticals Corporation
Morishima et al ³⁴ (2013), Japan	Trial-based CUA, societal, US \$	1. Omalizumab 2. Placebo	1. QALY 2. Exacerbation 3. Mortality 4. Proportion of responders	ICER for omalizumab add-on therapy was US \$755,200 (95% CI, \$614,200-\$298,500) per QALY gained compared with placebo	Omalizumab was not cost-effective in Japan	Ministry of Health, Labour and Welfare of Japan and Japan Society for the Promotion of Science

Faria et al ³⁵ (2014), the United Kingdom	Model- based CEA, UK NHS, £	1. Omalizumab 2. Usual care	1. QALY 2. Exacerbation 3. Routine visits 4. Initiation therapy	ICER varies from £30,109 to £57,557 per QALY gained depending on population. Omalizumab likely cost-effective if QALY mapped from asthma-specific measures to the EQ-5D	Omalizumab favorable in severe subgroups and under optimistic assumption regarding asthma mortality and improved QALY	National Institute for Health and Clinical Excellence
Ismaila et al ¹² (2014), Canada	Trial-based CUA, Canadian Public Healthcare, Can\$	1. Fluticasone propionate/salmeterol 2. Fluticasone propionate, no dose change 3. Fluticasone propionate, increased dose	1. QALY 2. Emergency unit/GP/specialist visit 3. Exacerbations	The probability of fluticasone propionate/salmeterol being cost-effective compared with increased dose fluticasone propionate and no dose change fluticasone propionate at \$50,000 per QALY gained was 75%	Fluticasone propionate/salmeterol is cost-effective for patients 12 y and older with inadequately controlled asthma	GlaxoSmithKline Canada, Inc
Martin et al ³⁶ (2014), the United Kingdom and the United States	Model- based CEA, UK NHS and US payer, £ and US \$	1. Extrafine-particle ICS pMDI 2. Standard size—particle ICS pMDI	1. Asthma exacerbations 2. Asthma control measures 3. Hospitalization	Using adjusted odds of risk-domain asthma control and overall control as asthma control measures, extrafine-particle ICS had 92% and 98% probability of cost-effectiveness in the United Kingdom	Extrafine-particle ICS is dominant compared with standard size —particle ICS in both the United Kingdom and the United States	Teva Pharmaceuticals
Petrou et al ³⁷ (2014), the United Kingdom	Trial-based CEA and CUA, UK NHS, £	1. Nebulized MgSO ₄ 2. Placebo	1. ASS 2. Hospitalization 3. Pediatric QOL 4. Days off school	MgSO ₄ had a 67.6% probability of being cost-effective at GBP 20,000 per QALY gained threshold	The probability of MgSO ₄ being cost-effective in severe acute asthma in children is <70%	None or not reported
Willson et al ³⁸ (2014), the United Kingdom	Trial-based CUA, UK NHS, £	1. Tiotropium add-on 2. Usual care (ICS/LABA)	1. Asthma control measures 2. Inpatient resource use 3. Outpatient visits 4. Comedication	Add-on tiotropium therapy resulted in an ICER of £21,906 per QALY gained	Tiotropium add-on is cost-effective for patients with uncontrolled asthma	Boehringer Ingelheim

(continued)

TABLE II. (Continued)

Author (year), country	Model type, perspective, currency	Comparators	Primary effectiveness outcomes	Results	Stated conclusion	Sponsor
Levy et al ³⁹ (2015), Spain	Model- based CUA, Spanish NHS, €	1. Omalizumab 2. Usual care	1. QALY 2. Exacerbations	ICERs for omalizumab were €462.08/exacerbation avoided (347.65-606.22) and €26 864.89/QALY gained (21,632.07-33,859.49)	Omalizumab produces favorable ICERs and acceptable for Spain NHS	Novartis Pharmaceuticals Corporation
Rodriguez-Martinez et al ⁴⁰ (2015), Colombia	Model- based CUA, Colombian NHS, COP and US \$	1. Daily ICS 2. Intermittent ICS	1. QALY 2. Exacerbations	Daily therapy had lower cost of US \$704.62 and greatest gain of QALY (0.9238) for school children	Daily ICS therapy dominates intermittent ICS therapy	NIH Career Development Award

AQLQ, Asthma Quality of Life Questionnaire; *BAI*, breath-actuated metered-dose inhaler; *BDP/F*, beclomethasone dipropionate/formoterol; *BFO*, budesonide-formoterol combination; *Can\$*, Canadian dollar; *CEA*, cost-effectiveness analysis; *CMA*, cost-minimization analysis; *COP*, Colombia pesos; *CUA*, cost-utility analysis; *DALY*, disability-adjusted life-year; *DPI*, dry powder inhaler; *efBDP-FOR*, extrafine-particle beclomethasone dipropionate-formoterol; *ER*, emergency room; *GINA*, Global Initiative for Asthma; *GP*, general practitioner; *ICS*, inhaled corticosteroid; *Inr\$*, international dollar; *LABA*, long-acting beta-agonist; *LTRA*, leukotriene receptor antagonist; *MDI*, metered-dose inhaler; *MgSO₄*, magnesium sulfate; *QALW*, quality-adjusted life weeks; *QALY*, quality-adjusted life-year; *SC*, successful control; *SPI*, salmeterol/fluticasone; *SOM*, School of Medicine.

assessments). A higher proportion of post-NIH studies compared with pre-NIH studies have incorporated asthma-specific ED visits, asthma-specific outpatient visits, asthma-specific medications, and intervention-specific resources. Specifically, 100% of the post-NIH studies have incorporated asthma-specific medication and intervention-specific resources, whereas only 50%^{13,18,19,22,26,27} and 66.7%^{13,19,22-26,41} of the pre-NIH studies incorporated these measures, respectively. Of the 12 pre-NIH and 14 post-NIH studies assessed for sufficiency, with respect to the core outcomes, 11^{13,18-27} (91.7%) and 14 (100%) studies included at least 1 of the core outcome outlined.

Supplemental outcomes. With regard to supplemental outcomes, only 7 studies (26.9%) included asthma-specific outpatient visit categories, 6 studies (23.1%) included asthma school or work absences, and 5 studies (19.2%) included respiratory health care use.

Emerging outcomes. None of the 26 studies (0%) included asthma-specific remote visits or academic or job-related outcomes.

Other issues that prevent robust cross-study comparison

The iterative process resulted in the identification of 5 domains regarding other issues that prevent robust cross-study comparison: Costs and resource use, Adherence, Time, Utility, and Other issues (Table III).

Cost and resource use. Of the 26 studies assessed, 3 studies^{29,39,42} (11.5%) identified issues related to cost and resource use. Most mentioned was the lack of justification of the cost assumptions built into the CEA models. The level of rigor in terms of identifying and justifying the cost assumptions was not satisfactory in certain studies, while these studies relied on sensitivity analyses to protect against such criticism. Two studies^{29,43} emphasized the lack of data regarding hospitalizations due to severe exacerbation and unscheduled visits to general practitioners in clinical trials. Indirect costs were not measured in studies with societal perspective in 2 studies.^{19,32} Two studies^{24,25} used cost data that were appropriate to only 2 states in the United States, thus not being able to generalize the conclusions to the broader population of the United States. Secondary data used to estimate costs where primary data could have been a better source for cost estimation in the CEA model were identified in 1 study.²¹ One study¹³ mentioned the reliance on expert panel opinion regarding resource use and expenditure in their CEAs, as opposed to the use of stronger evidence such as claims data or systematic reviews of cost studies.⁴⁴

Adherence. Of the 26 studies assessed, 5 studies^{22,24,25,36,39} (19.2%) emphasized issues regarding asthma medication adherence. The limitation that was mentioned most was the lack of incorporating adherence levels of asthma medication that could be projected to real-life situations rather than in clinical trial situations, thus identifying the limited generalizability/external validity of the adherence measures used in asthma CEAs.

One²² of the 5 studies mentioned the nonexistence of ideal measures of adherence, which were, in turn, replaced with proxy measures. These studies suggested the use of active/dynamic (electronic) monitoring as ideal measures of adherence and recommended further investigation into identifying strategies/techniques that would improve current measures of adherence.

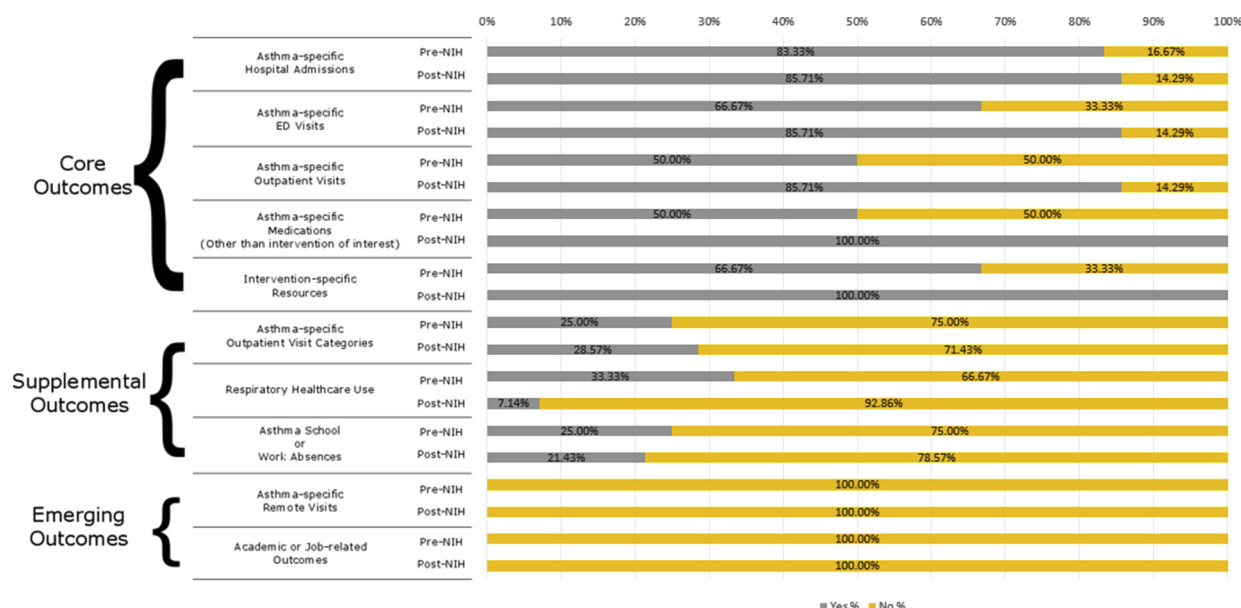


FIGURE 2. Percentage of studies incorporating NIH-recommended asthma outcomes by pre-NIH (N = 12 studies) and post-NIH (N = 14 studies) guideline publication.

In addition, adherence differences between countries and demographic characteristics were highlighted. Some authors³⁶ mentioned that systematic comparison of adherence between countries would allow for a standardized way to map different country-specific measures to each other, which can then be used in comparing the cost-effectiveness of therapies among different countries.

Another important issue that was mentioned was the lack of standardized use of measures that assess asthma compliance and control (ie, Asthma Control Questionnaire or Asthma Control Test), which evaluates patient perception about illness and therapy, current symptoms, adherence, side effects, and control altogether.²²

Time. With regard to the time component of CEAs, 5^{13,18,23,28,31} of the 26 studies identified issues in the evidence base regarding the use of asthma treatment schemes that are not commonly incorporated into CEA models. For example, treatment scheme such as switching from one regimen to another during the course of a patient's life-course is not incorporated into CEA models.

Lack of long-term data regarding health outcomes and costs/consequences has been mentioned by 4 studies.^{12,17,27,30}

Utility. Two^{12,29} of the 7 studies in the domain of utility discussed the issue regarding studies continuing to derive utilities from published studies as secondary data rather than obtaining utility values from primary data collection. There were several novel issues that were identified in the utility domain such as "the inability to use patient-level meta-analysis for estimating health-related quality-of-life (HRQOL) utilities" identified by Campbell et al.¹⁸ Other common issues that were found were the validity and reliability of mapping of asthma-specific quality-of-life measures to the EuroQol five-dimensional questionnaire or the 36-item short form health survey,¹² the general lack of

HRQOL studies within Asian countries,³⁴ and the lack of using standardized measures for asthma control.²²

Other issues. Within the domain "other," the most discussed and influential issue was the fact that information regarding missing data is not readily available and/or verifiable and rationale for using imputation on the missing subjects were not stated within the CEA outcome measure inputted into the models. In addition, in 3 studies, the justification of willingness-to-pay (WTP) thresholds based on gross domestic product (GDP) was questioned. Last, 1 study mentioned that there is a general lack of high-quality information regarding childhood asthma.

DISCUSSION

Previous systematic reviews of asthma CEAs have focused mainly on assessing the monetary value of asthma interventions^{4,6} without an emphasis placed on the asthma outcomes used in defining value. This review has thus focused on the use of asthma outcome measures within CEAs, as the primary objective, using the guidelines set forth by the NIH through the asthma outcomes workshop, to provide a unique perspective with regard to assessing the quality of asthma medication CEAs.

Based on the comparison between the pre-NIH and the post-NIH studies, there has been a significant increase in the use of NIH-recommended core outcomes. However, there seems to be potential improvements that can be made in incorporating supplemental and emerging outcomes. None of the emerging outcomes were used in the asthma CEAs, which is likely because studies measuring emerging outcomes such as school ratings have not been conducted⁴⁵ and/or the perspective of the study did not necessitate the use of such values.^{46,47} As asthma health practitioners and researchers continue to make progress in updating, expanding, and modifying the recommendations for asthma CEA research, continuous effort needs to be made in planning,

TABLE III. Thematic analysis of other issues (besides the inclusion of NIH-recommended outcomes) that prevent robust cross-study comparison in asthma CEAs

Cost and resource use (N = 13)	Adherence (N = 13)	Time (N = 10)	Utility (N = 7)	Other (N = 24)
Specific details regarding the cost assumptions (similarity between treatments) not rigorously justified (3)	Lack of identifying and incorporating adherence levels of medication within study to project real-life CEA of medication rather than in clinical trial situation (6)	Issues in the evidence base regarding asthma patient treatment scheme (switching from one regimen to another) (5)	Many studies still derive utilities from published studies as secondary data rather than primary data collection (2)	Missingness information not verifiable and rationale for imputation not stated (6)
Clinical trials lack data regarding hospitalizations due to severe exacerbation and unscheduled visits to the GP (2)	Ideal measure of adherence (ie, active monitoring) not measured but used proxy (2)	Lack of long-term clinical trials and/or claims analysis to provide data needed to estimate the long-run costs and consequences (4)	Inability to use patient-level meta-analysis for estimating HRQOL utilities (1)	Lack of justification regarding the use of WTP in relation to GDP. Is WTP in relation to GDP even appropriate? (3)
Cost incurred by carers not measured or incorporated (2)	Issues in the literature regarding compliance/adherence differences between countries and demographic characteristics (2)	Lack of information regarding childhood asthma (1)	Issues in the validity and reliability regarding the mapping of AQLQ to EQ-5D utility scores to estimate the HRQOL of health states (1)	Lack of evidence regarding potential confounders/covariates, ie, socioeconomic status and BMI linked to asthma control; thus, unrecognized confounding factors not completely characterized or identified (3)
Gathering data and relying solely on patient-reported resource use and expenditure or expert panel (2)	No one measure of asthma compliance and control allows evaluation of patient perception about illness and therapy, current symptoms, adherence, side effects, and control; need unified and easy test to assess all these areas (1)		Within acute care context, difficulty in measuring direct HRQOL via SG or TTO; thus, mapping used to determine the HRQOL from published data sources (1)	Lack of information regarding adverse events regarding treatments (3)
Secondary data source used to estimate costs (2)	Adherence to completing ACQ and PEF diary card poor in trials. Need a better way to improve the adherence to the questionnaires (1)		General lack of studies regarding HRQOL within Asian countries; thus, use of outside samples to estimate the HRQOL in the Asian population (1)	Study powered on primary effectiveness but not powered on ICER (2)
Data not collected on prescription charges paid by trial enrollees (1)	Issues in the evidence base regarding asthma patient treatment adherence trajectory (1)		Lack of standardization regarding the use of asthma control measures (1)	Lack of comparative CEA of ICSs in 2 different populations (2)
Cost data used are based on only 2 states (US); thus, the data may not be representative in other states or countries (1)				No clear guideline on whether children with asthma seen in ED qualify as patients with persistent asthma and should be started on controller medication; GINA yes, NHLBI no (1) General lack of information regarding the EVPI on further research, such as developing prediction method (1)

(continued)

TABLE III. (Continued)

Cost and resource use (N = 13)	Adherence (N = 13)	Time (N = 10)	Utility (N = 7)	Other (N = 24)
				Lack of clinical trials that meet the inclusion criteria for meta-analysis regarding cost, utilities, asthma health outcomes (1)
				Issues in drug-response prediction methods (genetic testing) (1)
				Clinical data on the effectiveness of drugs may not be available in Asian countries (1)

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; EQ-5D, EuroQol five-dimensional questionnaire; EVPI, expected value of perfect information; GINA, Global Initiative for Asthma; GP, general practitioner; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; NHLBI, National Heart, Lung, and Blood Institute; PEF, peak respiratory flow; SG, standard gamble; TTO, time trade-off.

designing, analyzing, and reporting asthma CEA results through the use of clinically and societally relevant measures (ie, such as those recommended by the NIH) that aid in providing accurate information regarding the value of asthma interventions. For supplemental and emerging outcomes, we urge future research to accommodate measures that have not been used as much in asthma CEA studies such as school or work productivity. Notably, although ideally the full range of NIH-recommended asthma outcomes should be used in all studies, we acknowledge that studies in specific settings or using specific time frames may not be able to include all outcomes due to their specific design. Thus, we recommend that future NIH recommendations consider incorporating specific guidelines in conducting subgroup analyses according to trajectories of outcomes and settings being studied.

As the secondary objective of this review, the thematic assessment of the other issues that prevent robust cross-study comparison of asthma CEAs indicated that there are several domains that displayed the need for improvement in future research. Within the cost and resource use domain, the most prominent issue that was delineated was the lack of specific details regarding the cost assumptions and data sources, which are subsequently not rigorously justified. Within the adherence domain, lack of identifying and incorporating medication adherence levels to better project real-life situations was the most common issue. Within the time domain, the discrepancies in asthma treatment schemes and adherence trajectories were mostly mentioned. Within the domain of utility, the issue regarding studies still deriving utilities from published studies as secondary data rather than primary data collection was identified. Last, within the other domain, information regarding missing values not being verifiable and the rationale for imputation not being stated were highlighted as well as the lack of justification regarding the use of WTP in relation to GDP.

As mentioned in another review⁴ that identified similar issues in CEAs, many times the justification and rationalization for the use of specific cost and resource use measures are not appropriately stated. This issue not only pertains to studies within the asthma field but also exists in many other disease areas⁴⁸ because of issues in (1) the difficulty in accurately assessing the cost and resource use

and (2) the variability regarding location and insurance status. Although variability is justifiable because of differences in asthma management practice, the specific details regarding cost and resource use should always be mentioned to allow for the identification and potential replication of the study. In addition, CEAs should look to identify and incorporate indirect cost such as the cost incurred by carers. The overall issue in the cost and resource domain may potentially be remedied through providing standardized direct and indirect cost values suggested by updated guidelines (ie, new NIH recommendations).

With regard to asthma medication adherence, incorporating real-life adherence and its trajectory were identified. Again, this issue does not only pertain to studies within the asthma field but technologies that accurately measure real-life asthma medication adherence may offer opportunities.^{49,50} The advent of these new technologies and efforts to identify the effect the technologies have on asthma adherence is promising and should be used in asthma medication CEAs.⁵¹ Furthermore, the recent standardization of respiratory medication adherence taxonomy may provide a way forward.⁵²

Regarding the time domain, there has not been any incorporation of treatment scheme in CEAs. Future research is desperately needed to identify the trajectory of treatment schemes that patients with asthma undergo, thereby incorporating the specific and detailed treatment transition (ie, step-up and step-down) within the assessment of cost-effectiveness of asthma medications. In addition, time necessary to treat needs to be consistently assessed across studies, such that conclusions and comparisons are made without bias. Both treatment scheme trajectory and time necessary to treat are important variables that may affect the overall cost and effect (ie, HRQOL) of interventions that patients with asthma use. We urge future NIH recommendations to incorporate the aforementioned measures to make better judgments regarding the cost-effectiveness of asthma interventions.

With the recent movement in setting forth guidelines and recommendations⁵³ for identifying and capturing both general (eg, EuroQol five-dimensional questionnaire) and asthma-specific (eg, Asthma Quality of Life Questionnaire) utility values directly in asthma research studies, the concerns regarding

using secondary data sources to infer asthma-specific utility states should be resolved. Specifically, more published data to identify appropriate HRQOL, via meta-analysis of HRQOL utilities of asthma-specific health states, should provide a more robust measure that may as well resolve problems regarding the validity of HRQOL of asthma-specific health states that have been a concern in a recent utility validation study.⁵⁴ In addition, asthma health state definition and derivation based on FEV have been at best weakly correlated to symptoms, hospitalizations, and asthma-specific quality of life.^{55,56} Thus, perhaps moving toward defining health states on the basis of asthma control measures⁵⁷⁻⁶⁵ and implementing decision models^{18,66,67} that will not be subjected to the variability inherent in health states derived from FEV would provide decision makers better assessment of the actual cost-effectiveness of asthma interventions.

The issue regarding the lack of justification regarding the use of WTP in relation to GDP has been raised by Shiroiwa et al⁶⁸ and justifies the inappropriateness of WTP based on GDP due to the lack of scientific grounding. Our review indicated only 3 studies that raised the issue regarding WTP, yet almost all the studies that assessed the cost-effectiveness of medications made the assessment of the probability of cost-effectiveness using the traditional WTP in relation to GDP. Meanwhile, Shiroiwa et al⁶⁸ suggest a new classification of WTP based on surveying different populations within 6 countries (ie, Japan, Korea, Taiwan, Australia, the United Kingdom, and the United States), which provides a different classification of the WTP threshold. But because of the complexity⁶⁹ of translating 1 unit of quality-adjusted life-years to WTP and the lack of effort in scientifically rigorously identifying the WTP threshold for different populations, the issue regarding using the appropriate WTP threshold may be possible only with further research.

On the basis of our review, we found that there is a general lack of asthma CEAs from Asian countries. Perhaps the lack of necessity in terms of assessing the cost-effectiveness of asthma interventions may have played a role but nonetheless future research in Asian countries would provide valuable information with regard to cross-country comparisons.

Last, the issue regarding missing data being unverifiable and the rationale for using imputation not being stated was identified in several studies. The lack of identification and detailed reporting of missingness (ie, missing values due to withdrawal from clinical trials or from loss to follow-up) will result in biased estimates that directly feed into the cost-effectiveness. Therefore, future studies should aim to identify all possible biases that the source data may have been influenced by and either (1) make efforts to reduce the bias or (2) identify different source data that present less bias.

In comparison to the findings in the NIH recommendation report, this review provides an in-depth thematic analysis of issues that were outlined through the NIH recommendation report in addition to issues that were not described in the NIH recommendation report. Both the NIH recommendation report and our review emphasizes the importance of explicit listing of analytical assumptions, development of survey instruments that capture patient-reported measures, development of methods to evaluate long-term outcomes, and utilization of indirect measures (ie, productivity loss and caregiver burden) in asthma studies. In addition, this review outlines issues that were identified within asthma CEA studies that were not described in the NIH recommendation report such as reporting/dealing with missing

data and issues that pertain specifically to CEA studies such as incorporating treatment schemes and justification of WTP thresholds in CEA models.

This systematic review has several limitations. The first being our relatively narrow focus and the fact that only NIH-recommended outcomes were quantitatively compared and not all other issues that prevent cross-study comparison. Although an overall cross-study comparison of asthma CEAs is outside the scope of this review, we believe that there is an urgent need for cross-study comparison studies (ie, meta analyses or combined CEAs) in the future that compares across all aspects of CEAs. In the meantime, we believe that this study provides a unique perspective, specifically with regard to asthma outcomes, but also by thematically identifying other important issues that need to be tackled for future research to be more comparable. Next, we included articles only in English, which may be a source of bias regarding the assessment of asthma outcomes. However, we believe that our assessment of asthma outcomes in the framework of NIH-recommended guidelines included the vast majority of asthma CEAs, and that non-English articles would have provided limited additional value.⁷⁰ In addition, we did not compare pre- and post-NIH recommendation studies in terms of the potential improvement post-NIH studies may have made in resolving issues besides the inclusion of NIH-recommended outcomes. Because this review's secondary objective was to mainly thematically analyze the aforementioned issues, we did not conduct a comparative analysis. Last, we did not use assessment tools such as the quality of health economic studies or Consolidated Health Economic Evaluation Reporting Standards to assess the quality of the studies included.⁷¹⁻⁷³ However, our study was intended to specifically address the use of NIH-recommended asthma outcomes; thus, other quality assessment tools were considered less relevant for this study.

CONCLUSIONS

Within the last 5 years, a large proportion of CEAs of asthma medications have been using NIH-recommended core outcomes. However, there is still a lack of studies incorporating NIH-recommended supplemental and emerging outcomes. In addition, to allow for robust cross-study comparisons, future work should focus on further standardizing of cost data, time frames, quality-of-life measures, and incorporation of adherence. Ultimately, this will produce more accurate, reliable, and reproducible cost-effectiveness estimates, which, in turn, will provide decision makers with appropriate and consistent estimates of the value of asthma interventions.

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