INCORPORATING ADHERENCE IN COST-EFFECTIVENESS ANALYSIS: USING ASTHMA AS A CASE STUDY

BUNCHAI CHONGMELAXME

A Thesis Submitted to the Graduate School of Naresuan University
in Partial Fulfillment of the Requirements
for the Doctor of Philosophy in (Pharmaceutical Sciences)
2019

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has been approved by the Graduate School as partial fulfillment of the requirements for the Doctor of Philosophy in Pharmaceutical Sciences of Naresuan University

Oral Defense Committee

..... Chair
(Associate Professor Surasak Saokaew, Ph.D.)

..... Advisor
(Assistant Professor Piyameth Dilokthornsakul, Ph.D.)

..... Co Advisor
(Professor Nathorn Chaiyakunapruk, Ph.D.)

..... Internal Examiner
(Associate Professor Teerapon Dhippayom, Ph.D.)

..... Internal Examiner
(Associate Professor Nilawan Upakdee, Ph.D.)

Approved

.....
(Professor Paisarn Muneesawang, Ph.D.)

for Dean of the Graduate School

Title	INCORPORATING ADHERENCE IN COST-EFFECTIVENESS ANALYSIS: USING ASTHMA AS A CASE STUDY
Author	BUNCHAI CHONGMELAXME
Advisor	Assistant Professor Piyameth Dilokthornsakul, Ph.D.
Co-Advisor	Professor Nathorn Chaiyakunapruk, Ph.D.
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ABSTRACT

Introduction:

Cost-effectiveness analysis (CEA) is a well-established framework that is used to estimate the incremental costs per unit of the benefit provided by an intervention. While CEA is increasingly used to inform value assessment of the interventions by healthcare professionals and policy makers, most do not take into account medication adherence in their analyses. One important aspect that still lacks clarity is how to incorporate adherence in the analysis. This dissertation is conducted to acknowledge the abovementioned gap in current understanding in regard to the method of incorporating medication adherence in the CEA by using asthma as a case study. It is comprised of three individual studies chapter by chapter. The first study is to (1) explore the extent of CEA of asthma considering adherence as part of their analyses, and (2) summarize the methods of incorporating adherence in the economic models. The second study is to (3) associate medication adherence and severe asthma exacerbation, and its findings would deliver current evidence of such quantitative interrelations that were incorporated in the CEA of an added on omalizumab compared with the standard care in the third study, which is to (4) evaluate the impact of incorporating medication adherence affecting exacerbation on the results of cost-effectiveness analysis.

Methods:

In the first study, a systematic review was conducted in 4 databases; PubMed, EMBASE, NHS EED, and the Tufts CEA registry. Model-based CEA of asthma were identified, while the outcomes of interest were the number of studies incorporating adherence in the analysis, and the incorporating methods. All the CEA were reviewed to summarize adherence data, methods of incorporating adherence, and the impact of adherence on the cost-effectiveness results. In the second study, another systematic review was undertaken in the following databases; PubMed, Cochrane CENTRAL, EMBASE and ClinicalTrials.gov. Randomized-controlled trials, cohort and case-control studies which investigated the effect of adherence to controller medications on severe asthma exacerbation were included. A pairwise meta-analysis under a random-effects model was performed to provide pooled estimates of the associations between adherence and severe exacerbation. Lastly, a Markov model economic evaluation was conducted to determine the impact of incorporating adherence on the CEA's results among patients with severe persistent asthma using an added on omalizumab compared to the standard care treatment in Thailand. A quantitative interrelations between adherence and exacerbation were incorporated in the Markov model, and the outcomes of interest were the numbers of exacerbations, life years (LY), quality-adjusted life years (QALY), lifetime costs, and the incremental cost-effectiveness ratios (ICER) of individual adherence levels.

Results:

In the first study, from 1,587 articles, 23 studies were decision model-based CEA of asthma, of which, four CEA (17.4%) incorporated adherence in the analyses. Only the method of incorporating adherence by adjusting treatment effectiveness according to adherence levels was demonstrated in this review in which two approaches were used to derive the associations; the first was to apply a mathematical formula developed by an expert panel, and the second was to extrapolate the associations from previous published studies. Secondly, the meta-analyses revealed that the odd of exacerbation among the patients with greater than or equal to (≥) 80% adherence was lowered by 47% [odds ratio, OR = 0.53 (95% confidence interval, CI: 0.42, 0.66), $P < 0.001$] compared to less than (<) 80%. When compared to < 20% adherence, a 33% reduction in the odds [OR = 0.67 (95% CI: 0.53, 0.86), $P = 0.001$]

was associated with the patients achieving ≥ 50% adherence, while a decrease in exacerbation was not associated with 20 - 49% adherence [OR = 0.94 (95% CI: 0.85, 1.04), *P* = 0.22]. In addition, a 2.4 fold increase in the odds [OR = 2.4 (95% CI: 2.1, 2.7), *P* < 0.001] was associated with the discontinuation of treatment. Lastly, the economic evaluation of incorporating adherence among 100 severe asthmatic patients showed that patients using an added on omalizumab with ≥ 80% adherence experienced a lower number of exacerbations [-43.88% (95% credible interval, CrI: -47.94%, -39.26%)] compared with the standard care, while those with < 80% adherence experienced a higher number [13.51% (95% CrI: 5.58%, 23.11%)]. All patients were associated with increased LY, and demonstrated a trend towards an increase in QALY, however, their lifetime costs were substantial, resulting in considerable ICER.

Conclusion:

In this dissertation, we gather all relevant evidence regarding the current knowledge of the methods used to incorporate adherence in the CEA of asthma, demonstrate the method of incorporating adherence using the associations of adherence affecting severe exacerbation, as well as evaluate its impact on the results of cost-effectiveness. Our findings are evidence which will allow researchers, healthcare professionals and policy makers to incorporate adherence in their economic analysis for a better informed policy decision-making and future research development in regard to this area.

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CHAPTER I: INTRODUCTION

Background and rational

Cost-effectiveness analysis (CEA) is a well-established framework that is used to estimate the incremental costs per unit of the incremental benefits provided by an intervention [1]. Results of the cost-effectiveness referred to as an incremental cost-effectiveness ratio (ICER) is used as a supportive document, enabling healthcare professionals and policy makers to make effective decisions relating to health technology assessment (HTA) of the interventions [2]. To date, CEA is increasingly used to inform value assessment of the interventions by healthcare professionals and policy makers. However, most do not consider adherence of the patients in their analyses. Previous literature reviews investigated the CEA that included adherence in the analyses. A systematic review by *Rosen* et al [3] demonstrated that among 177 studies, less than one-third (54) were integrated suboptimal adherence in the analyses. A study by *Hughes* et al [4] evaluated the impact of non-adherence on the results of cost-effectiveness among different drug therapies. The authors included 22 studies, and showed non-adherence reduced the efficacy of therapies but its impact on healthcare costs were varied. Another study by *Cleemput* et al [5] reviewed literature on the economics of therapeutic non-adherence, and identified methodology flaws. Eighteen studies were included, and being assessed according to their definition, measurement of adherence, study design, as well as identification and valuation of costs and outcomes. The results indicated that most studies lacked methodological rigor, and failed to meet qualitative standards. The most updated review conducted in 2007 by *Hughes* et al [6] highlighted the importance of integrating adherence in the CEA. Although the methods of incorporating adherence were characterized, there was a great deal of inconsistency in adherence definitions, and the integrating methods from study to study. In addition, the authors only included 10 studies in the analysis which resulted in limited generalizability of the findings across therapeutic areas.

This dissertation was conducted to acknowledge the abovementioned gap in the current understanding of the method of incorporating adherence in CEA. Due to a growing number of CEA across therapeutic areas, we scoped the diseases of interest

to increase a feasibility in conducting this dissertation, and chose asthma as the selected case study because it is one of the most commonly known chronic respiratory diseases, affecting approximately 300 million people worldwide, and its prevalence has been increasing over the last few decades [7, 8]. Healthcare utilizations for asthma were very high and expected to reach 2% of the total healthcare expenditure in developed countries [7]. In Thailand, there is currently a total of 6,808 deaths due to asthma, which is approximately 1.4% of the top fifty causes of death, and is considered as one of the top twenty throughout the country [9]. While non-adherence is a common and costly problem for the treatment of asthma, the evidence revealed that 50% of children and adults did not take their prescribed medications which was associated with uncontrolled symptoms, and an increase in exacerbation rates and deaths [10, 11]. The importance of adherence was demonstrated in previous studies, and showed that its increase was associated with the improvement of asthma control and lung function, as well as reducing exacerbation rates and healthcare utilizations [12-17].

While CEA is increasingly used to inform value assessment of the interventions, most do not take into account adherence in their analyses. One important aspect that still lacks clarity is how to incorporate it in the analysis. To our knowledge, no previous studies have provided an insight into the methods of incorporating adherence in the CEA of asthma, thus information on such practices is still limited. This dissertation is comprised of 3 separate studies which were carried out to address the various points of this question. The first was conducted to (1) explore the extent of studies considering adherence as part of the CEA, and (2) summarize the methods of incorporating adherence in the economic models. The findings would provide an insight of how frequently CEA of asthma considered adherence, and current knowledge of the methods used to incorporate it in the economic models. The second study was conducted to (3) assess the associations between adherence and severe asthma exacerbation, and the findings would deliver relevant evidence of such quantitative interrelations that were incorporated in the CEA of an added on omalizumab compared with the standard care in the third study, which was conducted to (4) evaluate the impact of incorporating adherence affecting

exacerbation on the results. The conceptual framework of this dissertation is outlined in Figure 1.

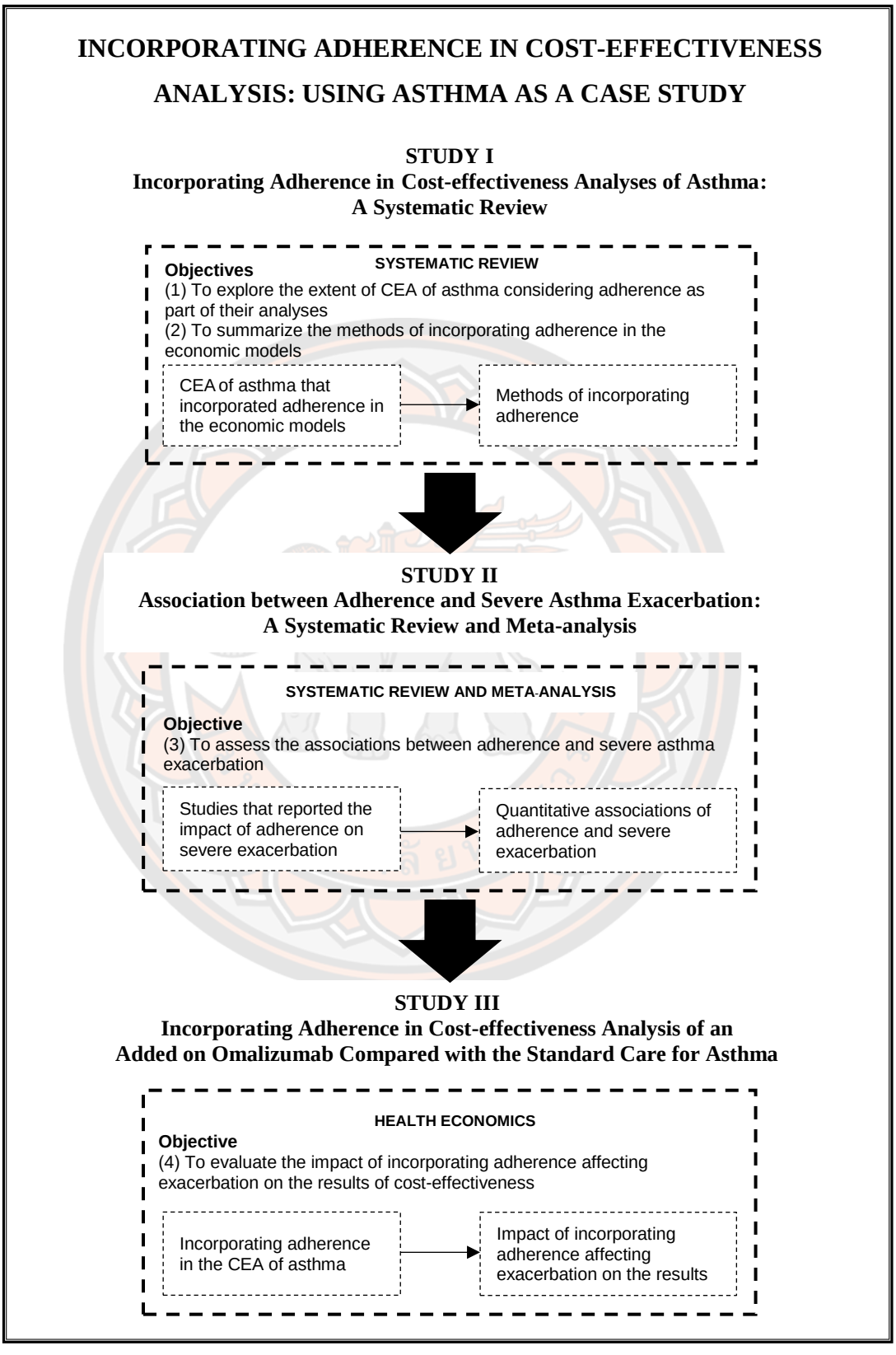


Figure 1. Conceptual framework

Expected benefits

In this dissertation, we gathered all relevant evidence regarding the current knowledge of the methods used to incorporate adherence in the CEA of asthma, demonstrated the method of incorporating adherence using the associations of adherence affecting severe exacerbation, and evaluated the impact of incorporating adherence on the cost-effectiveness results. We believe that the value of this is manifold: to provide researchers, healthcare professionals and policy makers with current evidence of the extent of studies considering adherence as part of the CEA of asthma, and the methods of incorporating it in the economic models, as well as demonstrating our method using the association of adherence and severe exacerbation, while evaluating its impact on the results. Our findings are evidence that will allow researchers, healthcare professionals and policy makers to incorporate adherence in their economic analysis for better informed policy decision-making and future research development in this area.

CHAPTER II: LITERATURE REVIEW

Economic evaluation

Economics is defined as " the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses" [18]. The objective of economics is to maximize human welfare or utility. It is important that the allocation of resources is done efficiently in the community. Economic evaluation is the process of systematic identification, measurement, and valuation of the inputs and outcomes among alternative activities which is conducted to determine the relative efficiency of the health interventions (or programs) . More specifically, economic evaluation is the understanding and use of economic evidence in the decision-making process. The objective of this is to identify the best intervention (or program) based on available evidence, and to provide decisions to the policy makers regarding the value of a particular intervention (or program) [1].

Types of economic evaluation

Economic evaluation can be classified into 2 categories: partial and full. Partial economic evaluation measures costs and/ or health outcomes of intervention which can be either involved in a comparison between alternative interventions or not. The types of partial economic evaluation are cost description, outcome description, cost-outcome description, cost analysis, and outcome analysis. Full economic evaluation measures costs and health outcomes of interventions compared to 2 or more alternative interventions. The types of this are cost-minimization, benefit, effectiveness, and utility analyses [19] (Table 1).

Table 1. Types of economic evaluation

Is there comparison or alternative?	No		Yes
	Only cost measured	Only outcome measured	
No	Cost description	Outcome description	Cost-outcome description
Yes	Cost analysis	Outcome analysis	*Full economic evaluation* 1) Cost-minimization analysis 2) Cost-benefit analysis 3) Cost-effectveness analysis 4) Cost-utlity analysis

Are both costs and outcomes measured?

Cost-minimization analysis (CMA) is used to compare the costs of intervention and comparator in which health outcomes are presumed to be equal. The analysis may be useful in only some circumstances because the health outcomes are rarely the same [1]. Cost-benefit analysis (CBA) is used to compare the costs and health outcomes expressed in monetary value which is estimated by willingness-to-pay (WTP) or human capital approaches. The WTP is assessed by patients making a decision on monetary value that satisfies the trade-off between health benefit and money, while human capital estimates monetary value in terms of productive value of the people. Two methods used to calculate the results: net benefit and cost-to-benefit ratio. Net benefit uses health benefits minus the cost of interventions, and cost-to-benefit ratio uses costs divided by the benefits. A positive net benefit indicates the intervention is worthwhile, while the intervention that shows less cost-to-benefit ratio is considered a preferred intervention.

Cost-effectivness analysis (CEA) is used to compare the cost of interventions with health outcomes, measured in the identical unit, i.e., the reduction in blood pressure, life years (LY) gained. The additional costs and health outcomes are used to

calculate the incremental cost-effectivness ratio (ICER) by using incremental costs divided by incremental outcomes. The alternative intervention that shows less ICER is considered a preferred intervention. Cost-utility analysis (CUA) is used to compare the cost of interventions with health outcomes that do not necessarily need to be measured in the same unit. When alternative interventions produce outcomes in terms of both quantity and quality of life, the effects are expressed in a utility unit comprised of both length of life and subjective levels of well-being. The best known utility measurement is quality-adjusted life years (QALY) which is the comprehensive outcome measurement including both quality and survival information. The alternative interventions are relatively compared using cost per utility unit (or cost per QALY gained), and that with less ICER is considered a preferred option. Given many researchers apply the terms of CEA and CUA synonymously [20], we correspondingly refer both as a CEA in this dissertation.

Framing and designing the economic analysis

Randomized-controlled trial (RCT) is frequently used as a vehicle for economic evaluations [21].The evidence revealed that over 30% of economic evaluations that were included in the National Health Service (NHS) Economic Evaluation Database, used the data from a single RCT. There were several reasons that supported conducting this type of study [22]. Firstly, an economic evaluation alongside RCT provides access to the data among individual patients to which a variety of analytical techniques regarding the clinical and economic perspectives can be applied. Secondly, using the data from RCT delivers an early opportunity to generate results of cost-effectiveness, because the RCT is performed due to a lack of knowledge on treatment effects. Lastly, trial-based economic evaluations are likely to demonstrate low marginal costs when compared to another type of study. However, the use of a single RCT does not always provide a sufficient basis to conduct an economic evaluation, which is limited by the study methodology, i.e., characteristics of parcitipants, interventions, comparators, time horizons, and study settings as well as failure to integrate all relevant information from other trials, observational studies, and meta-analyses [23], especially adherence data of the patients which is the main focus of this disseration. Taking these limitations into account, the use of trial-based

economic evaluation was out of the scope of this dissertation. We focused on economic evaluation using decision analytical modelling, because our primary objective was on the methods of incorporating adherence in the economic model.

When conducting an economic evaluation using decision analytical modelling, many factors needed to be considered to maintain progression, and prevent any analytical pitfalls that may occur throughout the study. The choice of study perspective is an important methodological decision, because it initially defines which costs and health outcomes would be counted and valued. The broadest perspective is a societal one that includes all costs and health outcomes in the analysis, while other perspectives are government, healthcare, payer, and patient or family. The target population is for whom the intervention is intended, and should be clearly identified in the analysis. An example of the target population are individuals of a given sex and age, who live in specific regions and suffer from diseases, etc. Alternative interventions and comparators should be clearly defined along with their contents, i.e., descriptions of treatments, doses, and durations. The choices of comparators can be those routinely used in general practice or existing standards of care, while time horizon is generally used to capture all the costs and health outcomes that would happen in the future. Regarding the relevant data on costs and health outcomes, these can be collected via primary or secondary data sources accordingly.

Economic evaluation guidelines

Economic evaluation guidelines are used to design and conduct economic evaluation study, and they also included a template for evaluating and reporting the study. The guidelines are classified into 3 categories: (1) published recommendations (2) guidelines, and (3) submission guidelines [24] (Table 2). Firstly, economic evaluation recommendations are defined as the country-specific recommendations, published by experts in the field but are not "officially" recognized or required by the healthcare decision makers for reimbursement. They are used in 10 countries; Austria, China, Croatia, Denmark, Hungary, Italy, Russian Federation, Spain, South Africa, and the United States (US). Secondly, economic evaluation guidelines are defined as country-specific "official" guidelines that are recognized or required by the healthcare decision makers for reimbursement. They are used in 24 countries/ regions; Baltic

(Latvia, Lithuania, Estonia) , Belgium, Brazil, Canada, Colombia, Cuba, Egypt, France, Germany, Ireland, Malaysia, Mexico, MERCOSUR (Argentina, Brazil, Paraguay, Uruguay), New Zealand, Norway, Portugal, South Korea, Slovak Republic, Slovenia, Sweden, Switzerland, Taiwan, and the Netherlands. Lastly, economic evaluation submission guidelines are defined as country-specific "official" guidelines or policies concerning drug submission requirements with economic evaluation, which are required by the healthcare decision makers for reimbursement. They are used in 8 countries; Australia, England & Wales, Finland, Israel, Poland, Scotland, Spain, and Thailand.

Table 2. Economic evaluation recommendations/guidelines/submission guidelines worldwide

Regions	Recommendations	Guidelines	Submission guidelines
1) Africa	South Africa	Egypt	
2) America-Latin		Brazil Colombia Cuba Mexico MERCOSUR (Argentina, Brazil, Paraguay, Uruguay)	
3) America-North	United States	Canada	
4) Asia	China	Taiwan South Korea Malaysia	Israel Thailand
5) Europe	Austria Denmark	Baltic (Latvia, Lithuania,	England & Wales Finland

Regions	Recommendations	Guidelines	Submission guidelines
	Hungary	Estonia)	Poland
	Italy	Belgium	Scotland
	Russian Federation	France	Spain-Catalonia region
	Spain	Germany	
	Croatia	Ireland	
		Netherlands	
		Norway	
		Portugal	
		Slovak Republic	
		Slovenia	
		Sweden	
		Switzerland	
6) Oceania		New Zealand	Australia

Medication adherence

Adherence of the patients includes 2 different aspects: compliance and persistence. Compliance is defined as the extent to how a patient acts in accordance with the prescribed dose and interval of a treatment regimen, while persistence is the duration of time from initiation to discontinuation of therapy [25]. Adherence can be defined as the extent of how a person' s behaviour corresponds with agreed recommendations from a healthcare provider [26]. Pharmacoadherence is another adherence term defined in a study by *Chisholm-Burns and Spivey* [27] as the extent to which a patient followed a given therapeutic medication regimen agreed on in partnership with healthcare professionals.

Different procedures have been used to estimate adherence: (1) subjective (2) objective, and (3) biomedical [26]. The subjective method is used to rate medication-taking behaviour by healthcare providers or the patients themselves [28], and is the most commonly used, but the drawback of this is the degree of overestimating when providers rate their patients [29-31]. Similarly, rating inaccuracy is another issue for the patients who refuse to follow the providers' advice [32]. The objective method consists of counting (or weighing) , electronic monitoring, and secondary database

analysis [29, 33]. Counting (or weighing) is used to calculate the number of doses that have been taken by the patients between visits, and is more reliable than the subjective way [34]. However, counting inaccuracy is frequently observed, resulting in overestimation [35], while important adherence data, e. g. , timing of dosage, patterns of missed dosages, is not taken into account by using this method [26]. Electronic monitoring devices can be integrated into medication dispensers, and record the date and time when they were opened [36-38]. It helps identify adherence data, e. g. , medication-taking patterns, timing of dosage, and describes patients' adherence with specific dose at particular time. Unfortunately, this method is limited due to the expensive devices and the bulkiness of the containers [37, 38]. Secondary database analysis uses primary adherence data, e. g. electronic prescriptions and pharmacy insurance claims, to assess patients refilled patterns based on the assumption that they correlate with their medication-taking behaviour [37]. The major problem is the incomplete data due to the lack of availability and quality acquired from different sources. The biochemical method is the most accurate which is used to estimate the amount of drug or its metabolite in the body fluid, and should be performed with caution since several factors can influence its detection, i. e. , diet, absorption, digestion, and excretion [38].

Patients' refilled patterns can be calculated using different equations (Table 3). Continuous single interval measure of medication availability (CSA) uses days' supply of medication divided by days in the interval, while continuous measure of medication acquisition (CMA) uses days' supply of medication divided by the total days from the beginning to the end of the term. Compliance rate (CR) uses the sum of the days' supplies minus days' supply obtained at the last dispensation divided by the total days from the first up to but excluding the last dispensation. Days between fills adherence rate (DBAR) uses the days' supply subtracted from days between dispensations divided by the days between dispensations. The dividend is subtracted from 1 to become adherence value, and that multiplying by 100 to provide adherence percentage. Continuous single interval measure of medication gaps (CSG) uses days of treatment gap divided by days in the interval. While continuous measure of medication gaps (CMG) uses total days of treatment gaps divided by the total days of the study period.

Continuous multiple interval measure of oversupply (CMOS) uses total days of treatment gaps or surplus divided by the days of the study period. Medication possession ratio (MPR) is the ratio of the days' supply of medication to the days of the study period. Modified medication possession ratio (mMPR) is adapted by using days' supply of medication divided by the sum of the days between dispensations, and days' supply of medication obtained at the last dispensation, then multiplied by 100 to become the percentages. A percent adherence value or medication refill adherence (MRA) uses the total days' supply of medication divided by the total days of the study period, then multiplied by 100. Proportion of days covered (PDC) uses the total days' supply divided by the total days of the study period which is capped at 1 to prevent overestimating the results.

Table 3. Measurements of adherence

Measurements	Equations	Values represented
CR	(Days' supply of medication - day supplies obtained at the last dispensation)/total days from the first up to, but excluding the last dispensation	Adherence for period between fills
CMA	Days' supply of medication throughout the study period/total days from the beginning to the end of the term	Adherence for cumulative time period
CMG	Days of treatment gap throughout the study period/total days from the beginning to the end of the term	Non-adherence for cumulative time period
CSA	Days' supply of medication/days in the interval	Adherence for interval
CSG	Days of treatment gap/total days in the interval	Non-adherence for interval
CMOS	Days of treatment gap (+) or surplus* (-)/total days of the study period	Non-adherence for cumulative time period
DBAR	[1 - [(last dispensation date - first dispensation date) - days' supply of medication]/(last dispensation date - first dispensation date)] × 100	Adherence (%)
MPR	Days' supply of medication : days of the study period	Ratio of medication available
mMPR	Days' supply of medication/[(last dispensation date - first dispensation date) + last days' supply] × 100	Adherence (%)
MRA	(Days' supply of medication/total days of the study period) × 100	Adherence (%)

Measurements	Equations	Values represented
PDC	(Days' supply of medication/total days of the study period) × 100, * capped at 1	Days of medication available (%)

CR, compliance rate; CMA, continuous measure of medication acquisition; CMG, continuous measure of medication gaps; CSA, continuous single interval measure of medication availability; CSG, continuous single interval measure of medication gaps; CMOS, continuous multiple interval measure of oversupply; DBAR, days between fills adherence rate; MRA, medication refill adherence; MPR, medication possession ratio; mMPR, modified medication possession ratio; PDC, proportion of days covered

Note: *Surplus (due to early refill or over refill) results in over-estimating medication for the time period.

A Comparison of the measurements of adherence

In general, non-adherence is found to be higher with inhaled medications than tablets, and increases comparatively following the doses prescribed per day [39]. A study by *Rand* et al [40] asssessed the use of inhalers, prescribed to be taken 3 times a day, among the participants from 2 centers in the US Lung Health Study clinical trial. The authors recorded adherence of the participants by using self-report and canister weight change, then compared these findings with the data retrieved from a microprocessor monitoring device, the Nebulizer Chronolog (NC), which recorded the date and time of individual inhaler actuation. The results demonstrated 73% of the participants reported using their inhalers an average of 3 times daily, but the NC data revealed only 15% of them used it 2.5 or more times daily. Another study by *Coutts* et al [41] investigated the use of inhaled prophylactic treatment in children with moderate to severe asthma. All subjects were issued with a diary card and an initialised NC to score their inhaler use, and the results revealed that all children reported better adherence than the recording, while the underuse of medications was recorded as 55% of the study days. The patients with 2 times daily adhered to their treatment on 71% of days compared with only 18% for those on a 4 times daily regimen. Even though these monitoring devices generate more accurate information of adherence than other methods, the drawback is that they are not able to record whether the medication was actually taken despite being removed from an inhaler canister. Some of the newer electronic devices now have integrated flow sensors that have the capability of tracking actual inhaler use, which may be considered as one of the methods used to measure adherence of the patients using inhaled medications.

A systematic review by *Engelkes* et al [42] reviewed the methods of measuring adherence to controller medications among asthmatic patients, with various methods being used from study to study. Of the 24 included studies, refilled prescription data was most commonly used. Despite its convenience and competitiveness, the major problems were the lack of data completeness, and the quality of evidence collected from different sources [37]. Electronic monitoring devices identified patient adherence with specific doses at particular times. Unfortunately, the use of these device applications were limited, presumably due to their expense and inconvenience [38]. The number of unit doses taken by the patients

were calculated by counting and weighing them. Although this method was reliable, inaccuracies were frequently observed [35]. Self-reported use of medications was often used, but the drawback of this was the healthcare providers' over-estimation when rating their patients' adherence [30], while inaccuracies were observed when patients refused to follow the providers' advice [32]. Biochemical measurement assessed the amount of drug or its metabolite in the body fluid. While many elements were able to influence the method of detection, e.g. diet, absorption, etc., this was the most accurate adherence measurement for systemic medications [38]. Unfortunately, this only applied to some medications that were used in clinical practices, such as, theophylline and omalizumab [39].

Measuring adherence is challenging because it depends not only on individual factors (patient behaviour and clinical characteristics), but also external factors (friends, family, and healthcare providers). There is currently no unified best practice, so with respect to some advantages of the abovementioned methods, use of combined approaches may be desirable. Further research is warranted to develop new approaches that will add greater value to the measurement of adherence for patient care.

Methods of incorporating adherence in cost-effectiveness analysis

Several reviews investigated the methods of incorporating adherence in the CEA. A study by *Hughes* et al [4] investigated the techniques used to accommodate non-adherence, and estimate its impact on the cost-effectiveness results. The authors included a total of 22 CEA, and showed that only a few adapted clear adherence definitions, while the remaining did not clearly define this, and provided no useful information. The majority of studies employed a decision tree model, while others used the Markov model. Most studies applied the sources of adherence data from the clinical studies followed by the values that were based on assumptions or expert opinions, while some studies did not state the data sources. For a change in the likelihoods of disease progressions or assessed outcomes in non-adherence patients, many studies relied on expert opinions, and only a few made reference to evidence-based sources of the clinical trials. The results of this review demonstrated non-

adherence could affect the study findings by decreasing the efficacy of medications, but its effects on healthcare costs were varied.

Another review by *Cleemput* et al [5] identified the methodology flaws and formulated recommendations for future economic evaluation. Eighteen studies were included in this review demonstrating a variety of non-adherence terms and its measurements. Most of the studies used multiplicative method to estimate costs associated with non-adherence by multiplying non-adherence rates with hospital charges or expenses, i.e., multiplied non-adherence rates with the costs of healthcare services or used the number of hospitalization days multiplied by per diem. The method may not be a good representative of the cost because it did not reflect the real value. It is important to be aware of adherence definitions and the relevant data that were applied in the analysis. Measuring every single cost item in detail would be ideal, and the most valid approach despite being resources-demanding. In addition, treatment costs are needed to be adjusted according to non-adherence or experts' assumptions. The availability of non-adherence data with qualified evidences is crucial.

A review by *Hughes* et al [6] highlighted the importance of adherence, and identified the CEA that integrated adherence in their analyses. The authors included 10 studies, and indicated that the explicit definition of adherence was not given in all of them. Most studies used data in RCT and other clinical studies as a source of adherence data, and applied the simple assumptions related to the interrelation between non-adherence and the outcomes, i.e., non-adherence did not gain any health benefit. The decision-tree model with different adherence levels was used in the majority of studies, while the remainder used the Markov model. Only some studies demonstrated the impact of varying adherence rates in their sensitivity analyses. In this review, the authors summarized some methods of integrating adherence in CEA. The decision-tree model incorporated either branches of different adherence levels or adherence and non-adherence were recommended for acute conditions, while the Markov model was used for chronic diseases. Generally, non-adherent patients would experience a higher risk of disease progression than those who adhered, and this would affect healthcare costs, clinical outcomes, and the cost-effective results. The

most important concern was the quality of evidence for adherence data whether this generalized to be a representative of a wider population.

The most recent review by *Hiligsmann* et al [42], summarized the importance of incorporating adherence in CEA using osteoporosis as an example. The authors showed that several studies attempted to include adherence in the analyses, by assuming a medication cost and the risk of fracture to be proportional to non-adherence [43-45]. Only 1 study [46] reduced treatment efficacy using a proportional factor of the effect; suggesting 20% reduction of the benefits according to an experts' advice. Non-adherence could reduce the treatment effectiveness which resulted in the lower bone density and a higher fracture rate [47]. Furthermore, its effect on the costs could represent in opposite directions; reducing treatment costs, but increasing healthcare costs. The impact on the total cost would depend on the risks of the study population being investigated [4].

CHAPTER III: INCORPORATING ADHERENCE IN COST-EFFECTIVENESS ANALYSES OF ASTHMA: A SYSTEMATIC REVIEW

Research questions

1) How many cost-effectiveness analysis (CEA) of asthma take adherence into consideration?

2) Which methods have been used to incorporate adherence in the economic analysis?

Research objectives

1) To explore the extent of the studies which considered adherence as part of the economic analyses

2) To summarize the methods of incorporating adherence in the economic models

Methods

Search strategy

A literature search was performed from inception to February 2018 using 4 databases; PubMed, EMBASE, NHS EED, and the Tufts CEA Registry. The search filters used for identifying economic evaluations were combined with various search terms including cost-effectiveness, cost-utility, economic evaluation, and asthma [48]. All the search terms are presented in Appendix: Table A1, and the bibliographies of retrieved articles were examined for the studies that were not indexed in the aforementioned databases.

Study selection

Initially, the titles and abstracts were screened to identify the potential studies, and only the ones published in English were included. Decision model-based CEA of the pharmacological interventions for asthma which included the results of incremental costs per unit of the benefits were identified. The outcomes of interest were the number of studies that incorporated adherence in the analyses, and the

methods of incorporating adherence in the economic models. The full texts of relevant studies were assessed by 2 investigators [Bunchai Chongmelaxme (BC) and Piyameth Dilokthornsakul (PD)], and all disagreements between them were resolved by an arbitrator [Nathorn Chaiyakunapruk (NC)].

Data extraction and quality assessment

Data extraction was undertaken by the 2 investigators (BC and PD), using a standardized data collection form. The extracted data included authors' names, year of publication, country of origin, study objectives, the characteristics of participants and interventions, comparator, outcomes, type of economic analysis, perspective, cycle length, time horizon, adherence data, and results. All of the studies were assessed by the 2 investigators (BC and PD) , for their methodological qualities using the Consensus on Health Economic Criteria-extended (CHEC-extended), and the quality of reporting using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [49-51] (Appendix: Table A2).

Data analysis

The number of CEA that incorporated adherence in the analyses were calculated as the percentage of studies considering adherence as part of the economic analyses. All the CEA were reviewed to summarize adherence data, methods of incorporating adherence, and the impact of adherence on the results.

Results

The initial search yielded 1,587 articles, of which 344 duplicates were removed, and the remaining 1,243 articles were screened through the titles and abstracts. A total of 1,080 articles were excluded because of their irrelevance to asthma and the CEA, which resulted in 163 of them being assessed for their eligibility. A further 140 articles were excluded for the following reasons; non-English (n = 13), duplications (n = 17), non-decision model-based CEA (n = 42), as well as the abstracts, reviews, correspondence, and letters to the editor (n = 68). This yielded a total of 23 CEA of asthma, of which 4 incorporated adherence in the analyses. A flow diagram of the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) is shown in Figure 2, and the results of the initial search are presented in Appendix: Table A1.

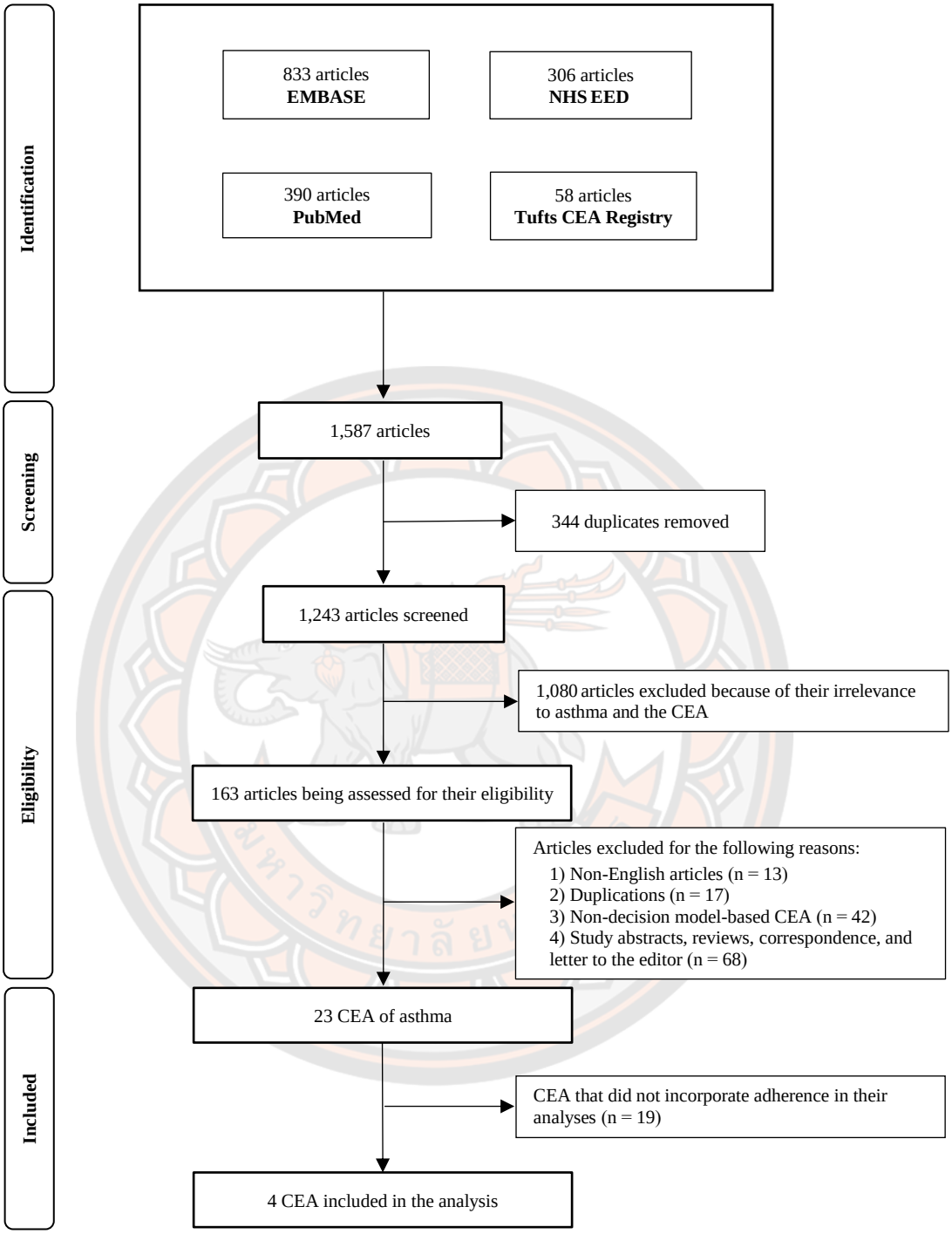


Figure 2. The PRISMA flow diagram describes the study selection process

General characteristics

Twenty-one studies (91.3%) were conducted to carry out the cost-effectiveness of interventions in a single country: United States (US) (8) [52-59], Columbia (3) [60-62], United Kingdom (UK) (3) [63-65], Canada (2) [66, 67], Italy (2) [68, 69], Australia (1) [70], Germany (1) [71], and Sweden (1) [72], whereas 2 studies (8.7%) were conducted in multiple countries; UK, Netherlands, and Spain [73], and 2 World Health Organization (WHO) sub-regions, countries in Sub-Saharan Africa with very high adult and child mortality, and countries in South East Asia with high adult and child mortality [74]. The characteristics of 23 CEA are shown in Table 4.

Table 4. Characteristics of the included studies

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
Altawalbeh [52]	2016	US	Older adults, ≥ 66 years, with asthma	Inhaled corticosteroids plus long acting beta-agonists	Inhaled corticosteroids plus leukotriene receptor antagonists	1) Costs 2) QALY 3) ICER	Markov	Healthcare	20 y
Bruggenjurgen [71]	2010	Germany	Adults with moderate to severe asthma	Combination inhaler: 1) Beclomethasone dipropionate plus formoterol fumarate	Separated inhalers: 1) Beclomethasone dipropionate plus formoterol fumarate	1) Costs 2) ICER	NR	Healthcare	6 m
Campbell [53]	2010	US	Patients with moderate to severe asthma	Omalizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER	Markov	Healthcare	Life time

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
Dewilde [72]	2006	Sweden	Patients with severe asthma	Omalizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER	Markov	Societal	Life time
Doan [66]	2011	Canada	Children with asthma	Bronchodilators (metered-dose inhaler)	Bronchodilators (wet nebulization)	1) Costs 2) ICER	Decision tree	Hospital	2 d
Doull [63]	2007	UK	Adults and adolescents, and children with asthma	Combination inhaler: Salmeterol xinafoate plus fluticasone propionate	1) Fluticasone propionate (same dose) 2) Fluticasone propionate (increased dose) 3) Salmeterol xinafoate plus fluticasone propionate (separated	1) Costs 2) QALY 3) ICER	NR	Societal	1 y

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
					inhalers) 4) Budesonide plus formoterol (combination inhaler)				
Faria [64]	2014	UK	Adults and adolescents, and children with severe asthma	Omalizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER	Markov	Healthcare	Life time
Fuhlbrigge [54]	2006	US	Women, 35 years, with asthma	Inhaled corticosteroids	No inhaled corticosteroids	1) Costs 2) QALY 3) ICER	Markov	Societal	10 y
Gerzeli [68]	2012	Italy	Adults with moderate to severe asthma	Combination inhaler: 1) Beclomethasone plus formoterol	Combination inhaler: 1) Fluticasone propionate plus	1) Costs 2) QALY 3) ICER 4) Time	Markov	Healthcare	Life time

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
					salmeterol	spent in control state			
Ismaila [67]	2014	Canada	Patients with asthma	Combination inhaler: 1) Salmeterol xinafoate plus fluticasone propionate	1) Fluticasone propionate (same doses: low, medium, high) 2) Fluticasone propionate (increased doses: from low to medium, medium to high)	1) Costs 2) QALY 3) ICER	NR	Healthcare	1 y
Marchetti [69]	2004	Italy	Adults with moderate to	1) Beclomethasone 2) Beclomethasone-	1) Beclomethasone	1) Costs 2) QALY	Decision tree and	Healthcare and	2 m

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
			severe asthma	extrafine 3) Fluticasone propionate 4) Budesonide	2) Beclomethasone -extrafine	3) ICER	Markov	societal	
Norman [65]	2013	UK	Adults and adolescents, and children with severe asthma	Omalizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER 4) No. of exacerbations	Markov	Healthcare	Life time
Paggiaro [73]	2013	UK, Netherlands and Spain	Patients with asthma	Combination inhaler: 1) Fluticasone propionate plus salmeterol (medium and high doses)	Combination inhaler: 1) Beclomethasone plus formoterol	1) Costs 2) QALY 3) ICER	Markov	Healthcare	6 m
Rodriguez-Martinez	2013	Columbia	Children with asthma	1) Budesonide 2) Fluticasone	Beclomethasone dipropionate	1) Costs 2) QALY	Markov	Healthcare	1 y

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
[62]				propionate 3) Ciclesonide		3) ICER			
Rodriguez-Martinez [60]	2015	Columbia	Children with asthma	Inhaled corticosteroids (daily therapy)	Inhaled corticosteroids (intermittent)	1) Costs 2) QALY 3) ICER	Markov	Healthcare	1 y
Rodriguez-Martinez [61]	2016	Columbia	Children with asthma	Budesonide (800 µg) once-daily	Budesonide (400 µg) twice-daily	1) Costs 2) QALY 3) ICER	Markov	Healthcare	1 y
Shih [55]	2007	US	Adults and adolescents with mild to moderate asthma	Combination inhaler: 1) Fluticasone propionate plus salmeterol	1) Fluticasone propionate 2) Non-fluticasone propionate inhaled corticosteroids 3) Leukotriene modifiers	1) Costs 2) ICER	Decision tree	Healthcare	1 y

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
Simonella [70]	2006	Australia	Adults with asthma	1) Current treatment (eighty-nine percent of the patients were in contact with the health care system, and 60% of them used inhaled corticosteroids, half of whom used it regularly) 2) Optimal treatment (all patients were in contact with the health system, except those with very mild disease, were deemed to use inhaled	No treatment	1) Costs 2) YLD 3) ICER	NR	Healthcare	1 y

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
				corticosteroids regularly and those with moderate or severe disease were deemed to use combined inhaled corticosteroids plus long acting beta-agonists)					
Stanciole [74]	2012	Two WHO sub-regions: 1) AfrE 2) SearD	Patients with asthma	1) Inhaled corticosteroids (low dose) 2) Inhaled corticosteroids (medium dose) 3) Inhaled corticosteroids plus	Placebo	1) Costs 2) DALY 3) ICER	NR	NR	Life time

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
				long acting beta-agonists (low dose) 4) Inhaled corticosteroids plus leukotriene receptor agonists					
Whittington [56]	2017	US	Adults with Severe asthma	Mepolizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER	Markov	Healthcare	Life time
Wu [57]	2007	US	Adults with severe asthma	Omalizumab plus standard therapy	Standard therapy	1) Costs 2) QALY 3) ICER	Markov	Societal	10 y
Zafari [58]	2014	US	Adults with asthma	Full-adherence scenario: Inhaled corticosteroids or inhale corticosteroids plus long-acting beta-	*Status quo* scenario (current status of adherence): Inhaled	1) Costs 2) QALY 3) ICER 4) No. of exacerbati	Markov	Societal	10 y

First author	Year	Country	Participant	Intervention	Comparator	Outcome measure	Model type	Perspective	Time horizon
				agonist	corticosteroids or inhale corticosteroids plus long-acting beta-agonist	ons			
Zafari [59]	2016	US	Patients with moderate to severe asthma	Omalizumab	Standard therapy	1) Costs 2) QALY 3) ICER 4) No. of exacerbations	Markov	Healthcare	5 y

AfrE, Countries in Sub-Saharan Africa with very high adult and child mortality; DALY, disability-adjusted life years; ICER, incremental cost-effectiveness ratios; QALY, quality-adjusted life years; SearD, Countries in South East Asia with high adult and child mortality; UK, United Kingdom; US, United States; YLD, years-lived with disability

Study participants

Among 23 CEA, 6 of them investigated the CEA in all patients with asthma; moderate to severe [2 (8.7%)] [53, 59], severe [1 (4.3%)] [72], and at varying levels of asthma [3 (13.0%)] [67, 73, 74]. Seven studies investigated the CEA in adults with asthma; moderate to severe [3 (13.0%)] [68, 69, 71], severe [2 (8.7%)] [56, 57], and at varying levels [2 (8.7%)] [58, 70], while 4 (17.4%) [60-62, 66] only investigated children at varying levels**.** Other groups of study participants are shown in Table 4**.**

Pharmacological interventions

Six studies compared the use of standard therapy plus monoclonal antibodies; omalizumab [5 (21.7%)] [53, 57, 64, 65, 72], and mepolizumab [1 **(**4.3%)] [56], to the standard therapy, and one other (4.3%) [59] compared omalizumab to it also. Two studies (8**.** 7%) [68, 73] compared 2 different combination inhalers; beclomethasone dipropionate plus formoterol, and fluticasone propionate plus salmeterol. One study (4.3%) [63] compared the combined salmeterol xinafoate plus fluticasone propionate with fluticasone propionate, salmeterol xinafoate plus fluticasone propionate **(** separated inhalers**)** , and budesonide plus formoterol **(** combination inhaler**)** , whereas one (4. 3%) [67] only compared the combined salmeterol xinafoate plus fluticasone propionate with fluticasone propionate. One study (4.3%) [55] compared the combined fluticasone propionate plus salmeterol with fluticasone propionate, non-fluticasone propionate inhaled corticosteroids, and leukotriene receptor antagonists (LTRA) . One study (4. 3%) [69] compared beclomethasone, beclomethasone-extrafine, budesonide, and fluticasone propionate with beclomethasone dipropionate or beclomethasone dipropionate-extrafine. Other pharmacological interventions are shown in Table 4.

Types of decision-analytic model, perspectives and time horizons

Eighteen studies reported models used in the analyses, while the majority of them [15 (83.3%)] [52-54, 56-62, 64, 65, 68, 72, 73] applied the Markov models, 2 (11.1%) [55, 66] used decision tree models, and 1 (5.6%) [69] applied both. Twenty-two studies reported the perspectives. Most [16 (72.7%)] [52, 53, 55, 56, 59-62, 64, 65, 67-71, 73] used the healthcare perspective, 5 (22.7%) [54, 57, 58, 63, 72] used the

societal perspective, and 1 (4.5%) [66] used the hospital perspective which included all the costs pertaining to the emergency department, and admissions. The 2 most commonly reported time horizons were lifetime (30.4%) [53, 56, 64, 65, 68, 72, 74], and 1 year (30.4%) [55, 60-63, 67, 70], while other time horizons are shown in Table 4.

Incorporating adherence in cost-effectiveness analyses

Among 23 CEA, 4 **(17.4%)** incorporated adherence in the analyses**.** A study by *Shih* et al [55] estimated the cost-effectiveness of fluticasone propionate plus salmeterol administered in a single-inhaler compared with fluticasone propionate, non-fluticasone propionate inhaled corticosteroids, and LTRA. The results showed that fluticasone propionate plus salmeterol was the most cost-effective strategy. A study by *Rodriguez-Martinez* et al [62] compared budesonide, ciclesonide and fluticasone propionate with beclomethasone dipropionate, and revealed that fluticasone propionate was cost-effective, while budesonide and ciclesonide were dominated by beclomethasone dipropionate. Another study by *Rodriguez-Martinez* et al [61] compared once-daily budesonide with a twice-daily dose, and demonstrated that a once-daily dose was the dominant strategy. A study by *Zafari* et al [58] investigated the cost-effectiveness of improving adherence to controller medications, comparing between the hypothetical scenario in which all patients were fully adherent to the medications (full-adherence), and *status quo* scenario (the current status of patient adherence). The authors showed that full-adherence was cost-effective.

Adherence data including the definitions, therapeutic levels, and data sources, varied from study to study (Table 5). *Shih* et al [55] used patients' refill patterns that were adapted from observational studies and claim data [75-79]. *Rodriguez-Martinez* et al [62] applied an assumption of decreasing adherence over time for a twice-daily dose of inhaled corticosteroids (ICS), assessed by counting the remaining doses in the inhaler based on a randomized-controlled trial (RCT) [80]. Subsequently, the authors applied a difference in adherence between once and twice-daily administrations which was adapted from a randomized, single-blind, clinical trial [81]. Likewise, *Rodriguez-Martinez* et al [61] applied an assumption of decreasing adherence over time for a once-daily dose of ICS, assessed by using a

device that recorded the date and time of an inhaler actuation based on an observational study [82], and used the difference in adherence levels between once and twice-daily administrations, adapted from a randomized, single-blind, clinical trial [81]. *Zafari* et al [58] calculated adherence levels using the proportion of days covered (PDC) of patients that were extrapolated from the RCT [83].

Table 5. Adherence data

First author (year)	Adherence data		
	Definitions	**Levels**	**Data sources**
Shih (2007) [55]	Refill patterns among patients with mild to moderate persistent asthma	1) Salmeterol/fluticasone propionate: 34% 2) Fluticasone propionate: 19% 3) Non-fluticasone propionate inhaled corticosteroids: 19% 4) Leukotriene modifiers: 38%	Observational studies/patients claim data [75-79]
Rodriguez-Martinez (2013) [62]	The reported frequency of administration by counting the remaining doses in an inhaler, and applied the assumptions regarding decreased adherence over time	1) Budesonide and ciclesonide (once-daily): 88% (3 months), 62% (9 months) and 61% (12 months) 2) Beclomethasone dipropionate and fluticasone propionate (twice-daily): 77% (3 months), 54% (9 months) and 53% (12 months)	Randomized controlled trial [80] and randomized single-blind trial [81]
Zafari (2014) [58]	Proportion of days covered by patients	1) Patients who were not using any controller medication: 0% 2) Patients who received low-dose controller therapy: 25%	Randomized controlled trial [83]

First author (year)	Adherence data		
	Definitions	**Levels**	**Data sources**
		3) Patients who received medium or high dose of controller therapy: 75%	
Rodriguez-Martinez (2016) [61]	The reported frequency of administration using a device that recorded the date and time of an inhaler actuation, and applied the assumptions regarding decreased adherence over time	1) Budesonide (once-daily): 47.6% (2 months), 39.6% (4 months), 35.9% (6 months), 28.5% (8 months), 29.7% (10 months) and 28.5% (12 months) 2) Budesonide (twice-daily): 58.3% (2 months), 48.5% (4 months), 43.9% (6 months), 34.9% (8 months), 36.4% (10 months) and 34.9% (12 months)	Observational study [82] and randomized single-blind trial [81]

Methods of incorporating adherence

Only the method of incorporating adherence by adjusting treatment effectiveness, according to adherence levels was demonstrated in this review**.** Two approaches were used to derive the associations between adherence and effectiveness**.** The first was to apply the mathematical formula that assumed the effectiveness slowly decreased at the first, following an exponential curve as adherence fell below 100**%** , and increased the rate when it was below 30**%** , following a linear curve**.** This mathematical formula was derived based on the consultation with an expert panel involved pulmonologists and allergists as demonstrated below,

% Treatment effectiveness = % adherence rate

If adherence rate ≤ 30%

% Treatment effectiveness = 1 - exp (-5 * (% adherence rate - 0.2287))

If adherence rate > 30%

The authors assumed an exponential decline with the constant rate equal to 5, and applied a modifying factor of 0.2287 to confirm the intersection between non-linear, and linear functions at an adherence rate of 30% . The adherence-adjusted effectiveness was taken into account as an input parameter, and incorporated in the economic model**.**

This approach was developed by *Shih* et al [55], and used in the other 2 studies by *Rodriguez-Martinez* et al [61, 62]. In the *Shih* et al study, the effectiveness measures included the proportion of patients that were free of symptoms, and from the use of rescue medications**.** A decision tree model was used to follow the patients at 3-month intervals throughout the year study period, starting at the initiation of their medications**.** Patients were assumed to have the opportunity of switching to another therapy or withdrawing from the study, and at the end, they were in one of the following health states: (1) free of symptoms (2) experienced mild symptoms, but had not needed rescue medications (3) experienced mild symptoms that required the use of rescue medications, and (4) experienced one or more exacerbations. In *Rodriguez-Martinez* et al studies, the effectiveness was the proportion of patients at risk of exacerbation**.** The Markov model which consisted of 3 health states: (1) no symptoms

(2) suboptimal control, no exacerbation, and (3) exacerbation, was applied to the studies using a cycle length of 1 week over a 12-month period.

The second approach of deriving the associations between adherence and effectiveness, was to extrapolate the relationships from previous published studies**.** This approach was used in a study by *Zafari* et al [58]. Firstly, they calculated adherence levels based on an actual dose of ICS, taken by patients in a RCT [83], resulting in the PDC values of 0%, 25% and 75%. Secondly, an association between each of the 25% decreasing PDC and relative risk (RR) of 1.26 for the rates of exacerbation was adapted from a retrospective cohort study [84]. The authors combined those PDC values with this RR, and then estimated the RR of exacerbation to be approximately 2 for the patients with PDC of 25%, and 1.2 for PDC of 75%. For those who did not use any medication or having PDC of 0%, the authors applied the RR of 1.53 obtained from a systematic review and meta-analysis of RCT which compared the clinical outcomes of using ICS versus no controller medication [85]. Lastly, those RR associated PDC were adjusted based on follow-up periods of the studies resulting in the RR of 1.40, 1.36 and 1.09 for patients with PDC of 0%, 25% and 75%, respectively. The adherence-adjusted RR were then applied to the model**.** In this study, the authors developed the Markov model which used a cycle length of 1 week throughout the 10-year time horizon, in which the patients transitioned between the following health states: (1) controlled asthma (2) partially controlled asthma (3) uncontrolled asthma (4) exacerbation, and (5) death.

Impact of adherence on cost-effectiveness results

Out of 4 CEA, 2 (50.0%) assessed the impact of adherence on cost-effectiveness results. *Shih* et al [55] performed one-way sensitivity analysis by varying adherence levels for all the ICS to be 70**%** , and assumed the associations between adherence and effectiveness of the clinical outcomes; proportion of patients that were free of symptoms, and free of rescue medication use, to be fully exponential or linear**.** The results showed that single-inhaler salmeterol and fluticasone propionate remained cost-effective**.** Another study by *Zafari* et al [58] varied the RR of exacerbation associated PDC, and determined that the full-adherence scenario was

cost-effective, as long as each of the 25% increases in the PDC reduced the exacerbation rates by at least 1.1 fold.

Quality of studies

According to the CHEC-extended, all studies clearly identified the description of the interventions, study designs, time horizons, perspectives, costs, outcomes, discounting, input parameters' uncertainty, and study conclusions. Most studies clearly described their research questions [20 (87.0%)] [52, 54-70, 72, 73], potential conflicts of interest [19 (82.6%)] [52-54, 56, 57, 59, 61-68, 70-74], study populations [18 (78.3%)] [52-62, 64-67, 69, 71, 72], ethical issues [16 (69.6%)] [52, 54-62, 64, 65, 68, 70, 73, 74], and generalizability of the study findings [9 (39.1%)] [52, 55, 57, 58, 61, 62, 64, 66, 68] (Appendix: Table A3). For the quality of reporting the studies estimated by CHEERS, all of them provided the explicit statements of background and objectives, comparators, choice of health outcomes, measurement and valuation of the outcomes, estimating resources and costs, currency, price date and conversion, analytical methods, incremental costs and outcomes, study findings, limitations, generalizability, and current knowledge. Most studies reported their settings and locations [22 (95.7%)] [52-55, 57-74], study perspective [22 (95.7%)] [52-73], source of funding [22 (95.7%)] [52-68, 70-74], study assumptions [21 (91.3%)] [52-69, 72-74], and measurement of effectiveness [20 (87.0%)] [52-67, 69, 70, 72, 73] (Appendix: Table A4).

Discussion

In this chapter, we investigated the extent of studies that considered adherence as part of the economic analyses, and the methods of incorporating it in the economic models. The findings showed that very low numbers of the CEA of asthma incorporated adherence in the analyses, and only the method of incorporating adherence by adjusting treatment effectiveness, according to adherence levels was demonstrated in this review. Two approaches were used to derive the associations between adherence and effectiveness; the first was to apply the mathematical formula developed by an expert panel, and the second was to extrapolate the associations from previous published studies.

Incorporating adherence by adjusting treatment effectiveness according to adherence levels was the only method, exploited in the economic analysis for asthma, while different methods were observed for other diseases**.** A literature review by *Hiligsmann* et al [42] revealed that recent CEA of the interventions for osteoporosis [46, 86, 87] integrated the probabilities of patients that can be at risk of discontinuation over time. The patients were assumed to have a risk of stopping therapy in each cycle. In addition, offset time of the treatment that was similar to the treatment duration, was also applied to the analysis. During this time, the treatment effectiveness is assumed correspondingly. This approach is based on 2 implicit assumptions, first, patients did not receive any medications after stopping the therapy, and second, the effectiveness of interventions throughout the offset time estimated by the author; the RR of fracture reduction linearly declined to zero by the end of time. Some limitations are recognized by using this method. Firstly, many patients, in fact, can restart their medications any time after they discontinued their therapy. The evidence revealed that one-third of patients restarted their medications within 6 months of discontinuation. Secondly, the information of treatment effectiveness during the offset time still lacked supported data, therefore, it is difficult to estimate the effectiveness of interventions during the long-term.

The approach recommended by *Hiligsmann* et al, is to apply real-world estimates among the patients who complied with the medications. Using this approach, patients were classified into 2 groups: (1) compliant patients (Medication possession ratio, MPR ≥ 80%), and (2) poor compliance (MPR < 80%), were assigned the probabilities of being adhered or not based on the real-world adherence data. The associations between adherence levels and the RR of fracture reduction were also assumed accordingly. This approach is in line with what we found in a study by *Zafari* et al [58]. Both studies classified adherence levels into various groups. However, the difference is that in *Zafari* et al study, patients who did not use any medication were applied the RR obtained from a systematic review and meta-analysis of RCT, while in *Hiligsmann* et al studies [47, 88], the authors used this information that was derived from a real-world database. Even though a systematic review and meta-analysis of RCT demonstrates the highest quality of evidence compared to other types of study design [89], using adherence data extrapolated from this will not be

able to provide real-world facts since the pooled estimates were calculated based on the RCT. Therefore, using such data adapted from the real-world database would provide more accurate findings, but the quality of evidence is needed to be confirmed whether it is sufficiently high to synthesize the information that meets healthcare requirements.

Using the Markov model captures the entire cohort of patient adherence in the economic analysis, but not that of individuals. It is noteworthy to highlight the method of incorporating adherence that is exploited in a study by *Slejko* et al [90], who applied a microsimulation modelling technique to determine the real-world adherence scenario of patients with statin therapy for the primary prevention of cardiovascular (CV) disease. A Markov model was modified to simulate individual adherence to statins, by integrating 3 additional health states in the existing Markov structure; these health states represented the different levels of adherence that were measured as the PDC: (1) PDC < 20% (2) 20% ≤ PDC < 80% (3) PDC ≥ 80%. They assigned transition probabilities between the PDC levels, and applied the associations between changes in adherence to statins and the risk of CV events, according to pharmacy claims data that particularly reflected patient adherence history. The microsimulation technique identifies individual patients by tracking their characteristics and disease backgrounds, and then uses the recorded information to adjust the transition probabilities, effectiveness, utility values and costs, to reflect the patient history over the study period. The use of microsimulation models have a potential to provide more accurate data than the cohort-based ones. The drawbacks of this are the difficulty in obtaining relevant input parameters, and more detail required for the data set in the modelling approach, therefore, there is a greater variance in the results due to the random variations of individual outcomes [91]. With respect to some advantages of this technique, microsimulation modelling might be considered another method apart from ours above that can be used for conducting future economic analyses which incorporate adherence in the models.

Among the included CEA which incorporated adherence in the models, RCT was used as a source of adherence data in 2 studies, while observational studies were applied in the other 2. Although RCT minimizes the potential biases and confounders that may arise from study methodology and the clinical heterogeneities, it restricts the

characteristics of participants, types of intervention, and the outcomes of interest. This raises concerns on generalizability of the study findings that may be limited by restrictions. Adherence data would ideally be derived from observational studies or patient claims. Many factors, i.e., age, comorbidities, and the number of medications, are associated with patient adherence [92], and have an impact on economic consequences. However, it is vital to ensure the quality of observational studies to obtain accurate estimates based on real world evidence under specified contexts.

While the aim of this work was to conduct a systematic review that complied with a PRISMA guideline, some of its limitations were acknowledged. Firstly, the majority of included studies failed to report the structural assumptions and validation methods of their economic models, as well as the values, ranges, and probability distributions among input parameters. Caution should be exercised when interpreting the study findings because biases arising from these could affect their reported outcomes, and thus limited the generalizability of the results. This suggests that further research with rigorous methodology pertaining to this area is warranted to prevent the potential for biases and imprecisions. Secondly, some of the non-English articles were identified through our search results, however, only the studies published in English were included in this review due to the lack of experts in other languages. This may be one of the reasons why a limited number of studies incorporating adherence have been identified. In addition, although a number of non-decision model-based CEA were identified from the search results, the primary objective was to summarize the methods of incorporating adherence in the economic models by only using the model-based CEA. The current review will provide the most updated evidence relating to the methods of incorporating adherence in the CEA of asthma based on justified assumptions and study methodology.

Conclusion

This systematic review gathered all relevant evidence in regard to the CEA of asthma, and summarized the methods of incorporating adherence in the economic models. A very low number of CEA incorporated adherence in the analyses, and all of them adjusted treatment effectiveness according to adherence levels, applied to the models. The findings will provide healthcare professionals and policy makers with

current evidence of the methods used to incorporate adherence in the economic analysis.

CHAPTER IV: ASSOCIATION BETWEEN ADHERENCE AND SEVERE ASTHMA EXACERBATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Research question

How different levels of adherence affect severe asthma exacerbation?

Research objective

To assess the association between adherence and severe asthma exacerbation

Methods

Search strategy

A literature search was performed from inception to November 2018 on the following databases: PubMed, CENTRAL, EMBASE and ClinicalTrials.gov. All the search terms are presented in Appendix: Table A5. The bibliographies of retrieved articles were also examined to identify relevant studies that were not indexed in the aforementioned databases.

Study selection

Initially, the titles and abstracts were screened to identify potential studies**.** Randomized controlled trials (RCT), cohort and case-control studies that investigated the impact of adherence to controller medications were identified, and the outcome was severe asthma exacerbation, defined as hospitalizations, emergency department (ED) visits or treatment with systemic corticosteroid [93-95]. Only studies published in English were included, and their full texts were assessed by Bunchai Chongmelaxme (BC) and Piyameth Dilokthornsakul (PD), with all disagreements between the investigators being resolved by a third reviewer [Nathorn Chaiyakunapruk (NC)].

Data extraction and quality assessment

Data extraction was undertaken by BC and PD, using a standardized form. This included the authors' name, year of publication, country of origin, study design, the characteristics of participants and interventions, adherence data, outcome, duration, and results. All studies were assessed for their methodological qualities using Cochrane risk of bias tool for RCT [96], and Newcastle-Ottawa scale for cohort and case-control studies [97] (Appendix: Table A6).

Data analysis

A meta-analysis was performed to provide pooled odds ratio (OR) along with 95% confidence interval (CI), and the Dersimonian and Laird random-effects models were employed to take into account both within and between study variability. Heterogeneity among the studies was assessed using the chi-squared (χ^2) and I^2 statistical test [98]. The thresholds of I^2 were interpreted as follows: might not be important (0 - 40%); may represent moderate heterogeneity (30 - 60%); may represent substantial heterogeneity (50 - 90%); and considerable heterogeneity (75 - 100%). Once a heterogeneity was observed, the potential sources of this was explored correspondingly. All the analyses were performed using STATA version 15.0 (Stata Corp., College Station, Tex).

Results

The initial search yielded 8,061 articles, of which 2,530 duplicates were removed. The remaining 5,531 articles were screened via titles and abstracts. A total of 2,431 articles were excluded because of their irrelevance to asthma and the study designs. This resulted in 3,100 articles being assessed for their eligibility, 34 of which were included in this review for qualitative synthesis, and 8 of which for quantitative synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Figure 3. Results of the initial search are presented in Appendix: Table A5.

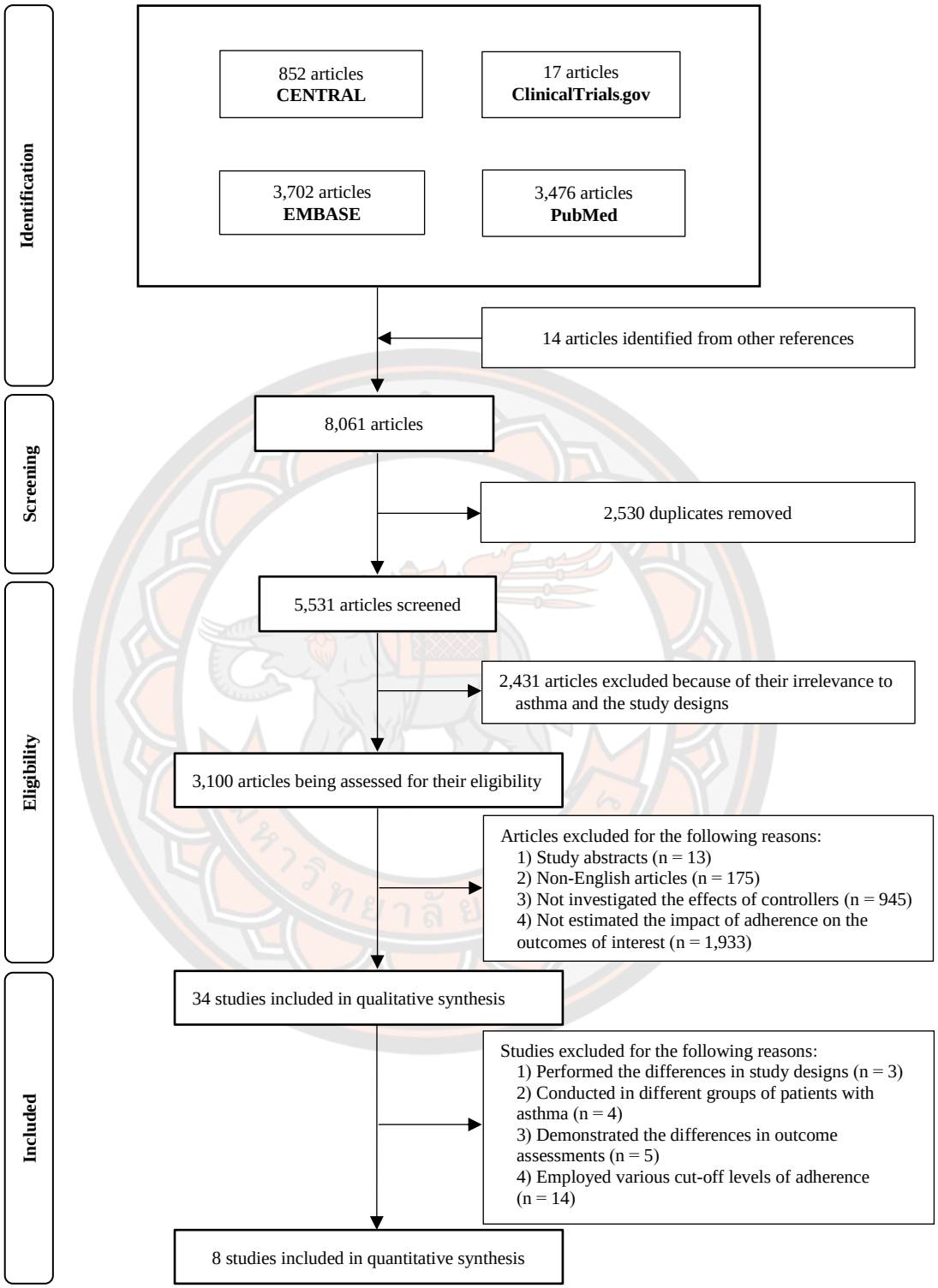


Figure 3. The PRISMA flow diagram describes the study selection process

General characteristics

Nineteen studies of the 34 studies (55.8%) were conducted in North America (United States, US [12, 17, 84, 99-113] and Canada [114]). Eleven (32.3%) were from Europe (United Kingdom, UK [115-120], Italy [121, 122], Netherlands [123, 124] and Spain [125]). Two (5.9%) were from South America (Brazil) [13, 126], while another two (5.9%) were from Asia (Korea [127] and Singapore [128]). The majority of them were cohort [30 studies (88.2%)] [12, 13, 17, 84, 99-102, 104-113, 115-120, 122, 123, 125-128], and only four of them had a different design; RCT [103], nested case-control [124], combined cohort and case-crossover [114], as well as combined case-crossover and case-case-time control [121]. The study sample sizes ranged from 37 to 97,743, while treatment durations were from 3 to 70.6 months (Table 6).

Table 6. Characteristics of the studies

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
Bukstein (2003) [99] US	Prospective cohort	6 - 15	65	104	ICS + LTRA	The number of prescriptions refilled by patients	12
Bukstein (2007) [100] US	Retrospective cohort	0 - 4	58.7	11407	1) ICS 2) All controller medications	The number of prescriptions refilled by patients	12
Camargo (2007) [112] US	Retrospective cohort	0 - 8	62	10976	1) ICS 2) LTRA	MPR; the number of medication days supplied, divided by the length of follow-up	12
Corrao (2016) [121] Italy	1) Case-crossover 2) Case-case-time-control	18 - 40	48.2	2335	ICS	The number of prescriptions refilled by patients	12
De Llano (2018) [125] Spain	Prospective cohort	18 - 75	35	197	ICS	1) Self-report use of medications; 10-item Test of Adherence to Inhalers 2) Electronic prescription refill rate; the number of prescriptions dispensed at pharmacies, divided by the total number of prescriptions in the study period, and multiplied by 100	6

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
Delea (2008) [101] US	Retrospective cohort	≥ 12	41	12907	ICS/LABA	MPR; the number of medication days supplied, divided by the length of follow-up	6
Elkout (2012) [115] UK	Retrospective cohort	0 - 18	62	3172	1) ICS 2) LTRA 3) ICS/LABA 4) ICS + LABA	MPR; the number of medication days supplied, divided by the length of follow-up	24
Engelkes (2016) [123] Netherlands	Retrospective cohort	5 - 18	59	14303	ICS	MPR; the number of medication days supplied, divided by the length of follow-up	NR
Herndon (2012) [102] US	Retrospective cohort	2 - 18	60	18456	1) ICS 2) LTRA	MPR; the number of medication days supplied, divided by the length of follow-up	24
Hyland (2012) [116] UK	Retrospective cohort	21 - 61	35	166	ICS	The number of prescriptions refilled by patients	24
Ismaila (2014) [114] Canada	1) Retrospective cohort 2) Case-crossover	> 12	45.8	19126	ICS/LABA	MPR; the number of medication days supplied, divided by the length of follow-up	60
Kang (2018) [127] Korea	Cohort	≥ 20	34.15	22130	All controller medications	MPR; the number of medication days supplied, divided by the length of follow-up	70.6 ± 28.6

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
Krishnan (2012) [103] US	RCT	5 - 12	53.6	140	ICS	1) Self-reported use of medications; recorded daily on a study diary card 2) Recording the number of doses remaining; the number of doses used, divided by the number of doses prescribed, and multiplied by 100	12
Lasmar (2009) [13] Brazil	Prospective cohort	3 - 12	66.4	122	ICS	The number of doses refilled, divided by the number of doses prescribed, and multiplied by 100	48
Maio (2018) [122] Italy	Cohort	≥ 18	39.4	493	All controller medications	NR	12
Makhinova (2015) [104] US	Retrospective cohort	5 - 63	51.8	32172	All controller medications	PDC; the number of days that the medication was available, divided by the number of days in the specific interval or study period	NR
Mathison (2005) [105] US	Cohort	13 - 88	NR	186	ICS/LABA	The number of prescriptions refilled by patients	12
Mattke (2010) [113] US	Retrospective cohort	0 - 65	43	41234	1) ICS 2) LTRA	MPR; the number of medication days supplied, divided by the length of follow-up	24

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
McMahon (2000) [117] UK	Cohort	12 - 45	NR	4535	ICS	The number of days for which a patient with ICS	3
Mcnally (2009) [106] US	Cohort	5 - 17	71	63	ICS + LTRA	Electronic monitoring device	12
Osman (1999) [120] UK	Cohort	≥ 18	43	754	ICS + LABA	The number of prescriptions refilled by patients	12, 24
Papi (2018) [118] UK	Retrospective cohort	≥ 18	34	7195	ICS	1) Self-report used of medications; 6-point medication adherence rating scale 2) MPR; the number of medication days supplied, divided by the length of follow-up	NR
Price (2013) [119] UK	Retrospective cohort	12 - 80	41	30354	ICS	MPR; the number of medication days supplied, divided by the length of follow-up	12
Rohan (2010) [107] US	Prospective cohort	5 - 17	70	92	ICS	Electronic monitoring device	9 - 12
Rust (2013) [108] US	Retrospective cohort	5 - 12	60	43156	ICS	PDC; the number of days that the medication was available, divided by the number of days in the specific interval or study period	3

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
Santos (2008) [126] Brazil	Prospective cohort	≥ 18	25	160	ICS	1) The number of capsules actually used during the period, divided by the number of capsules that should have been used, and multiplied by 100 2) The inhalers were weighted at the time of dispensing, and after 30 days of use	6
Smith (2007) [110] US	Retrospective cohort	2 - 17	55	1474	ICS	The number of prescriptions refilled by patients	24
Smith (2009) [109] US	Cohort	5 - 62	32.6	3013	ICS + LTRA + ICS/LABA	MPR; the number of medication days supplied, divided by the length of follow-up	12
Stern (2006) [12] US	Retrospective cohort	6 - 99	40.9	97743	All controller medications	1) MPR; the number of medication days supplied, divided by the length of follow-up 2) The number of prescription refilled by patients	12
Tay (2018) [128] Singapore	Cohort	≥ 18	47.6	340	ICS + LAMA + ICS/LABA	MPR; the number of medication days supplied, divided by the length of follow-up	12
Vasbinder (2016) [124] Netherlands	Nested case-control	5 - 12	57	646	1) ICS 2) ICS/LABA	MPR; the number of medication days supplied, divided by the length of follow-up	12

First author (y) / Country	Study design	Patient characteristics		Sample size	Types of controller treatment	Measurements of adherence	Duration (m)
		Age (y)	*Male (%)*				
Weinstein (1997) [111] US	Cohort	2 - 17	62	37	Theophylline	Serum levels of theophylline	12
Williams (2004) [84] US	Retrospective cohort	18 - 50	33.3	405	ICS	1) CMA; the cumulative days' supply, divided by the total number of days between refills during the observation period 2) CMG; the total days of treatment gaps, divided by the total number of days between refills during the observation period	24
Williams (2011) [17] US	Cohort	12 - 56	31.5	298	ICS	MPR; the number of medication days supplied, divided by the length of follow-up	6

CMA, continuous multiple interval measure of medication availability; CMG, continuous multiple interval measure of medication gaps; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; MPR, medication possession ratio; NR, no reported; PDC, proportion of days covered; UK, United Kingdom; US, United States

The largest number of studies [10 (29.4%)] were conducted on adults [84, 116, 118, 120-122, 125-127], followed by children and adolescents [8 (23.5%)] [99, 102, 106, 107, 110, 111, 115, 123], adolescents and adults [6 (17.6%)] [17, 101, 105, 114, 117, 119], children [6 (17.6%)] [13, 100, 103, 108, 112, 124], as well as children, adolescents and adults [4 (11.8%)] [12, 104, 109, 113], respectively (Table 6). Inhaled corticosteroids (ICS) were employed in 15 studies (44.3%) [13, 17, 84, 103, 107, 108, 110, 116-119, 121, 123, 125, 126], followed by inhaled corticosteroids/ long-acting beta-agonists (ICS/LABA) [4 (11.8%)] [101, 105, 114, 120], inhaled corticosteroids/leukotriene receptor antagonists (ICS/LTRA) [2 (5.9%)] [99, 106], and other controller groups (Table 6). The majority of studies applied data from refilled prescriptions to measure adherence; medication possession ratio (MPR) [13 (38.4%)] [17, 101, 102, 109, 112-115, 119, 123, 124, 127, 128], the number of prescriptions refilled by patients [7 (20.7%)] [99, 100, 105, 110, 116, 120, 121], and proportion of days covered (PDC) [2 (5.9%)] [104, 108].

Electronic monitoring devices were used in 2 studies (5.9%) [106, 107], while counting/ weighing [1 study (2.9%)] [126], and biomedical measurement [1 study (2.9%)] [111], and other adherence measurements were less commonly used (Table 11). Various cut-off levels of adherence were used to compare the risk of exacerbation; greater than or equal to (≥) 80% vs less than (<) 80% [9 studies (26.6%)] [114, 115, 118, 122-126, 128], ≥ 50% and 20 - 49% vs < 20% [2 studies (5.9%)] [102, 127], > 80% and 50 - 80% vs < 50% [1 study (2.9%)] [109], and others (Table 7). Definitions of asthma exacerbation varied from study to study. Hospitalizations, ED visits or treatment with systemic corticosteroid, were the most commonly used [9 studies (26.6%)] [13, 106, 107, 116, 118, 119, 123, 125, 127], followed by hospitalizations or ED visits [4 (11.8%)] [12, 100, 109, 112], hospitalizations or treatment with systemic corticosteroid [2 (5.9%)] [105, 124], and others (Table 7).

Table 7. A summary of adherence data and the results

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	*Treatment effect*
Studies that reported the adherence affecting severe exacerbation according to adherence levels				
Camargo (2007) [112]	≥ Med; < Med *non-nebulized ICS (0.08), nebulized ICS (0.08), LTRA (0.16)	Combined: Hospitalizations/ED visits	1) ≥ Med vs < Med (non-nebulized ICS)	OR = 0.25 (95% CI: 0.13, 0.47), *P* = .003
			2) ≥ Med vs < Med (nebulized ICS)	OR = 0.32 (95% CI: 0.15, 0.68), *P* < .001
			3) ≥ Med vs < Med (LTRA)	OR = 0.30 (95% CI: 0.14, 0.66), *P* = .003
Delea (2008) [101]	75 - 100%; 50 - < 75%; 25 - < 50%; < 25%; Per 25% increase	1) Combined: Hospitalizations/ED visits 2) Systemic corticosteroid	Hospitalizations/ED visits	
			1) 25 - < 50% vs < 25%	OR = 0.79 (95% CI: 0.64, 0.99), *P* = .041
			2) 50 - < 75% vs < 25%	OR = 0.74 (95% CI: 0.58, 0.94), *P* = .013
			3) 75 - 100% vs < 25%	OR = 0.68 (95% CI: 0.54, 0.87), *P* = .002
			4) Per 25% increase	OR = 0.90 (95% CI: 0.89, 0.92), *P* < .001
			Systemic corticosteroid	
			1) 25 - < 50% vs < 25%	OR = 0.99 (95% CI: 0.90, 1.08), *P* = .760
			2) 50 - < 75% vs < 25%	OR = 0.93 (95% CI: 0.84, 1.03), *P* = .171
			3) 75 - 100% vs < 25%	OR = 0.93 (95% CI: 0.84, 1.04), *P* = .214
				OR = 0.97 (95% CI: 0.94, 0.996),

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
			4) Per 25% increase	*P* = .027
			Hospitalizations/ED visits	Mean (SD) = 0.01 (0.13)
			1) < 25%	Mean (SD) = 0.01 (0.13)
			2) 25 - 50%	Mean (SD) = 0.01 (0.12)
			3) 50 - < 75%	Mean (SD) = 0.01 (0.11)
			4) ≥ 75%	Mean (SD) = 0.01 (0.12)
			5) All	
			Systemic corticosteroid	Mean (SD) = 0.08 (0.33)
			1) < 25%	Mean (SD) = 0.10 (0.37)
			2) 25 - 50%	Mean (SD) = 0.09 (0.38)
			3) 50 - < 75%	Mean (SD) = 0.09 (0.37)
			4) ≥ 75%	Mean (SD) = 0.09 (0.36)
			5) All	
Elkout (2012) [115]	80 - 120%; < 80 - 120%	Systemic corticosteroid	1) 80 - 120% vs < 80 - 120% (ICS)	OR = 1.02 (95% CI: 1.00, 1.04), *P* = .18
			2) 80 - 120% vs < 80 - 120% (LTRA)	OR = 1.34 (95% CI: 0.79, 2.27), *P* = .26
			3) 80 - 120% vs < 80 - 120% (ICS/LABA)	OR = 1.12 (95% CI: 0.58, 2.11), *P* = .53
			4) 80 - 120% vs < 80 - 120% (ICS + LABA)	OR = 1.43 (95% CI: 0.75, 2.71), *P* = .27
Engelkes (2016) [123]	1) Quartile 4 (87); Quartile 1 (37)	Combined: Hospitalizations/ED visits/systemic corticosteroid	1) > Quartile 4 vs < Quartile 1	Rate ratio = 0.83 (95% CI: 0.71, 0.95)
	2) ≥ 0.8; < 0.8		2) ≥ 0.8 vs < 0.8	Rate ratio = 0.88 (95% CI: 0.79, 0.97)

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
Herndon (2012) [102]	≥ 50%; 20 - 49%; 0 - 19%	Hospitalizations, ED visits	Hospitalizations	
			1) 20 - 49% vs 0 - 19% (ICS)	OR = 1.27 (95% CI: 1.04, 1.55)
			≥ 50% vs 0 - 19% (ICS)	OR = 0.96 (95% CI: 0.67, 1.36)
			2) 20 - 49% vs 0 - 19% (LTRA)	OR = 0.80 (95% CI: 0.52, 1.23)
			≥ 50% vs 0 - 19% (LTRA)	OR = 0.75 (95% CI: 0.42, 1.35)
			ED visits	
			1) 20 - 49% vs 0 - 19% (ICS)	OR = 0.96 (95% CI: 0.84, 1.09)
			≥ 50% vs 0 - 19% (ICS)	OR = 0.56 (95% CI: 0.43, 0.72)
			2) 20 - 49% vs 0 - 19% (LTRA)	OR = 0.94 (95% CI: 0.80, 1.12)
			≥ 50% vs 0 - 19% (LTRA)	OR = 0.68 (95% CI: 0.53, 0.86)
Hyland (2012) [116]	≥ 75%; < 75%	Combined: Hospitalizations/ED visits/systemic corticosteroid	Correlation between adherence and outcomes	r = 0.21, *P* = .007
Kang (2018) [127]	≥ 50%; 20 - 49%; < 20%	Combined: Hospitalizations/ED visits/systemic corticosteroid	1) 20 - 49% vs < 20% (mild)	OR = 1.040 (95% CI: 0.878, 1.231), *P* = .6507
			≥ 50% vs < 20% (mild)	OR = 1.147 (95% CI: 0.985, 1.33), *P* = .0768
			2) 20 - 49% vs < 20% (moderate)	OR = 0.652 (95% CI: 0.538, 0.790), *P* < .0001
			≥ 50% vs < 20% (moderate)	OR = 0.828 (95% CI: 0.707, 0.971), *P* = .0202
			3) 20 - 49% vs < 20% (severe)	OR = 0.632 (95% CI: 0.277, 1.441), *P* = .2752
			≥ 50% vs < 20% (severe)	OR = 0.362 (95% CI: 0.185, 0.708), *P* = .0030

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
Krishnan (2012) [103]	≥ 80%; 50 - 79%; < 50%	ED visits, systemic corticosteroid	1) ED visits 2) Systemic corticosteroid	OR, *P* = .58 No. of OCS use, *P* = .56
Lasmar (2009) [13]	NR	Combined: Hospitalizations/ED visits/systemic corticosteroid	Patients w/o exacerbations vs with exacerbations	Med adherence levels: 70.9% vs 44%, *P* = .004
Maio (2018) [122]	≥ 80%; < 80%	NR	≥ 80% vs < 80%	OR = 0.39 (95% CI: 0.15, 1.03)
Makhinova (2015) [104]	≥ 50%; < 50%	Systemic corticosteroid	Adherent patients had 0.11 fewer OCS claims compared with non-adherent patients	B = -0.11125, *P* < .0001
Mattke (2010) [113]	Quartile 4; Quartile 1	Hospitalizations, ED visits	Hospitalizations 1) Quartile 1 vs Quartile 4 (ICS) 2) Quartile 1 vs Quartile 4 (LTRA) ED visits 1) Quartile 1 vs Quartile 4 (ICS) 2) Quartile 1 vs Quartile 4 (LTRA)	 Med (range), *P* > .05 Med (range) = 34 (22 - 52) vs 13 (8 - 22), *P* < .05 Med (range), *P* > .05 Med (range) = 80 (62 - 102) vs 36 (27 - 49), *P* < .05
Mcnally (2009) [106]	1) Quartile 4; Quartile 1 (ICS) 2) Quartile 4; Quartile 1 (LTRA) *ICS: Quartile	Combined: Hospitalizations/ED visits/systemic corticosteroid (health care utilization)	Only low adherence groups among both ICS and LTRA increased their health care utilization	No. of health care utilization, *P* < .05

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	*Treatment effect*
	1 (0.62); Quartile 4 (0.20) LTRA: Quartile 1 (0.71); Quartile 4 (0.17)			
Papi (2018) [118]	≥ 80%; < 80% (good score for all the questions)	Combined: Hospitalizations/ED visits/systemic corticosteroid	≥ 80% vs < 80%	OR = 1.3 (95% CI: 0.93, 1.84)
Price (2013) [119]	100%; ≥ 70 - 99%; ≥ 50 - 69%; < 50%	Combined: Hospitalizations/ED visits/systemic corticosteroid	100% vs ≥ 70 - 99% vs ≥ 50 - 69% vs < 50%	Higher exacerbation rates by better adherence
Rohan (2010) [107]	1 SD above the mean; Mean adherence; 1 SD below the mean	Combined: Hospitalizations/ED visits/systemic corticosteroid (health care utilization)	1 SD above the mean vs Mean adherence vs 1 SD below the mean	Mean = 0.65 vs 0.70 vs 0.76
Rust (2013) [108]	≥ 50%; < 50%	Hospitalizations, ED visits	1) ≥ 50% vs < 50% (hospitalizations) 2) ≥ 50% vs < 50% (ED visits)	OR = 1.61 (95% CI: 1.43, 1.85), *P* < .05 OR = 1.08 (95% CI: 1.02, 1.14), *P* < .05
Santos (2008) [126]	≥ 80%; < 80%	1) Exacerbation (NR) 2) ED visits	1) ≥ 80% vs < 80% 2) ED visits	OR = 0.84 (95% CI: 0.42, 1.66) Mean (SD) = 0.9 (1.9) vs 1.4 (2.6), *P* = .2
Smith	> 80%; 50 -	Combined:	1) 50 - 80% vs < 50%	OR = 1.59 (95% CI: 0.86, 2.96),

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
(2009) [109]	80%; < 50%	Hospitalizations/ED visits		*P* = .14
			2) > 80% vs < 50%	OR = 2.11 (95% CI: 1.09, 4.12), *P* = .03
Tay (2018) [128]	≥ 80%; < 80%	Systemic corticosteroid	≥ 80% vs < 80%	OR = 0.675 (95% CI: 0.313, 1.455), *P* = .316
Vasbinder (2016) [124]	≥ 80%; < 80%	Combined: Hospitalizations/systemic corticosteroid	1) ≥ 80% vs < 80% (ICS)	RR = 1.067 (95% CI: 0.391, 2.916), *P* = .899
			2) ≥ 80% vs < 80% (ICS/LABA)	RR = 4.340 (95% CI: 1.204, 15.640), *P* = .025
Williams (2004) [84]	Per 25% increase in adherence	Hospitalizations, ED visits, systemic corticosteroid	1) Per 25% increase in CMA (OCS)	Rate ratio = 0.75 (95% CI: 0.58, 0.97)
			2) Per 25% increase in CMG (hospitalization)	Rate ratio = 2.01 (95% CI: 1.06, 3.79), *P* < .05
			3) Per 25% increase in CMG (ED visit)	Rate ratio = 1.25 (95% CI: 0.84, 1.85)
			4) Per 25% increase in CMG (OCS)	Rate ratio = 1.26 (95% CI: 0.95, 1.67)
			Correlation between CMA and outcomes	
			1) Hospitalizations	r = -0.130
			2) ED visits	r = -0.159, *P* < .05
			3) OCS	r = -0.179, *P* < .05
			Correlation between CMG and outcomes	
			1) Hospitalizations	r = 0.147
			2) ED visits	r = 0.171, *P* < .05
			3) OCS	r = 0.190, *P* < .05

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
Williams (2011) [17]	Per 25% increase in adherence	1) Combined: Hospitalizations/ED visits/ systemic corticosteroid 2) Hospitalizations 3) ED visits 4) Systemic corticosteroid	1) Per 25% increase (exacerbation) 2) Per 25% increase (hospitalizations) 3) Per 25% increase (ED visits) 4) Per 25% increase (OCS)	HR = 0.89 (95% CI: 0.81, 0.97), *P* = 0.009 HR = 0.99 (95% CI: 0.65, 1.51), *P* = 0.971 HR = 0.87 (95% CI: 0.73, 1.03), *P* = 0.114 HR = 0.90 (95% CI: 0.80, 1.00), *P* = 0.043
Weinstein (1997) [111]	≥ 5 mg/L; < 5 mg/L	Hospitalizations, ED visits, systemic corticosteroid	Hospital days 1) ≥ 5 vs < 5 mg/L (1 year prior to admission) 2) ≥ 5 vs < 5 mg/L (1 year follow-up) ED visits 1) ≥ 5 vs < 5 mg/L (1 year prior to admission) 2) ≥ 5 vs < 5 mg/L (1 year follow-up) Systemic corticosteroid 1) ≥ 5 vs < 5 mg/L (1 year prior to admission) 2) ≥ 5 vs < 5 mg/L (1 year follow-up)	Med (range) = 9 (0 - 9) vs 6.5 (0 - 19), *P* = .49 Med (range) = 0 (0 - 9) vs 0 (0 - 6), *P* = .92 Med (range) = 4 (1 - 18) vs 6 (2 - 11), *P* = .23 Med (range) = 0 (0 - 9) vs 2 (0 - 9), *P* = .06 Med (range) = 2 (0 - 12) vs 3 (0 - 11), *P* = .44 Med (range) = 2 (0 - 9) vs 3.5 (0 - 8), *P* = .16

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	*Treatment effect*
Studies that reported the adherence affecting severe exacerbation according to the number of refilled prescriptions, number of days that a subject used medications, discontinuation of therapy, and others				
Bukstein (2003) [99]	≥ 6 prescriptions; ≤ 5 prescriptions	Systemic corticosteroid	≥ 6 vs ≤ 5 fills	OR = 0.46 (95% CI: 0.20, 1.06)
Bukstein (2007) [100]	≥ 2 prescriptions;1 prescription	Combined: Hospitalizations/ED visits	1) ≥ 2 vs ≤ 1 fills (ICS)	OR = 0.61 (95% CI: 0.37, 0.99), *P* = .48
			2) ≥ 2 vs ≤ 1 fills (all controllers)	OR = 0.80 (95% CI: 0.59, 1.10)
Corrao (2016) [121]	Discontinued; continued	Systemic corticosteroid	1) Discontinued vs continued (case-crossover)	OR = 2.50 (95% CI: 1.11, 5.56)
			2) Discontinued vs continued (case-case-time control)	OR = 3.23 (95% CI: 1.00, 10.00)
De Llano (2018) [125]	1) > 80%; ≤ 80% 2) = 50; < 50	Combined: Hospitalizations/ED visits/systemic corticosteroid	1) > 80% vs ≤ 80%	OR = 0.83 (95% CI: 0.33, 2.12)
			2) = 50 vs < 50	OR = 0.73 (95% CI: 0.30, 1.80)
Ismaila (2014) [114]	1) ≥ 80%; < 80% 2) Discontinued; continued	1) Combined: Hospitalizations/ED visits/ systemic corticosteroid 2) Hospitalizations, ED visits, systemic corticosteroid	1) ≥ 80% vs < 80% (exacerbation, retrospective cohort)	OR = 0.48 (95% CI: 0.44, 0.54), *P* < .001
			≥ 80% vs < 80% (exacerbation, case-crossover)	OR = 0.808 (95% CI: 0.763, 0.855)
			≥ 80% vs < 80% (hospitalizations)	OR = 0.49 (95% CI: 0.42, 0.57), *P* < .001
			≥ 80% vs < 80% (ED visits)	OR = 0.48 (95% CI: 0.36, 0.64), *P* < .001
			≥ 80% vs < 80% (OCS)	OR = 0.46 (95% CI: 0.42, 0.52), *P* < .001
			2) Discontinued vs Continued (exacerbation)	OR = 0.42 (95% CI: 0.38, 0.48), *P* < .001

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	***Treatment effect***
			Discontinued vs Continued (hospitalizations)	OR = 0.41 (95% CI: 0.35, 0.49), *P* < .001
			Discontinued vs Continued (ED visits)	OR = 0.31 (95% CI: 0.21, 0.46), *P* < .001
			Discontinued vs Continued (OCS)	OR = 0.36 (95% CI: 0.32, 0.40), *P* < .001
Mathison (2005) [105]	Continued; Discontinued	1) Combined: Hospitalizations/systemic corticosteroid 2) ED visits	1) Discontinued vs Continued 2) Discontinued vs Continued (ED visits)	OR = 1.79 (95% CI: 0.89, 3.62) Mean (SD) = 2.74 (0.29) vs 2.58 (0.16)
McMahon (2000) [117]	90 days; 1 - 89 days; 0 day	1) Combined: Hospitalizations/systemic corticosteroid 2) Hospitalizations	Hospitalizations/OCS 1) 90 vs 1 - 89 days 2) 90 vs 0 days Hospitalizations 1) 90 vs 1 - 89 days 2) 90 vs 0 days	 OR = 0.98 (95% CI: 0.58, 1.67) OR = 1.30 (95% CI: 0.74, 2.27) OR = 0.98 (95% CI: 0.58, 1.67) OR = 1.30 (95% CI: 0.74, 2.27)
Osman (1999) [120]	1) ≥ 7 prescriptions; < 7 prescriptions (LABA) 2) ≤ 4 prescriptions; 5 - 7 prescriptions; ≥ 8 prescriptions	Hospitalizations, systemic corticosteroid	Hospitalizations 1) ≥ 7 LABA ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 1) ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 2) 2) < 7 LABA ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 1) ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 2) OCS 1) ≥ 7 LABA ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 1) ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 2)	 N = 18% vs 15% vs 9% N = 19% vs 7% vs 7% N = 8% vs 7% vs 13% N = 7% vs 10% vs 13% Mean = 2.8 vs 2.1 vs 2.5 Mean = 4.6 vs 3.2 vs 3.4

First author (y)	Cut-off levels of adherence	Definitions of asthma exacerbation	Results	
			Group comparison	*Treatment effect*
	(ICS)		2) < 7 LABA ≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 1)	Mean = 0.9 vs 1.2 vs 1.5
			≤ 4 vs 5 - 7 vs ≥ 8 ICS (year 2)	Mean = 1.8 vs 2.0 vs 2.2
Smith (2007) [110]	1 - 2 fills; 0 fill	ED visits	1) 1 - 2 vs 0 fill (year 2000)	OR = 0.08 (95% CI: 0.05, 0.15), *P* < .001
			2) 1 - 2 vs 0 fill (year 2001)	OR = 0.15 (95% CI: 0.09, 0.24), *P* < .001
Stern (2006) [12]	1) ≥ Med vs < Med	Combined: Hospitalizations/ED visits	1) ≥ Med vs < Med	OR = 0.912 (95% CI: 0.881, 0.944), *P* < .001
	2) ≥ Quartile 3 vs < Quartile 3		2) ≥ Quartile 3 vs < Quartile 3	OR = 0.862 (95% CI: 0.827, 0.898), *P* < .001
	3) ≥ 2 vs < 2 fills		3) ≥ 2 vs < 2 fills	OR = 0.938 (95% CI: 0.906, 0.971), *P* = .002
	4) ≥ 3 vs < 3 fills		4) ≥ 3 vs < 3 fills	OR = 0.909 (95% CI: 0.877, 0.942), *P* < .001
	5) ≥ 4 vs < 4 fills		5) ≥ 4 vs < 4 fills	OR = 0.894 (95% CI: 0.860, 0.929), *P* < .001
	6) ≥ 6 vs < 6 fills d (0.1370), Quartile 3 (0.3288)		6) ≥ 6 vs < 6 fills	OR = 0.891 (95% CI: 0.851, 0.933), *P* < .001

CMA, continuous multiple interval measure of medication availability; CMG, continuous multiple interval measure of medication gaps; ED, emergency department; HR, hazard ratio; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists;

LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; Med, median; MPR, medication possession ratio; NR, no reported; OCS, oral corticosteroids; OR, odds ratio; PDC, proportion of days covered; RR, risk ratio; SD, standard deviation; UK, United Kingdom; US, United States

Association between adherence to controller medications and severe asthma exacerbation

Studies that reported the adherence affeccting severe exacerbation according to adherence levels

The studies by *McNally* et al [106] and *Rohan* et al [107] showed that the decline in adherence was related to the increase in numbers of exacerbation. Another study by *Mattke* et al [113] demonstrated patients with the highest quartile adherence to LTRA had fewer exacerbations than the lowest quartile, but this did not apply to ICS. In a study by *Makhinova* et al [104], the patients with ≥ 50% adherence showed less exacerbation than patients with < 50% adherence, while other studies by *Delea* et al [101] and *Weinstein and Faust* [111] did not report any association. In a study by *Lasmar* et al [13], increase in adherence was found to reduce exacerbation. The studies by *Delea* et al [101] and *William* et al [17] demonstrated that every 25% increase in adherence was associated with decreased exacerbation, but a study by *William* et al [84] showed no association. A study by *Camargo* et al [112] concluded that the patients with ≥ median MPR experienced a reduction in exacerbation, compared to those wih < median MPR. Another study by *Engelkes* et al [123] showed that patients with ≥ 80% adherence experienced decreased exacerbation, compared to those with < 80% adherence. Conversely, some studies [103, 115, 118] did not find the association, while others [108, 109, 116, 119, 124] reported an increase in exacerbation, even though adherence increased (Table 7).

Studies that reported the adherence affecting severe exacerbation according to the number of refilled prescriptions, number of days that a subject used medications, discontinuation of therapy, and others

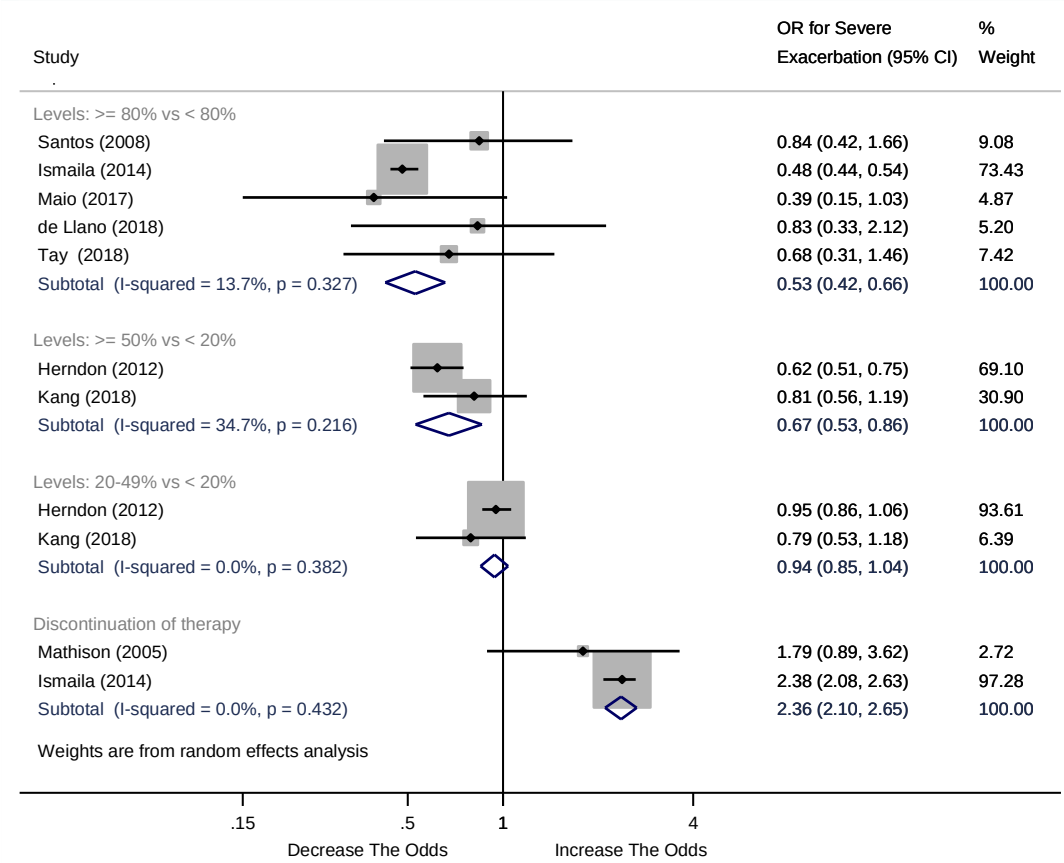
In a study by *Smith* et al [110], patients with some refilled prescriptions experienced a decreased in exacerbation, compared to people without prescriptions, while in a study by *Bukstein* et al [100], those with prescriptions for nebulized ICS ≥ 2 experienced a reduction of exacerbation but not for all controller medications. However, another study by *Bukstein* et al [99] did not find any difference between ≥ 6 and < 6 prescriptions. Similarly, a study by *McMahon* et al [117] did not find a difference between the patients with ICS for 90 days and < 90 days. In a study by

Corrao et al [121], the authors showed that discontinuation of therapy was associated with increased exacerbations. A study by *Osman* et al [120] demonstrated that patients treated with LABA who had low adherence to ICS, showed the highest number of exacerbations, and a study by *Stern* et al [12] reported the association between a decreased in exacerbation and adherent patients (Table 7).

A quantitative meta-analysis of the association between adherence levels and severe exacerbation

Among the 34 studies that reported such association, 26 were not included in a meta-analysis, because they performed the differences in study designs (3) [103, 121, 124], conducted in different groups of patients with asthma (4) [108, 109, 115, 118], demonstrated the differences in outcome assessments (5) [13, 17, 84, 104, 123], and employed various cut-off levels of adherence (14) [12, 99-101, 106, 107, 110-113, 116, 117, 119, 120] (Table 7).

Eight studies that reported the odds of exacerbation between various adherence groups were included in the analysis: ≥ 80% vs < 80% [114, 122, 125, 126, 128], ≥ 50% and 20 - 49% vs < 20% [102, 127], and discontinuation vs continuation of therapy [105, 114]. Results showed that the odds of exacerbation among the patients with ≥ 80% adherence were lowered by 47% [OR = 0.53 (95% CI: 0.42, 0.66), $P < 0.001$, $I^2 = 13.7\%$] compared to < 80%. When compared to < 20% adherence, a 33% reduction in the odds [OR = 0.67 (95% CI: 0.53, 0.86), $P = 0.001$, $I^2 = 34.7\%$] was associated with the patients achieving ≥ 50%, while a decrease in exacerbation was not associated with 20 - 49% adherence [OR = 0.94 (95% CI: 0.85, 1.04), $P = 0.22$, $I^2 = 0.0\%$]. In addition, a 2.4 fold increase in the odds [OR = 2.4 (95% CI: 2.1, 2.7), $P < 0.001$, $I^2 = 0.0\%$] was associated with the discontinuation of therapy. We found no substantial heterogeneity for all levels of adherence affecting severe exacerbation ($P \geq 0.05$), and the I^2 ranged from 0.0% to 34.7%, interpreting no or a minimal amount of heterogeneity (Figure 4).



OR, odds ratio; CI, confidence interval

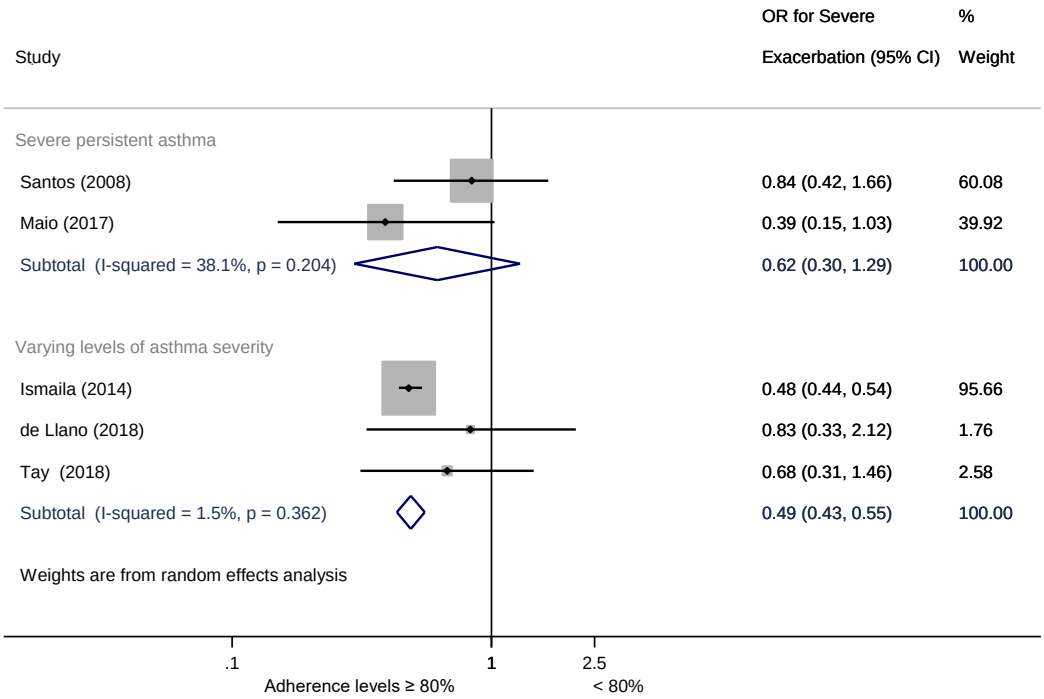
Figure 4. Forest plots of the association between adherence and severe exacerbation

Subgroup analysis

The subgroup analyses were carried out by taking into account the differences in the participants' characteristics: the severity levels of asthma, and the methods of measuring adherence across the studies.

Only the analyses that compared the odds of exacerbation among the patients with ≥ 80% compared to < 80% adherence were able to be performed, and the results showed that the odds were not different in severe asthmatic patients [OR = 0.62 (95% CI: 0.30, 1.29), $P = 0.201$, $I^2 = 38.1\%$] [122, 126], while they were lowered by 51%

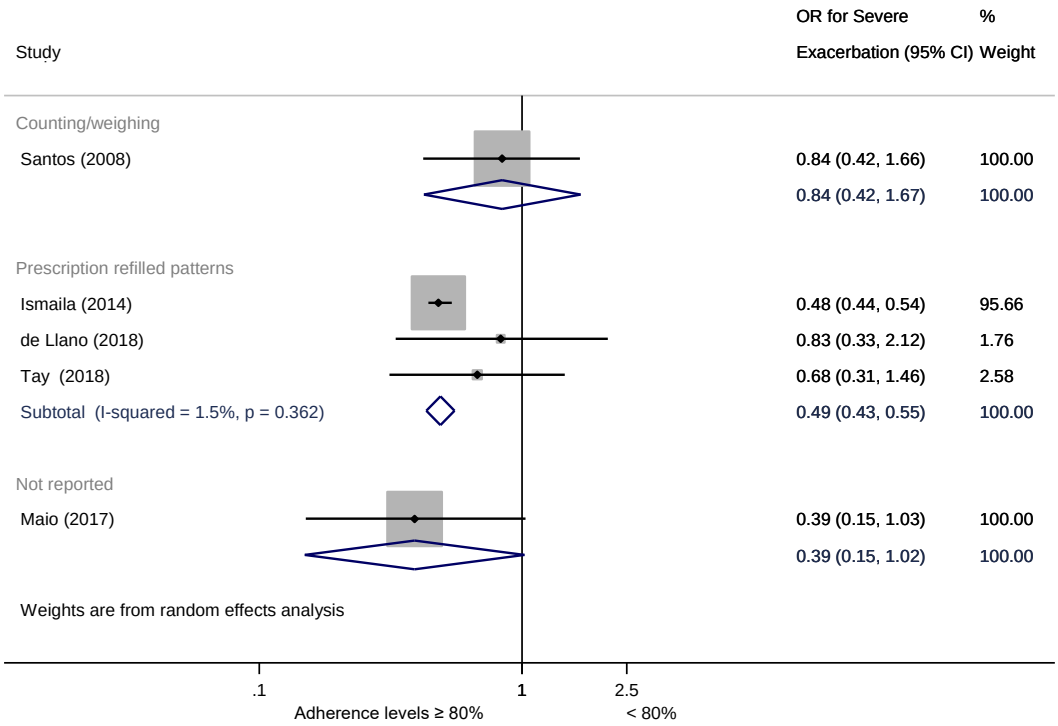
[OR = 0.49 (95% CI: 0.43, 0.55), *P* = 0.00, I^2 = 1.5%] among those with any level of asthma severity [114, 125, 128] (Figure 5).



OR, odds ratio; CI, confidence interval

Figure 5. Forest plots of a subgroup analysis of the association between adherence and severe exacerbation among patients with different severity levels of asthma

A decrease in the number of exacerbations were demonstrated among the patients whom were being estimated for their adherence using prescription refilled patterns [OR = 0.49 (95% CI: 0.43, 0.55), *P* = 0.00, I^2 = 1.5%] [114, 125, 128], while it was not different when using counting/weighing [OR = 0.84 (95% CI: 0.42, 1.67), *P* = 0.619] [126], and not reported [OR = 0.39 (95% CI: 0.15, 1.02), *P* = 0.055] [122] (Figure 6).



OR, odds ratio; CI, confidence interval

Figure 6. Forest plots of a subgroup analysis of the association between adherence and severe exacerbation among the patients whose adherence were estimated using different methods

Quality of studies

Infrequent disagreements between BC and PD occurred, and were resolved by NC. The majority of the included cohort and case-control studies [28 (84.8%)] [12, 17, 84, 100-102, 104, 107-110, 112-128] were shown to have low risk of bias, while the others [5 (15.2%)] [13, 99, 105, 106, 111] were moderate. A RCT by *Krishnan* et al [103] demonstrated some concerns regarding the risk of bias in the randomization process, deviations from the intended interventions, and measurement of the outcome, while the study showed low risk of bias in the missing outcome data, and a selection of the reported results (Appendix: Table A7).

Discussion

Although many studies having been conducted to investigate the relationship between adherence and asthma exacerbation, the effects at different levels of adherence are still unclear. A previous systematic review by *Engelkes* et al [129] included a total of 23 studies of adherence to controller therapy, and showed that good adherence tended to be associated with fewer asthma exacerbations. However, the review was not able to provide a quantitative summary since heterogeneity across studies was found to be substantial. A larger number of studies were included in this review (34 vs 23) , and we were able to perform the analysis to estimate the quantitative association between different levels of adherence and severe asthma exacerbation in a subset of those studies. Our findings are well aligned with the results from a previous review. Although the highest reduction in the odds of exacerbation was associated with patients achieving ≥ 80% adherence, the odds also reduced among those with ≥ 50% , and we further investigated the effect of discontinuation, which demonstrated a substantial increase in exacerbation when patients discontinued their therapy. We found no substantial heterogeneity for all levels of adherence affecting severe exacerbation, indicating the reliability and validity of our results regarding the association between different levels of adherence and severe exacerbation.

Many studies have determined the impact of adherence on clinical outcomes among patients with chronic conditions using 80% as a cut-off level, given the benefits gained from the improved outcome and the prevention of disease complications. A study by *Choudhry* et al [130] investigated the relationship between adherence and adverse coronary occurrences, and showed that patients with ≥ 80% adherence had a reduced risk of heart attacks. Another study by *Li and Huang* [131] reported that patients with ≥ 80% adherence to statin therapy were able to reduce the risk of hospitalization by 68% , compared to those with < 80% adherence. In a study by *Kim* et al [132], the authors evaluated the effect of antihypertensive medication adherence on cardiovascular disease mortality among patients with hypertension. The study revealed that, when compared to ≥ 80% adherence, the patients with < 50% adherence experienced higher mortality, and a greater risk of hospitalization compared to those with 50 - 80% adherence. In a study by *Rosenblum* et al [133], the

authors estimated the effect of adherence to antiretroviral therapy on the probability of virologic failure, and observed a decreased risk when adherence was > 50% .

Although patients with ≥ 80% adherence associated with the highest reduction in the odds of exacerbation, achieving the level of only 50% still demonstrated some clinical benefits. Our results justify the generalization that the higher level of adherence to medications, the better the health outcome will be. We believe that the current systematic review and meta-analysis provides the most updated evidence in this regard for asthma exacerbations.

Ideally, an increase in adherence would result in improved health outcomes and reduce complications, but some studies reported an inverse correlation which can be explained in several ways. First, patients with more severe symptom have better motivation for adherence to therapy, and they appear to take their medications more regularly when they feel their condition worsening. Second, patients with poor asthma control require more aggressive treatments by health care providers. Therefore, an increase in prescription medications may result in over-prescribing to patients. Furthermore, patients with poor inhalation technique may potentially have poor asthma control despite receiving optimum therapy. Lastly, healthcare providers may lack awareness of over-prescribed medications due to automated and telephone requests and multiple prescribers repeating prescriptions.

Although our findings indicated the highest reduction in the odds of exacerbation was associated with patients achieving ≥ 80% adherence, the results from a subgroup analysis among the ones with severe condition demonstrated a trend towards decreasing in the number of exacerbations, but did not rise to the level of statistical significance. This indicated the uncontrolled symptoms still existed among such patients. According to the Global Initiative for Asthma (GINA) management for severe asthma [95], these patients should be closely monitored and continuously reviewed their response and treatment every 3 - 6 months, and the ongoing management should involve a collaboration between the patients, the general practices, specialists, as well as other healthcare providers to optimize clinical outcomes and patient satisfaction. In addition, the analysis among the patients that were estimated their adherence using prescription refilled patterns showed a decrease in number of exacerbations were associated with the patients achieving ≥ 80%

adherence, but the results were not different when using other methods of measuring adherence. However, these findings were from a small number of studies, and further research is warranted to confirm the reliability and validity of such methods.

According to our results which indicated the association between different levels of adherence and severe exacerbation, how will health care professionals generalise our findings in their settings where those countries were not included in the analysis? We believe that a number of aspects should be taken into account rather than only considering the meta-analysis results. For example, demographic characteristics of patients, types of controller medications, methods used to measure adherence, definitions of severe asthma exacerbation, as well as the duration of study. Health care professionals should consider whether their settings are in line with the characteristics of studies, included in the individual levels of adherence affecting severe exacerbation; 5 studies for the levels of ≥ 80% vs < 80%, while other 2 studies each for ≥ 50% and 20 - 49% vs < 20% and continued vs discontinued therapy.

We believe that the value of this study is two-fold: to provide healthcare professionals with current evidence of the quantitative association between different adherence levels and severe asthma exacerbation, as well as an insight regarding adherence data in individual studies for future research development. The aim of this work was to conduct a systematic review and meta-analysis that complied with PRISMA guidelines but some limitations must be acknowledged. First, although the majority of studies were controlled for potential confounders by adjusting for patient demographics, less than half of the studies were adjusted for other important confounders (Appendix: Table A8 - A9) . Caution should be exercised when interpreting our findings because the pooled estimates may be prone to bias due to the effect of residual confounding across studies. Second, even though a total of 8 studies were included in our meta-analysis, the impact of some adherence levels on severe asthma exacerbation (≥ 50% and 20 - 49% vs < 20%, and continued vs discontinued therapy), were from only 2 studies each, raising concerns regarding generalizability of the study findings. Practical application of the findings needs to consider whether or not the health care settings are in line with the characteristics of individual studies. In addition, some of non-English articles were identified through our search results but only studies published in English were included in this review, which reduced the

number of studies available for this review, and subjected to language bias. Generally, studies which reported positive findings were most likely to be published in English-language journals, and studies with null or negative findings were more likely to be published in non-English-language journals [134]. In addition, we believe that most of high-quality studies were published in English and included in our systematic review.

Conclusion

This systematic review and meta-analysis gathered all relevant evidence, and quantified pooled estimates to assess the association between different levels of adherence and severe asthma exacerbation. The highest reduction in the odds of exacerbation was associated with patients achieving ≥ 80% adherence, and the odds also reduced among those with ≥ 50% , while a substantial increase in exacerbation was associated with discontinuation of therapy.

CHAPTER V: INCORPORATING ADHERENCE IN COST-EFFECTIVENESS ANALYSIS OF AN ADDED ON OMALIZUMAB COMPARED WITH THE STANDARD CARE FOR ASTHMA

Research question

How adherence of the patients affects the results of cost-effectiveness?

Research objective

To evaluate the impact of incorporating adherence on the results of cost-effectiveness

Methods

Overall description

The economic analysis was conducted among a hypothetical cohort of 100 Thai patients with severe persistent asthma. All patients received the standard care treatment, while the intervention of interest was omalizumab as an added on therapy. Using the results from chapter 4, levels of adherence affecting exacerbation were used to incorporate in a Markov model, which was adapted from a study by *Wongphan* et al [135]. The model consisted of 4 health states; day to day asthma (D2D), clinically significant exacerbation (CSE), clinically significant severe exacerbation (CSSE), and death (Figure 7). A biweekly cycle length was applied to the analysis which was carried out on the patients aged 18 throughout their lifetime. Costs and health outcomes; life years (LY) and quality-adjusted life years (QALY), were discounted using an annual rate of 3% based on Thailand's health technology assessment (HTA) guideline [136]. The incremental costs per QALY gained was calculated, and presented as the incremental cost-effectiveness ratio (ICER) of individual adherence levels.

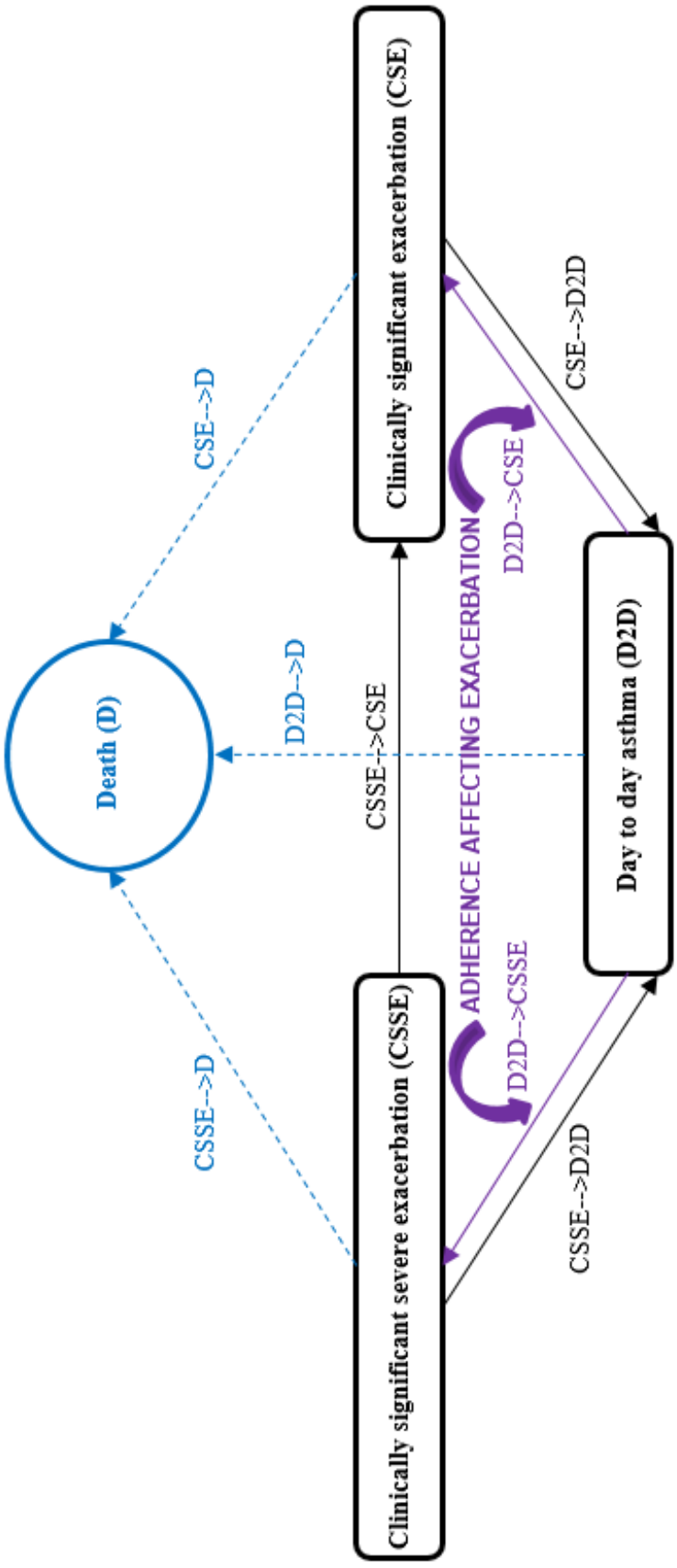


Figure 7. Markov model describes the disease progression in asthma

Model input parameters

The transition probabilities among each of the health states were based on a literature review of the studies and an expert panel [95, 135, 137]. The mortality rate of patients with D2D and CSE were applied from age-specific mortality rate of the Thai population (non-asthma death) [138], while that of patients with CSSE was adapted from the report burden of asthma in Thailand (death due to exacerbation) [139]. All patients received the standard care treatment which included inhaled corticosteroids (ICS) , leukotrience receptor antagonitsts (LTRA) , theophylline, as well as oral corticosteroids (OCS) , while the intervention was an added on omalizumab. The utility of patients were based on a cost-effectiveness analysis (CEA) of omalizumab in Thailand [57, 135, 140-143].

The societal perspective was applied to the analysis which cost of productivity loss was not estimated, since it would be counted in the disutility of QALY [136]. Patients with D2D were assumed to visit outpatient clinics once a month and incurred costs pertaining to their care, while patients with CSE were assumed to visit outpatient clinics or emergency departments, but not for admission, incurred costs relating to their care which included short-acting beta-agonists (SABA) , whereas ones with CSSE were assumed to be admitted, and received inpatient treatment. These were estimated from the Health Intervention and Technology Assessment Program (HITAP) costing database and the Thai Ministry of Public Health [144, 145]. Costs of the medications were collected from the Drug and Medical Supply Information Center, Ministry of Public Health [144]. The costs of food and transportation were adapted from the HITAP costing database which estimated these requirements among patients that visited healthcare settings [145]. All the costs were converted to 2019 values using the consumer price index, and reported in Thai Baht (THB).

The assumption of adherence affecting asthma exacerbation

According to the results in chapter 4, eight studies that reported the quantitative association between various levels of adherence and asthma exacerbation were included in a meta-analysis; greater than or equal to (≥) 80% vs less than (<) 80% [114, 122, 125, 126, 128], ≥ 50% and 20 - 49% vs < 20% [102, 127], and

discontinuation vs continuation of therapy [105, 114]. However, that of 6 studies were not able to be applied to our economic analysis because of the differences in severity levels of asthma [102, 105, 114, 125, 128], and the used controller medications [126]. Although the 2 studies by *Maio* et al [122], and *Kang* et al [127] reported the effectiveness data of adherence affecting exacerbation among severe asthmatic patients who used an added on omalizumab, we could only apply that data from *Maio* et al's study to our analysis model due to the limited information in regard to the adjustment on adherence levels reported in *Kang* et al's study. Our analysis was performed based on the primary assumption that compared to the patients with < 80% adherence, the odds of exacerbation among the ones with ≥ 80% were lowered by 61% [odds ratio, OR = 0.39 (95% confidence interval, CI: 0.15, 1.03)] equal to those who demonstrated 100% adherence (Table 8).

Table 8. Model input parameters

	Base-case values (range)	Distributions	Alpha	Beta	References
Epidemiological data					
Transition probabilities					
Standard care					
D2D to CSE	0.03010 (0.02709, 0.03311)	Beta	371.59678	12006.03391	[95, 135, 137]
D2D to CSSE	0.03290 (0.02961, 0.03619)	Beta	370.52114	10920.91461	[95, 135, 137]
CSE to D2D	0.06740 (0.06066, 0.07414)	Beta	357.26762	4957.27565	[95, 135, 137]
CSSE to D2D	0.06740 (0.06066, 0.07414)	Beta	357.26762	4957.27565	[95, 135, 137]
CSSE to CSE	0.04000 (0.03600, 0.04400)	Beta	367.79360	8,851.04640	[95, 135, 137]
Added on omalizumab					
D2D to CSE	0.01050 (0.00945, 0.01115)	Beta	379.12632	35822.38035	[95, 135, 137]

	Base-case values (range)	Distributions	Alpha	Beta	References
D2D to CSSE	0.01150 (0.01035, 0.01265)	Beta	378.74216	32641.31523	[95, 135, 137]
CSE to D2D	0.11000 (0.09900, 0.12100)	Beta	340.90240	2766.30124	[95, 135, 137]
CSSE to D2D	0.11000 (0.09900, 0.12100)	Beta	340.90240	2766.30124	[95, 135, 137]
CSSE to CSE	0.04000 (0.03600, 0.04400)	Beta	367.79360	8851.04640	[95, 135, 137]
CSSE to death	0.0000024 (0.0000021, 0.0000026)	Beta	383.15908	161098778.59930	[139]
Effectiveness					
Odds ratio of adherence affecting asthma exacerbation					
≥ 80% vs < 80%	0.39 (0.15, 1.03)	Log-normal	-0.94*	0.49†	[122]
Utility weights					
Standard care					
D2D	0.640 (0.576, 0.704)	Beta	137.298	77.792	[135, 140-142]

	Base-case values (range)	Distributions	Alpha	Beta	References
CSE	0.572 (0.515, 0.629)	Beta	163.420	123.028	[135, 140-142]
CSSE	0.326 (0.293, 0.359)	Beta	257.924	535.321	[135, 140-142]
Added on omalizumab					
D2D	0.646 (0.581, 0.711)	Beta	74.522	0.581	[57, 135, 143]
CSE	0.572 (0.515, 0.629)	Beta	163.420	123.028	[57, 135, 143]
CSSE	0.326 (0.293, 0.359)	Beta	257.924	535.321	[57, 135, 143]
Cost data (Thai Baht, 2019)					
Direct medical costs					
Prednisolone (5 mg)	5 (4, 6)	Gamma	61	0.1	[144]
Budesonide (200 mcg)	29 (22, 36)	Gamma	61	0.5	[144]

	Base-case values (range)	Distributions	Alpha	Beta	References
Montelukast sodium (10 mg)	69 (52, 86)	Gamma	61	1	[144]
Theophylline (250 mg)	26 (19, 32)	Gamma	61	0.4	[144]
Salbutamol (0.1 mg)	10 (7, 12)	Gamma	61	0.2	[144]
Omalizumab (150 mg)	35567 (26675, 44459)	Gamma	61	579	[144]
Outpatient visit	308 (231, 385)	Gamma	61	5	[145]
Inpatient treatment	1322 (992, 1653)	Gamma	61	22	[145]
Nebulization fee	656 (492, 820)	Gamma	61	11	[145]
Injection administration fee	53 (40, 67)	Gamma	61	1	[145]

	Base-case values (range)	Distributions	Alpha	Beta	References
Direct non-medical costs					
Food	57 (47, 68)	Gamma	114	1	[145]
Transportation	158 (135, 180)	Gamma	184	1	[145]

D2D, day to day asthma; CSE, clinically significant exacerbation; CSSE, clinically significant severe exacerbation

Note: In Log-normal distribution, logarithm of odds ratio (*), and standard error (†) were used to identify the shapes of data distribution, instead of alpha and beta values that were applied for Beta and Gamma distributions.

Analysis

The outcomes of interest were the numbers of exacerbations including CSE and CSSE cases, LY, QALY, lifetime costs, and the ICER, while the interpretation of the results were based on the willingness-to-pay (WTP) threshold of THB 160,000 per QALY gained, set by the sub-committee of the Thai working group on HTA [136]. A base-case analysis was carried out on patients using an added on omalizumab who achieved the adherence levels of ≥ 80% and < 80% compared to the standard care treatment. A probabilistic sensitivity analysis (PSA) was conducted to estimate the uncertainty of all input parameters using a Monte Carlo simulation with 1,000 iterations presented as a 95% credible interval (CrI).

Model validation

The economic model applied to this study was validated based on an assessment tool of health economic models [146], which covered various aspects of the model development. The validation of the conceptual model was examined for its appropriateness of representing the disease progression and conducting economic evaluations, by comparing it with other study models in regard to asthma [56, 59]. In input data validation, all parameters were investigated for their appropriateness of being used in the Thai context. The potential for bias, generalizability to the target population, and availability of alternative data sources were also considered accordingly. In the validation of the computerized model, a full adherence scenario of the patients was performed, using the value testing approach to identify logical errors and exploitable results. A number of patients among the 4 individual health states were also tracked to test the logic of the model over time. In operational validation, the model was examined for the appropriateness of the study outcomes; however, the external validation could not be performed due to the lack of other input data applied to the model.

Results

Base-case analysis

The numbers of asthma exacerbations

Out of 100 severe asthmatic patients, the ones using the standard care treatment developed 5,254 (95% CrI: 4966, 5499) exacerbations, while those using an added on omalizumab with ≥ 80% adherence were found to develop only 2,948 (95% CrI: 2766, 3121) cases, which showed an overall reduction of 43.88% (95% CrI: -47.94% , -39.26%). When compared between the patients using the standard care treatment and an added on omalizumab with < 80% adherence, a greater amount of the cases were 13.51% (95% CrI: 5.58%, 23.11%) (Table 9).

Table 9. Results of the numbers of asthma exacerbations

Treatment	The numbers of exacerbations	
	Estimated (n)	Percentage of preventable cases
Standard care	5254 (4966, 5499)	NA
Added on omalizumab with adherence levels		
1) ≥ 80%	2948 (2766, 3121)	-43.88% (-47.94%, -39.26%)
2) < 80%	5964 (5638, 6286)	13.51% (5.58%, 23.11%)

NA, not applicable

Note: Data are expressed as values (95% credible intervals).

Life years and quality-adjusted life years

The estimated LY of the patients using an added on omalizumab with ≥ 80% adherence was 2,754.72 (95% CrI: 2754.68, 2754.76) , while the standard care treatment was 2,754.36 (95% CrI: 2754.27, 2754.44); the ones using an added on omalizumab with ≥ 80% adherence had longer LY by 0.36 (95% CrI: 0.28, 0.44), and it was 0.11 (95% CrI: 0.03, 0.19) for < 80% adherence. In addition, patients using an added on omalizumab demonstrated a trend towards an increase in QALY; those with ≥ 80% adherence had more QALY than the standard care treatment by 136.64 (95%

CrI: -55.94, 324.97), and it was 57.93 (95% CrI: -113.84, 225.95) for < 80% adherence (Table 10).

Lifetime costs

The estimated lifetime cost for the patients using an added on omalizumab with ≥ 80% adherence was THB 99,840,546 (95% CrI: 77895438, 125725211), while that of the standard care treatment was THB 2,843,919 (95% CrI: 2518801, 3177692); those who used an added on omalizumab with ≥ 80% adherence had more lifetime cost by THB 96,996,628 (95% CrI: 74829075, 123158770). The greater lifetime cost were THB 97,646,245 (95% CrI: 75630043, 123740782) for < 80% adherence (Table 10).

Incremental cost-effectiveness ratios

Patients using an added on omalizumab showed a trend towards an increase in the QALY compared to the standard care treatment, but their lifetime costs were much higher, demonstrating considerable ICER [THB/QALY 709,891 (95% CrI: -5493687, 5696281) for ≥ 80% adherence, and THB/QALY 1,685,616 (95% CrI: -12173901, 12985839) for < 80% adherence] (Table 10).

Table 10. Results of the life years, quality-adjusted life years, lifetime costs, and the cost-effectiveness

Treatment	LY		QALY		Lifetime costs (THB)		ICER
	Estimated	Incremental	Estimated	Incremental	Estimated	Incremental	(THB/QALY)
Standard care	2,754.36 (2754.27, 2754.44)	NA	1566.31 (1455.38, 1665.00)	NA	2,843,919 (2518801, 3177692)	NA	NA
Added on omalizumab with adherence levels							
1) ≥ 80%	2754.72 (2754.68, 2754.76)	0.36 (0.28, 0.44)	1702.95 (1538.97, 1839.86)	136.64 (-55.94, 324.97)	99840546 (77895438, 125725211)	96996628 (74829075, 123158770)	709891 (-5493687, 5696281)
2) < 80%	2754.47 (2754.40, 2754.54)	0.11 (0.03, 0.19)	1624.24 (1487.94, 1738.84)	57.93 (-113.84, 225.95)	100490163 (78696406, 126307223)	97646245 (75630043, 123740782)	1685616 (-12173901, 12985839)

ICER, incremental cost-effectiveness ratios; LY, life years; NA, not applicable; QALY, quality-adjusted life years; THB, Thai Baht

Note: Data are expressed as values (95% credible intervals).

Sensitivity analysis

According to the regimen of omalizumab which is recommended for the injections either every 2 weeks or 4 weeks, the analysis was performed by varying the cycle length from 2 weeks used in the base-case to 4 weeks, and the findings showed using an added on omalizumab still demonstrated considerable ICER, while the others results (the numbers of exacerbations, LY, QALY, and the lifetime cost) were slightly different compared to base-case results (Appendix: Table A10 - A11). Based on the results of the PSA, all the ICER fell in the range of the Northwest quadrant (dominated: lower QALY and higher costs) and the Northeast quadrant (higher QALY and higher costs) in a cost-effectiveness plane (Figure 8).

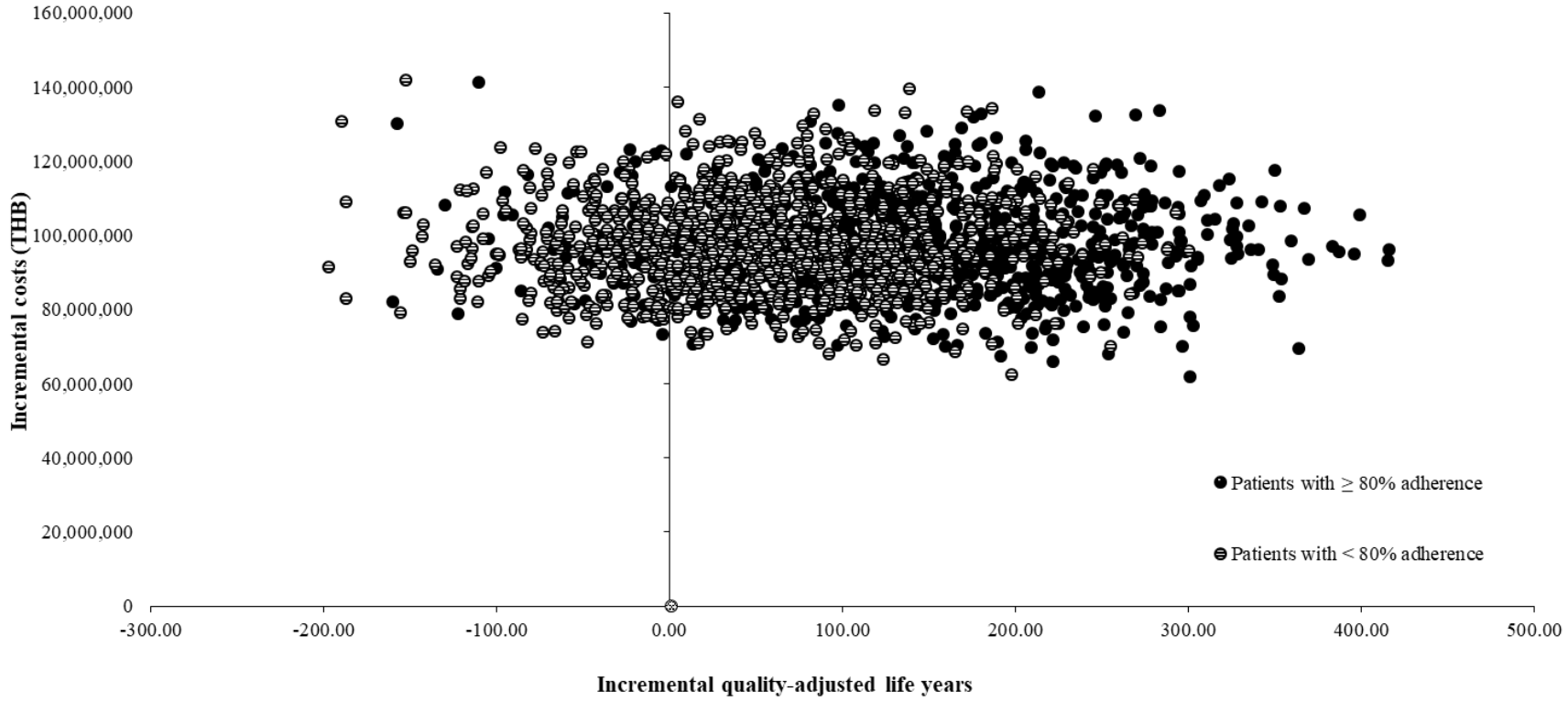


Figure 8. Cost-effectiveness plane of the patients using an added on omalizumab with greater than or equal to 80% adherence and less than 80% adherence

Discussion

We performed the CEA to evaluate the impact of incorporating adherence on the results, compared between severe asthmatic patients who used an added on omalizumab with ≥ 80% and < 80% adherence, and the standard care treatment in Thailand. Our findings showed that patients with ≥ 80% adherence experienced the lower number of exacerbations, while those with < 80% showed a greater amount. All the patients were associated with increased LY and demonstrated a trend towards an increase in QALY, while their lifetime costs were substantial, resulting in considerable ICER.

According to the quantitative associations between adherence to controller medications and severe asthma exacerbation demonstrated in chapter 4, when compared to the patients with < 80% adherence, those with ≥ 80% experienced a lower number of exacerbations to a greater extent (47%) than the ones who adhered to their medication by ≥ 50% vs < 20% (33%), and 20 - 49% vs < 20% (6%), respectively. However, these results were not able to be applied to our economic analysis because of the differences in severity levels of asthma, and the controllers used across the studies. We could only apply the results from a study by *Maio* et al [122], which showed the odds of exacerbation among the patients using an added on omalizumab with ≥ 80% adherence were lowered by 61% compared to < 80% adherence. Our economic analysis showed that the patients with ≥ 80% adherence were least likely to develop exacerbations, resulting in the higher LY and QALY. These findings were correlated with several studies [130-133] that determined the impact of adherence on clinical outcomes among the patients with chronic conditions using 80% as a cut-off level, given the benefits gained from the improved outcomes and the prevention of disease complications.

A systematic review by *Hughes* et al [4] investigated the techniques used to accommodate non-adherence, and estimated its impact on the cost-effectiveness results. The authors showed that non-adherence could affect the study findings by decreasing the efficacy of medications, but its effects on healthcare costs were varied. Our findings showed that even though the lower levels of adherence reduced the effectiveness of the treatment, the relevant costs were increased in the opposite direction to the decreased levels. Since the patients with ≥ 80% adherence were least

likely to experience exacerbations, treating these patients will reduce the treatment costs compared to < 80%, particularly asthma exacerbation, which incurs substantial expenditure. Compared to the standard care treatment, our economic analysis showed the patients using an added on omalizumab with ≥ 80% adherence experienced the lower number of exacerbations. All of them were associated with higher LY, and demonstrated a trend towards an increase in QALY, however, their lifetime costs were substantial. It is important for patients to achieve adherence to their treatment at the highest level, allowing them to obtain the most clinical and economic benefits. Healthcare professionals should consider encouraging their patients to achieve the levels of ≥ 80% adherence, given the benefits gained from both clinical and economic perspectives demonstrated in this study.

The primary objective of this chapter was to conduct a CEA to evaluate the impact of adherence on the results by incorporating adherence affecting exacerbation in our economic model. Although our cost-effectiveness findings demonstrated considerable ICER for an added on omalizumab compared to the standard care treatment, according to the results of a sensitivity analysis, these ICER were ranged from the Northwest quadrant (dominated: lower QALY and higher costs) to the Northeast quadrant (higher QALY and higher costs) in a cost-effectiveness plane. Patients using an added on omalizumab could prevent the numbers of exacerbations that may occur in the future, but their QALY were not much different when compared to the standard care treatment. This was mainly due to the mortality rate of the patients with CSSE applied to the model which was very low (6.2/100,000 patients), resulting in a greatly reduced number of deaths for the patients using both treatments. The impact of adherence will be greater on the amount of exacerbations and the lifetime costs in which higher levels of adherence will reduce the number of exacerbations, and decrease the total lifetime costs.

A systematic review of the methods used to incorporate adherence in the CEA of asthma demonstrated in chapter 3 showed, only the method of adjusting treatment effectiveness according to adherence levels was demonstrated among 4 CEA using 2 approaches; the first was to apply the mathematical formula developed by an expert panel, and the second was to extrapolate the associations from previous published studies. We incorporated adherence in our economic analysis based on the

second approach by using the effectiveness data of adherence affecting exacerbation that were derived from a cohort study by *Maio* et al [122]. These data compared the odds of exacerbation between the patients who used an added on omalizumab with ≥ 80% and < 80% adherence, which has never been incorporated in the CEA of asthma before. Ideally, adherence of the patients would be derived from observational studies or patient claims. Many factors, i.e., age, comorbidities, and the number of medications, are associated with its estimate, and have an impact on economic consequences [92]. We believe that the effectiveness of adherence affecting exacerbation applied in our study provide the most update data relevant to the patients with severe persistent asthma who use an added on omalizumab to date.

According to our cost-effectiveness results which indicated substantial ICER of an added on omalizumab, how will healthcare professionals and policy makers generalise our findings in regard to policy decision-making? We believe that a number of aspects should be taken into account rather than only considering the results of the individual ICER of the treatments. Firstly, a total number of asthma exacerbations should be clearly identified and considered since it is associated with an increased mortality rate of the patients and their relevant costs. Secondly, based on the current Global Initiative for Asthma (GINA) guidelines, an added on omalizumab is recommended for treating severe asthmatic patients whose symptoms are uncontrolled. They may develop exacerbation at any time despite receiving the standard care treatment, which demonstrates the risk of death over time. However, to date the cost of omalizumab is very high, therefore, most patients may not be able to afford the treatment. This crucial point should be brought to the table for discussion, and a special dispensation maybe considered for patients case by case. Lastly, it is important for all involved stakeholders to understand that the policy decisions should be made based on multiple aspects rather than only considering the economic standpoint.

Although this work was conducted based on the current HTA guidelines in Thailand, some limitations were acknowledged. Firstly, some input parameters; transition probabilities and utility weights, applied to the economic model were adapted from previous economic evaluation studies, which were somewhat out-of-date. However, this was the most relevant data that reflected the Thai population,

which was based on a literature review of the studies and the opinions of asthma experts. Secondly, the effectiveness data of adherence affecting exacerbation were applied based on a cohort study conducted in Italian population. This may not be directly related to Thai people, but we believe that it provided the most relevant information in regard to the association between adherence and asthma exacerbation among severe asthmatic patients using an added on omalizumab.

Conclusion

The current CEA of asthma was conducted by incorporating adherence of the patients in the analysis. Compared to the standard care treatment, severe asthmatic patients who used an added on omalizumab with ≥ 80% adherence experienced the lower number of exacerbations, while those with < 80% showed a greater amount. All the patients demonstrated a trend towards an increase in QALY, and their lifetime costs were substantial, resulting in considerable ICER.

CHAPTER VI: DISCUSSION AND CONCLUSION OF DISSERTATION

To date, CEA is increasingly used to inform value assessment of the interventions by healthcare professionals and policy makers, but most do not take into account adherence of the patients in their analyses. One important aspect that still lacks clarity is how to incorporate adherence in the analysis. This dissertation is conducted to acknowledge the abovementioned gap in current understanding in regard to the method of incorporating adherence in the CEA by using asthma as a case study.

In chapter 3, a systematic review of the methods used to incorporate adherence in the CEA of asthma was performed to explore the extent of studies incorporated adherence in their analyses, and our findings demonstrated that very low numbers of the CEA incorporated this (4 out of 23 studies), which were correlated with the findings in a literature review by *Rosen* et al [3] (54 out of 177 studies). The authors of this determined the quantitative results according to a systematic search without limiting the scope of the diseases of interest, thus, a number of studies (177) were included in the review. Despite the valuable information this study provided in regard to the quantitative results of the review, the authors did not deliver a qualitative summary regarding the methods of incorporating adherence in the analysis. One of the reasons could be due to the number of studies included in the review. In this dissertation, we narrowed the diseases of interest to only asthma. The advantage of doing this gave us the opportunity to provide not only the quantitative findings in terms of the extent of studies considering adherence as part of the analysis, but also the qualitative ones, such as the incorporating methods, an insight into adherence data, and many others. Healthcare professionals and policy makers who are interested in conducting research in this area may consider specifying the diseases of interest first. This will facilitate in reducing the number of included studies allowing the focus to concentrate on the relevant information study by study, and can afford the opportunity to improve the quality of the research. The methods of incorporating adherence in the CEA of asthma were characterized in this dissertation, while information on other diseases are still limited, therefore, a call for a comprehensive review of the methods that have been used in other disease areas is recommended.

According to a systematic review and meta-analysis of the associations between adherence to controller medications and severe asthma exacerbation demonstrated in chapter 4, even though a lot of attempts were made in order to perform the dose-response relationship of such interrelations, we were only able to provide the meta-analyses' results of 4 individual adherence levels; 1) ≥ 80% 2) ≥ 50% 3) 20 - 49% and 4) discontinuation of therapy, due to the limited availability of data in the included studies. Our results showed when compared to the patients with < 80% adherence, those with ≥ 80% experienced a lower number of exacerbations to a greater extent (47%) than the ones who adhered to their medication by ≥ 50% vs < 20% (33%), and 20 - 49% vs < 20% (6%), respectively. However, these findings were not able to be applied to our economic analysis because of the differences in severity levels of asthma, and the controller medications used across the studies. Only the results from a study by *Maio* et al [122], which showed the odds of exacerbation among the patients using an added on omalizumab with ≥ 80% adherence were lowered by 61% compared to < 80% adherence, allowing the use in our analysis. A systematic review with an included meta-analysis delivers the most valid information, since its findings were ascertained from many studies that were identified in comprehensive and systematic manners [89]. Though we were not able to apply the meta-analysis results of adherence affecting exacerbation to our economic analysis, we believe that using the data from this would provide the most reliable data based on valid statistical techniques of meta-analysis, which may be considered as one of the methods used to incorporate adherence in the economic model for the future economic analysis of asthma and other diseases.

Non-adherence of the patients could affect the results of cost-effectiveness by decreasing the efficacy of medications despite its varying effects on healthcare costs [4]. In chapter 5, we performed a CEA to evaluate the impact of incorporating adherence on the results, compared between severe asthmatic patients who used an added on omalizumab and the standard care treatment in Thailand. Our findings showed that even though the lower levels of adherence reduced the effectiveness of the treatment, the relevant costs were increased in the opposite direction to the decreased levels. Compared to the standard care treatment, patients using an added on omalizumab with ≥ 80% adherence experienced the lower number of exacerbations,

while those with < 80% showed a greater amount. All patients were associated with the higher LY and demonstrated a trend towards an increase in QALY, however, their lifetime costs were substantial, resulting in considerable ICER. It is important for patients to achieve adherence to their treatment at the highest level, allowing them to obtain the most clinical and economic benefits. Therefore, healthcare professionals should consider encouraging their patients to achieve the aforementioned adherence, given the benefits gained from both clinical and economic perspectives demonstrated in this study.

To date, omalizumab that is produced by Novartis Pharmaceutical Company, is the only one in the global market, and its cost in Thailand is very high at THB 17,644/vial. According to the American College of Cardiology [147], any decisions in regard to pricing should be made with an emphasis on assessed value by using both comparative effectiveness and cost-effectiveness, while the strategy on value-based pricing must categorize the impact on patient outcomes and not consider cost as the sole criteria. Although our findings showed that the use of an added on omalizumab resulted in considerable ICER, other aspects should be taken into account rather than only considering the economic standpoint. For example, a total number of exacerbations that could be prevented, and the moral rights of the patients with access to medical treatment for those whose symptoms are still uncontrolled despite receiving the standard care treatment.

In this dissertation, we gathers all relevant evidence regarding the current knowledge of the methods used to incorporate adherence in the CEA of asthma, and demonstrates our method using the association of adherence and severe exacerbation, while evaluating its impact on the results. Our findings are supported evidence that will allow researchers, healthcare professionals and policy makers to incorporate adherence in their economic analysis for a better informed policy decision-making and future research development in regard to this area.

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มหาวิทยาลัยนเรศวร

BIOGRAPHY

Name-Surname BUNCHAI CHONGMELAXME

Date of Birth 7 March 1985

Address 120/818 Sukhumwit 101/1 Bangna Bangkok 10260

Work Experience Abbott Laboratories Ltd., Thailand (2008 - 2013)

Abbott Laboratories is an American global pharmaceuticals and healthcare products company. It has 69,000 employees and operates in over 150 countries. The company is the market leader in inhalation and antiviral products all over the world.

2010 - 2013 Product Marketing Specialist

2008 - 2010 Medical Sales Representative

Other positions

Part-time assistant pharmacist, UK (2014)

Part-time pharmacist, Thailand (2013)

Education Background

2013 - 2014 Master of Business Administration
Strathclyde Business School
University of Strathclyde, UK

2004 - 2008 Bachelor of Science in Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences
Chulalongkorn University, Thailand

Publication

1) Chongmelaxme B, Chaiyakunapruk N, Dilokthornsakul P. Incorporating adherence in cost-effectiveness analyses of asthma: a systematic review. J Med Econ 2019;22(6):554-566.

2) Chongmelaxme B, Phisalprapa P, Sawangjit R, Dilokthornsakul P, Chaiyakunapruk N. Weight reduction is cost-effective for the treatment of non-alcoholic fatty liver disease in Thailand. Pharmacoeconomics 2019;37(2):267-278.

3) Chongmelaxme B, Lee S, Dhippayom T, Saokaew S, Chaiyakunapruk N, Dilokthornsakul P. The effects of telemedicine on asthma control and patients' quality of life in adults: a systematic review and meta-analysis. J Allergy Clin Immunol Pract 2019;7:199-216.

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evaluations of Haemophilus influenzae type b (Hib) vaccine: a systematic review. J Med Econ 2017;20:1094-1106.
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7) Sawangjit R, Chongmelaxme B, Phisalprapa P, Saokaew S, Thakkinstian A, Kowdley KV, Chaiyakunapruk N. Comparative efficacy of interventions on nonalcoholic fatty liver disease (NAFLD): A PRISMA-compliant systematic review and network meta-analysis. Medicine (Baltimore) 2016;95:e4529.

Awards

1) The Best Podium Research Presentation
Titled INCORPORATING ADHERENCE IN COST-EFFECTIVENESS ANALYSES OF ASTHMA: A SYSTEMATIC REVIEW
Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Asia Pacific 2018
8 - 11 September, Tokyo, Japan

2) Finalist Poster Research Presentation
Titled A COST-UTILITY ANALYSIS OF DABIGATRAN, ENOXAPARIN, AND USUAL CARE FOR VENOUS THROMBOPROPHYLAXIS AFTER HIP OR KNEE REPLACEMENT SURGERY IN THAILAND
Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Asia Pacific 2016
3 - 6 September, Singapore

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APPENDIX

Table A1. Search results

EMBASE

No	Key words	Results
1	exp health economics/	759165
2	exp health care cost/	258349
3	exp quality of life/	407588
4	economic$.tw.	275871
5	(cost? or costing? or costly or costed).tw.	626335
6	(price? or pricing?).tw.	46826
7	(pharmacoeconomic? or (pharmaco adj economic?)).tw.	7631
8	budget$.tw.	32424
9	expenditure$.tw.	63022
10	(value adj1 (money or monetary)).tw.	656
11	(fee or fees).tw.	20076
12	"quality of life".tw.	341261
13	qol$.tw.	57215
14	hrqol$.tw.	19927
15	"quality adjusted life year$".tw.	14482
16	qaly$.tw.	15313
17	cba.tw.	11933
18	cea.tw.	29905
19	cua.tw.	1222
20	utilit$.tw.	231342
21	markov$.tw.	24051
22	monte carlo.tw.	38366
23	(decision adj2 (tree$ or analys$ or model$)).tw.	23538
24	((clinical or critical or patient) adj (path? or pathway?)).tw.	8279
25	(managed adj2 (care or network?)).tw.	21187
26	or/1-25	2068371
27	asthma/	210539

No	Key words	Results
28	cost-effectiveness.ab. or cost-effectiveness.ti.	69508
29	cost-utility.ab. or cost-utility.ti.	5874
30	economic evaluation.ab. or economic evaluation.ti.	10447
31	28 or 29 or 30	77064
32	26 and 27 and 31	833

National Health Service Economic Evaluation Database (NHS EED)

No	Key words	Results
1	(asthma) AND (economic evaluation)	306

PubMed

No	Key words	Results
1	"Economics"[Mesh:NoExp]	26868
2	"Costs and Cost Analysis"[Mesh]	212433
3	"Economics, Dental"[Mesh:NoExp]	1891
4	"Economics, Hospital"[Mesh]	22668
5	"Economics, Medical"[Mesh:NoExp]	8936
6	"Economics, Nursing"[Mesh]	3978
7	"Economics, Pharmaceutical"[Mesh]	2741
8	economic*[Title/Abstract] or cost[Title/Abstract] or costs[Title/Abstract] or costly[Title/Abstract] or costing[Title/Abstract] or price[Title/Abstract] or prices[Title/Abstract] or pricing[Title/Abstract] or pharmacoeconomic*[Title/Abstract]	667503
9	expenditure*[Title/Abstract] not energy[Title/Abstract]	25150
10	value for money[Title/Abstract]	1296
11	budget*[Title/Abstract]	25327
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	797131
13	energy cost[Title/Abstract] OR oxygen cost[Title/Abstract]	3627

No	Key words	Results
14	metabolic cost[Title/Abstract]	1201
15	energy expenditure[Title/Abstract] OR oxygen expenditure[Title/Abstract]	22022
16	#13 or #14 or #15	25933
17	#12 not #16	791178
18	letter[Publication Type]	977413
19	editorial[Publication Type]	451143
20	historical article[Publication Type]	378748
21	#18 or #19 or #20	1789597
22	#17 not #21	756553
23	animals[mesh:noexp]	6160288
24	humans[mesh]	16907582
25	#23 not (#23 and #24)	4396874
26	#22 not #25	710410
27	Asthma[Mesh]	118482
28	cost-effectiveness[Title/Abstract] OR cost-utility[Title/Abstract] OR economic evaluation[Title/Abstract]	55568
29	#26 and #27 and #28	390

Tufts CEA Registry

No	Key words	Results
1	(asthma) AND (economic evaluation)	58

Table A2. CHEC-extended and CHEERS checklist

CHEC-extended

No.	Checklist details
1	Is the study population clearly described?
2	Are competing alternatives clearly described?
3	Is a well-defined research question posed in answerable form?
4	Is the economic study design appropriate to the stated objective?
5	Are the structural assumptions and the validation methods of the model properly reported?
6	Is the chosen time horizon appropriate in order to include relevant costs and consequences?
7	Is the actual perspective chosen appropriate?
8	Are all important and relevant costs for each alternative identified?
9	Are all costs measured appropriately in physical units?
10	Are costs valued appropriately?
11	Are all important and relevant outcomes for each alternative identified?
12	Are all outcomes measured appropriately?
13	Are outcomes valued appropriately?
14	Is an appropriate incremental analysis of costs and outcomes of alternatives performed?
15	Are all future costs and outcomes discounted appropriately?
16	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
17	Do the conclusions follow from the data reported?
18	Does the study discuss the generalizability of the results to other settings and patient/client groups?
19	Does the article/report indicate that there is no potential conflict of interest of study researcher**(**s**)** and funder**(**s**)**?
20	Are ethical and distributional issues discussed appropriately?

CHEERS-statement

No.	Checklist details
1) Title	Identify the study as an economic evaluation, or use more specific terms such as ‘‘cost-effectiveness analysis’’ and describe the interventions compared.
2) Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.
3) Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
4) Target population and subgroups	Describe characteristics of the base-case population and subgroups analysed including why they were chosen.
5) Setting and location	State relevant aspects of the system (s) in which the decision (s) need (s) to be made.
6) Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.
7) Comparators	Describe the interventions or strategies being compared and state why they were chosen.
8) Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
9) Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
10) Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and

No.	Checklist details
	their relevance for the type of analysis performed.
11) Measurement of effectiveness	Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.
12) Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes.
13) Estimating resources and costs	Single study–based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.

No.	Checklist details
14) Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
15) Choice of model	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.
16) Assumptions	Describe all structural or other assumptions underpinning the decision-analytic model.
17) Analytic methods	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
18) Study parameters	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
19) Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups.

No.	Checklist details
	If applicable, report incremental cost-effectiveness ratios.
20) Characterizing uncertainty	Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective). Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
21) Characterizing heterogeneity	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
22) Study findings, limitations, generalizability, and current knowledge	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.
23) Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.

No.	Checklist details
24) Conflicts of interest	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.

Table A3. Quality assessment of the study methodology

First author (year)	Checklist items																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Altawalbeh (2016) [52]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bruggenjurgen (2010) [71]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	N
Campbell (2010) [53]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Dewilde (2006) [72]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Doan (2011) [66]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	N
Doull (2007) [63]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Faria (2014) [64]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Fuhlbrigge (2006) [54]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Gerzeli (2012) [68]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ismaila (2014) [67]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Marchetti (2004) [69]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Norman (2013) [65]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Paggiaro (2013) [73]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Rodriguez-Martinez (2013) [62]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Rodriguez-Martinez (2015) [60]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

First author (year)	Checklist items																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Rodriguez-Martinez (2016) [61]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Shih (2007) [55]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	N	Y
Simonella (2006) [70]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y
Stanciole (2012) [74]	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Whittington (2017) [56]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Wu (2007) [57]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zafari (2014) [58]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Zafari (2016) [59]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

N, no; NA, not applicable; Y, yes

Table A4. Quality assessment of the reported studies

First author (year)	Checklist items																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Altawalbeh (2016) [52]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Bruggenjurgen (2010) [71]	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N
Campbell (2010) [53]	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N
Dewilde (2006) [72]	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N
Doan (2011) [66]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N
Doull (2007) [63]	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	N
Faria (2014) [64]	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Fuhlbrigge (2006) [54]	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Gerzeli (2012) [68]	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
Ismaila (2014) [67]	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N
Marchetti (2004) [69]	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N
Norman (2013) [65]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Paggiaro (2013) [73]	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y
Rodriguez-Martinez (2013) [62]	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y
Rodriguez-Martinez (2015) [60]	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

First author (year)	Checklist items																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Rodriguez-Martinez (2016) [61]	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y
Shih (2007) [55]	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Simonella (2006) [70]	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	Y
Stanciole (2012) [74]	N	N	Y	N	Y	N	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Whittington (2017) [56]	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Wu (2007) [57]	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zafari (2014) [58]	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Zafari (2016) [59]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y

N, no; Y, yes

Table A5. Search results

PubMed

No.	Key words	Found
1	asthma*	180,202
2	adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*	1,104,707
3	corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *Interleukin OR *mab	231,107
4	hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR exacerbat* OR mortality OR death	5,832,079
5	asthma* AND (adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*) AND (corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab) AND (hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR corticosteroid* OR exacerbat* OR mortality OR death)	3,476

Cochrane Controlled Register of Trials (CENTRAL)

No.	Key words	Found
1	asthma*	29,915
2	adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*	134,691

No.	Key words	Found
3	corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab	76,097
4	hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR exacerbat* OR mortality OR death	521,618
5	asthma* AND (adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*) AND (corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab) AND (hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR corticosteroid* OR exacerbat* OR mortality OR death) Filter: trials, non-PubMed source	852

EMBASE

No.	Key words	Found
1	asthma*	218,321
2	adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*	1,349,423
3	corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab	228,334
4	hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR exacerbat* OR mortality OR death	5,551,317

No.	Key words	Found
5	asthma* AND (adheren* OR complian* OR concordan* OR cooperat* OR co-operat* OR discontinu* OR dropout OR drop-out OR persisten* OR withdraw*) AND (corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab) AND (hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR corticosteroid* OR exacerbat* OR mortality OR death).ab,ti.	3,702

ClinicalTrials.gov

No.	Key words	Found
1	Studies With Results | Asthma | corticosteroid* OR leukotriene OR *lukast OR *xanthine OR theophylline OR long-acting beta* OR *terol OR long-acting muscarinic OR anticholinergic* OR tiotropium OR anti-immunoglobulin E OR anti-igE OR *mab | hospitali* OR admi* OR emergen* OR acute OR attack OR outpatient OR exacerbat* OR mortality OR death	17

Table A6. Newcastle-Ottawa quality assessment scale: case-control studies/cohort studies

Case-control study	Cohort study
Selection	***Selection***
1) Is the case definition adequate?	1) Representativeness of the exposed cohort
a) Yes, with independent validation*	a) Truly representative of the average ___ (describe) in the community*
b) Yes, e.g. record linkage or based on self-reports	b) Somewhat representative of the average ___ in the community*
c) No description	c) Selected group of users e.g. nurses, volunteers
	d) No description of the derivation of the cohort
2) Representativeness of the cases	2) Selection of the non-exposed cohort
a) Consecutive or obviously representative series of cases*	a) Drawn from the same community as the exposed cohort*
b) Potential for selection biases or not stated	b) Drawn from a different source
	c) No description of the derivation of the non-exposed cohort
3) Selection of controls	3) Ascertainment of exposure
a) Community controls*	a) Secure record (e.g. surgical records)*
b) Hospital controls	b) Structured interview*
c) No description	c) Written self-report
	d) No description

Case-control study	Cohort study
4) Definition of controls	4) Demonstration that outcome of interest was not present at start of study
a) No history of disease (endpoint)*	a) Yes*
b) No description of source	b) No
Comparability	***Comparability***
1) Comparability of cases and controls on the basis of the design or analysis	1) Comparability of cohorts on the basis of the design or analysis
a) Study controls for ____ (select the most important factor.)*	a) Study controls for ___ (select the most important factor.)*
b) Study controls for any additional factor*	b) Study controls for any additional factor*
Exposure	***Outcome***
1) Ascertainment of exposure	1) Assessment of outcome
a) Secure record (e.g. surgical records)*	a) Independent blind assessment*
b) Structured interview where blind to case/control status*	b) Record linkage*
c) Interview not blinded to case/control status	c) Self-report
d) Written self-report or medical record only	d) No description
e) No description	
2) Same method of ascertainment for cases and controls	2) Was follow-up long enough for outcomes to occur

Case-control study	Cohort study
a) Yes*	a) Yes (select an adequate follow up period for outcome of interest)*
b) No	b) No
3) Non-response rate	3) Adequacy of follow up of cohorts
a) Same rate for both groups*	a) Complete follow up - all subjects accounted for*
b) Non respondents described	b) Subjects lost to follow up unlikely to introduce bias - small number lost -> __% (select an adequate %) follow up, or description provided of those lost)*
c) Rate different and no designation	c) Follow up rate < __% (select an adequate %) and no description of those lost
	d) No statement

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability.

Table A7. Methodological quality assessment of the studies

First author (y)	Selection				Comparability		Outcome/exposure			Total score	Risk of bias
	1	*2*	*3*	*4*	*1*	*2*	*1*	*2*	*3*		
Bukstein (2003) [99]	*	*	-	*	-	-	*	*	*	6	Moderate
Bukstein (2007) [100]	*	*	*	*	*	*	*	*	*	9	Low
Camargo (2007) [112]	*	*	*	*	*	*	*	*	*	9	Low
Corrao (2016) [121]	*	*	*	*	*	*	*	*	*	9	Low
De Llano (2018) [125]	*	*	*	*	-	-	*	*	*	7	Low
Delea (2008) [101]	*	*	*	*	*	*	*	*	*	9	Low
Elkout (2012) [115]	*	*	*	*	*	*	*	*	*	9	Low
Engelkes (2016) [123]	*	*	*	*	-	-	*	*	*	7	Low
Herndon (2012) [102]	*	*	*	*	*	*	*	*	*	9	Low
Hyland (2012) [116]	*	*	*	*	-	-	*	*	*	7	Low
Ismaila (2014) [114]	*	*	*	*	*	*	*	*	*	9	Low
Kang (2018) [127]	*	*	*	*	*	*	*	*	*	9	Low
Lasmar (2009) [13]	*	*	*	*	-	-	*	*	-	6	Moderate
Maio (2018) [122]	*	-	*	*	*	*	*	*	*	9	Low
Makhinova (2015) [104]	*	*	*	*	*	*	*	*	*	9	Low

First author (y)	Selection				Comparability		Outcome/exposure			Total score	Risk of bias
	1	*2*	*3*	*4*	*1*	*2*	*1*	*2*	*3*		
Mathison (2005) [105]	-	*	*	*	-	-	-	*	*	5	Moderate
Mattke (2010) [113]	*	*	*	*	*	*	*	*	*	9	Low
McMahon (2000) [117]	*	*	*	*	*	*	*	*	*	9	Low
Mcnally (2009) [106]	*	*	*	*	-	-	-	*	*	6	Moderate
Osman (1999) [120]	*	*	*	*	-	-	*	*	*	7	Low
Papi (2018) [118]	*	*	-	*	*	*	*	*	*	8	Low
Price (2013) [119]	*	*	*	*	*	*	*	*	*	9	Low
Rohan (2010) [107]	*	*	*	*	-	-	*	*	*	7	Low
Rust (2013) [108]	*	*	*	*	*	*	*	*	*	9	Low
Santos (2008) [126]	*	*	*	*	*	*	*	*	*	9	Low
Smith (2007) [110]	*	*	*	*	*	*	*	*	*	9	Low
Smith (2009) [109]	*	*	*	*	*	*	*	*	*	9	Low
Stern (2006) [12]	*	*	*	*	*	*	*	*	*	9	Low
Tay (2018) [128]	*	*	*	*	*	*	*	*	*	9	Low
Vasbinder (2016) [124]	*	*	*	*	*	*	*	*	*	9	Low
Weinstein (1997) [111]	*	*	-	*	-	-	*	*	*	6	Moderate
Williams (2004) [84]	*	*	*	*	*	*	*	*	*	9	Low

First author (y)	Selection				Comparability		Outcome/exposure			Total score	Risk of bias
	1	*2*	*3*	*4*	*1*	*2*	*1*	*2*	*3*		
Williams (2011) [17]	*	*	*	*	*	*	*	*	*	9	Low

Table A8. Domains of potential confounders observed in the studies

Domain	Example of confounding variables
Patient demographics	Age, body mass index, gender, marital status, race/ethnicity, smoking status, socio-economic status
Concomitant medications	Antibiotics, anti-immunoglobulin E, inhaled corticosteroids, leukotriene receptor antagonists, long-acting beta-agonists, oral corticosteroids, short-acting beta-agonists, theophylline, long-acting beta-agonists plus inhaled corticosteroids
Disease co-morbidities	Allergic rhinitis, anxiety, bronchitis/bronchiolitis, cancer, cardiovascular disease, cerebrovascular disease, cystic fibrosis, diabetes, depression, epilepsy, human immunodeficiency virus/acquired immunodeficiency syndrome, hyperlipidemia, hypertension, migraines, obesity, pharyngitis, pneumonia, psychoses, sickle cell disease, sinusitis, tonsillitis, ulcers
Prior use of asthma care	Emergency department visits, hospitalizations, physician office visits
Geographic regions	Rural, urban
Insurance/payer type	Children's health insurance program, commercial, Medicaid, Medicare risk, self-insured
Time of first asthma prescription	Date, season, year
Number of asthma medication doses	Bronchodilators, inhaled corticosteroids, short-acting beta-agonists

Table A9. Confounding domains adjustment in the studies

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Bukstein (2003) [99]	-	-	-	-	-	-	-	-
Bukstein (2007) [100]	+	+	+	-	+	+	+	-
Camargo (2007) [112]	+	+	+	-	-	-	-	-
Corrao (2016) [121]	+	+	-	-	-	-	-	-
De Llano (2018) [125]	-	-	-	-	-	-	-	-

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Delea (2008) [101]	+	-	-	-	+	+	+	-
Elkout (2012) [115]	+	+	-	-	-	-	-	-
Engelkes (2016) [123]	-	-	-	-	-	-	-	-
Herndon (2012) [102]	+	-	+	+	+	+	-	-
Hyland (2012) [116]	-	-	-	-	-	-	-	-
Ismaila (2014) [114]	+	+	-	+	-	-	+	-

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Kang (2018) [127]	+	-	+	-	-	-	-	-
Krishnan (2012) [103]	-	-	-	-	-	-	-	-
Lasmar (2009) [13]	-	-	-	-	-	-	-	-
Maio (2018) [122]	+	+	+	-	-	-	-	-
Makhinova (2015) [104]	+	+	-	-	-	-	-	-
Mathison (2005) [105]	-	-	-	-	-	-	-	-

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Mattke (2010) [113]	+	-	+	+	+	+	-	-
McMahon (2000) [117]	+	+	-	+	-	-	-	+
Mcnally (2009) [106]	-	-	-	-	-	-	-	-
Osman (1999) [120]	-	-	-	-	-	-	-	-
Papi (2018) [118]	+	-	+	-	-	-	-	-
Price (2013) [119]	+	+	+	+	-	-	+	-

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Rohan (2010) [107]	-	-	-	-	-	-	-	-
Rust (2013) [108]	+	-	-	+	+	-	-	+
Santos (2008) [126]	+	-	-	-	+	-	-	-
Smith (2007) [110]	+	-	-	+	-	-	-	+
Smith (2009) [109]	+	+	-	-	+	-	-	-
Stern (2006) [12]	+	+	+	+	+	+	-	-

First author (y)	Confounding domain							
	Patient demographics	***Concomitant medications***	***Disease co-morbidities***	***Prior use of asthma care***	***Geographic regions***	***Insurance /payer type***	***Time of first asthma prescription***	***Number of asthma medication doses***
Tay (2018) [128]	+	-	+	-	-	-	-	-
Vasbinder (2016) [124]	+	+	-	-	-	-	-	-
Weinstein (1997) [111]	-	-	-	-	-	-	-	-
Williams (2004) [84]	+	+	-	-	-	-	-	-
Williams (2011) [17]	+	+	-	+	-	-	-	-

Table A10. The results of the numbers of asthma exacerbations (using 4-week cycle length)

Treatment	The numbers of exacerbations	
	Estimated (n)	**Percentage of preventable cases**
Standard care	5066 (4794, 5307)	NA
Added on omalizumab with adherence levels		
1) ≥ 80%	2873 (2711, 3040)	-43.29 (-47.43, -38.61)
2) < 80%	5729 (5421, 6020)	13.08 (5.94, 21.86)

NA, not applicable

Note: Data are expressed as values (95% credible intervals).

Table A11. The results of life years, quality-adjusted life years, lifetime costs, and the cost-effectiveness (using 4-week cycle length)

Treatment	LY		QALY		Lifetime costs (THB)		ICER
	Estimated	Incremental	Estimated	Incremental	Estimated	Incremental	(THB/QALY)
Standard care	2727.12 (2727.04, 2727.20)	NA	1549.64 (1450.31, 1649.56)	NA	3547744 (3187990, 3947517)	NA	NA
Added on omalizumab with adherence levels							
1) ≥ 80%	2727.46 (2727.42, 2727.50)	0.34 (0.27, 0.42)	1683.30 (1522.45, 1828.42)	133.66 (-56.99, 315.01)	99817882 (77468165, 125712554)	96270138 (74090229, 122077397)	720270 (-5443304, 6336357)
2) < 80%	2727.22 (2727.15, 2727.29)	0.10 (0.02, 0.18)	1604.78 (1469.50, 1722.16)	55.14 (-111.34, 213.03)	100345397 (78093234, 126256877)	96797653 (74715298, 122627406)	1755466 (-18109869, 12793599)

ICER, incremental cost-effectiveness ratios; LY, life years; NA, not applicable; QALY, quality-adjusted life years; THB, Thai Baht

Note: Data are expressed as values (95% credible intervals).