



## Evidence-based Practice Center Systematic Review Protocol

**Amendment Date(s): November 18, 2016**

**(Amendment Details – see Section VII)**

### Systematic Review of Intermittent Inhaled Corticosteroids and of Long-acting Muscarinic Antagonists for Asthma

#### I. Background and Objectives for the Systematic Review

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.<sup>1</sup> In the United States (US), the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.<sup>2</sup> Asthma can significantly impact patients' and families' quality-of-life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.<sup>3</sup> In the US, asthma contributes significantly to healthcare resource utilization and associated costs. For example, in 2012, asthma was one of the top twenty leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.<sup>4</sup>

#### **Rationale**

In 1989, the National Heart, Lung and Blood Institutes (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP) to address growing concern about asthma in the US. One of the first accomplishments of the NAEPP was to convene a panel of experts who summarized their recommendations in a document, National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma, in 1991. The guidelines address the diagnosis, evaluation, and treatment of asthma. Given the most recent report, EPR-3, was published in 2007<sup>1</sup>. NHLBI assessed the need for an update by requesting information from the public, NAEPP Coordinating Committee Members and its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.<sup>5</sup> The Working Group identified six high priority topics that should be updated. For each topic, key questions meriting a systematic literature review were formulated. NHLBI engaged AHRQ to perform the systematic reviews through its Evidence-based Practice Centers (EPC). This document represents the systematic review of “Intermittent inhaled corticosteroids and of long-acting muscarinic antagonists for asthma”. The review also will highlight areas of controversy and identify needs for future research on these priority areas.

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## Intermittent Inhaled Corticosteroid (ICS) Dosing

Scheduled, daily dosing of ICS is the preferred pharmacologic controller therapy for persistent asthma in patients of all ages.<sup>1</sup> “Controller therapy” will be used in this document to describe medications to be taken daily on a long-term basis to achieve and maintain control of persistent asthma.<sup>1</sup> “Intermittent” ICS dosing will be used in this document to describe the prescribed use of ICS that is not the same on a daily basis. As prescribed, intermittent ICS dosing may specify variations in the dose, frequency, or duration of administration of ICS. The determinant of ICS use with intermittent ICS dosing may be a patient decision (based on need), an index of worsening asthma or some other predefined criteria. Some examples of intermittent ICS dosing include initiating a temporary course of ICS in a patient not regularly taking ICS controller therapy or temporarily increasing the dose of ICS that is otherwise taken as controller therapy, either strategy in response to a measure of worsening asthma.<sup>1,6,7</sup> An extension of the use of intermittent ICS therapy is the combined use of ICS plus LABA as both a controller and quick relief therapy, particularly when the LABA is considered fast-acting.<sup>8</sup> “Quick relief” therapy will be used in this document to describe medication to be used as-needed for acute symptom relief.

EPR-3 suggests that intermittent ICS dosing schedules may be useful in some settings though the evidence at that time was insufficient to support the recommendation beyond experts’ judgment consensus.<sup>1</sup> Since the EPR-3 it was determined by the NHLBI Needs Assessment Workgroup that a sufficient number of studies have been published on the intermittent ICS dosing, warranting a systematic literature review.

## LAMA added to ICS or to ICS plus LABA

LAMAs were not included in the EPR-3 although since then, they have been studied as controller therapy for asthma and at least one LAMA has gained FDA approval for asthma management (Appendix Table 1).<sup>9</sup> This represents a new pharmacologic class of long-acting bronchodilators for consideration in the stepwise approach to asthma management and the NHLBI Needs Assessment workgroup determined this topic to be of importance for a potential EPR-3 update.

## II. The Key Questions

**Key Question 1a:** What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic or non-pharmacologic therapy in children 0 to 4 years old with recurrent wheezing?

**Key Question 1b:** What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in patients 5 years of age and older with persistent asthma?

**Key Question 1c:** What is the comparative effectiveness of ICS with LABA used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

**Key Question 2a:** What is the comparative effectiveness of LAMA as add on to ICS controller therapy compared to placebo or increased ICS dose in patients 12 years of age and older with uncontrolled, persistent asthma?

**Key Question 2b:** What is the comparative effectiveness of LAMA compared to other controller therapy as add on to ICS in patients 12 years of age and older with uncontrolled, persistent asthma?

**Key Question 2c:** What is the comparative effectiveness of LAMA as add on to ICS plus LABA compared to ICS plus LABA as controller therapy in patients 12 years of age and older with uncontrolled, persistent asthma?

For the above KQs, the following PICOTS criteria apply:

**Populations**

We will include all patients that meet the KQ specific criteria regardless of gender, race and ethnicity.

- KQ1a: Children 0 to 4 years of age with recurrent wheezing
- KQ1b-c: Patients 5 years of age and older with persistent asthma
- KQ2a-c: Patients 12 years of age and older with uncontrolled, persistent asthma

**Interventions**

This review is focused on pharmacologic interventions within the following classes of inhaled medications: ICS, LABA, and LAMA (Table 1). In addition, some of the pharmacologic interventions include more than one class of medications, in which case one drug from each of the specified classes is combined. Medications were selected if used for asthma management (regardless of FDA approval).

**Table 1. Inhaled active drug moieties used to manage asthma**

<b>Corticosteroid</b>	<b>LABA</b>	<b>LAMA</b>
Beclomethasone	Arformoterol	Acclidinium
Budesonide	Formoterol	Glycopyrrolate
Ciclesonide	Indacaterol	Tiotropium
Flunisolide	Olodaterol	Umeclidinium
Fluticasone	Salmeterol	
Mometasone	Vilanterol*	
Triamcinolone		

ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist  
 \* considered ultra-long-acting beta-agonist

The interventions for each of the KQs is as follows:

- KQ1a-b: Intermittent ICS dosing
- KQ1c: ICS+LABA used as controller and quick relief therapy
- KQ2a-b: ICS+LAMA as controller therapy
- KQ2c: ICS+LABA+LAMA as controller therapy

Table 2 demonstrates the interventions and comparators for each KQ in a tabular format. The definitions of “intermittent”, “controller therapy” and “quick relief therapy” are provided above as well as section VI. Definitions of Terms.

**Table 2. Intervention and Comparator per Key Question**

Interventions	Comparator(s)			
	No treatment, pharmacologic or non-pharmacologic therapy <sup>1</sup>	ICS controller therapy	ICS+LABA controller therapy	ICS+other controller therapy <sup>2</sup>
Intermittent ICS	1a	1a, 1b	---	---
ICS+LABA used as controller and quick relief therapy	--	1c	1c	---
ICS+LAMA controller therapy	--	2a <sup>3</sup>	2b	2b
ICS+LAMA+LABA controller therapy	--	---	2c	---

The first column represents interventions and the first row represents comparators of interest in this review. The key questions for each intervention are listed below the relevant comparator(s).

<sup>1</sup>Non-pharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers)

<sup>2</sup>Other controllers include cromolyn, leukotriene modifiers, immunomodulators, methylxanthines, systemic corticosteroids

<sup>3</sup>Same or increased ICS dose in the comparator arm relative to intervention dose.

## Comparators

We are interested in direct comparisons of therapies as described per KQ. Table 2 demonstrates the intervention and comparator for each KQ in a tabular format. The definition of “controller therapy” is provided above as well as in section VI. Definition of Terms.

- KQ1a: No treatment (placebo or control) **OR** pharmacologic therapy which includes controller therapy or as needed SABA **OR** non-pharmacologic therapy. Controller therapies include ICS, inhaled LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators, and systemic corticosteroids. Non-pharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers)
- KQ1b: ICS controller therapy
- KQ1c: ICS controller therapy **OR** ICS+LABA controller therapy
- KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or increased relative to the intervention arm dose.
- KQ2b: ICS+another controller therapy, including LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators and systemic corticosteroids.
- KQ2c: ICS+LABA controller therapy

Similar to the interventions, some of the pharmacologic comparators include more than one class of medications, in which case one drug from each of the specified classes is combined. Medications were selected if used for asthma management (regardless of FDA approval).

## Outcomes

Within the construct of the outcomes listed, we will include outcomes that fall within one of the listed categories below, using the definitions provided by each study.

- Asthma Control
  - Composite Measures

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- Asthma Control Test (ACT)
- Asthma Control Questionnaire (ACQ)
  - Spirometry including FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC
- Asthma exacerbations
- Asthma-specific quality of life
  - Asthma Quality of Life Questionnaire (AQLQ)
  - Pediatric Asthma Quality of Life Questionnaire (PAQLQ)
  - Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire (PACQLQ)
- Death, all-cause and asthma-specific
- Healthcare utilization
  - Asthma-related hospitalizations, emergency department visits, urgent care visits, outpatient visits
  - Additional asthma-medication use/need (e.g. need for rescue inhaler)
  - Additional resource use related to intervention (personnel time, equipment)

**Timing**

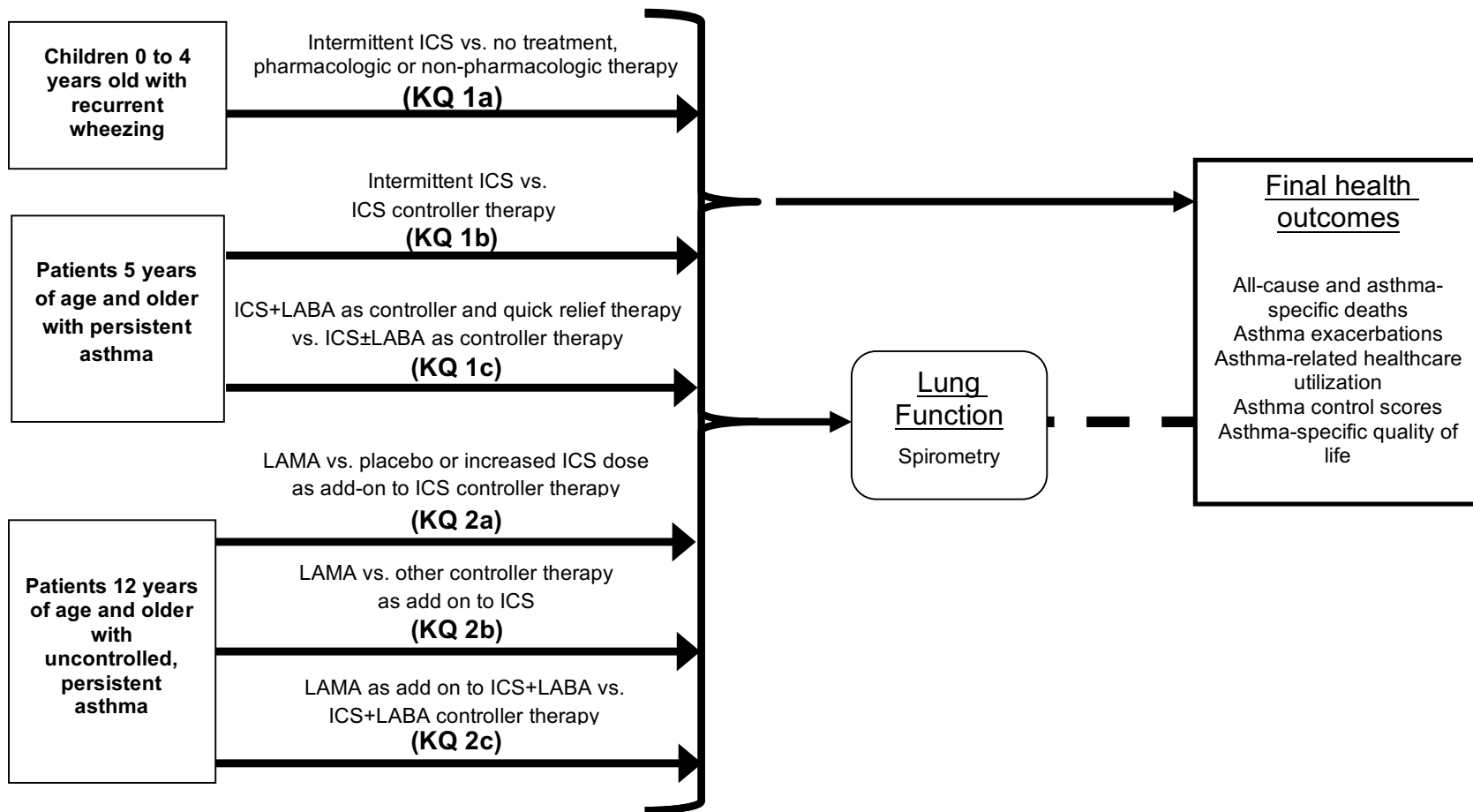
We will have no minimum study duration or length of follow-up.

**Setting**

We will have no requirements with respects to study setting.

### III. Analytic Framework

Figure 1. Analytic framework for pharmacologic treatment of asthma: intermittent ICS and LAMA



Abbreviations: ICS=inhaled corticosteroid; KQ=key question; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist

## IV. Methods

The methods for this comparative effectiveness review follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for the Evidence-based Practice Center (EPC) program.<sup>10</sup>

### Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are listed in Table 3, consistent with the PICOTS specified above. Please refer to section VI for the definition of terms used throughout this section, consistent with the rest of the protocol.

**Table 3. Inclusion and exclusion criteria**

Category	Inclusion Criteria	Exclusion Criteria
Population	KQ1a: Children 0 to 4 years of age with recurrent wheezing KQ1b-c: Patients 5 years of age and older with persistent asthma KQ2a-c: Patients 12 years of age and older with uncontrolled, persistent asthma	KQ1a: Patients 5 years of age and older KQ1b-c: Patients 4 years of age and younger; Patients with intermittent asthma KQ2a-c: Patients 11 years of age and younger; Patients with controlled, persistent asthma or with intermittent asthma
Intervention	KQ1a-b: Intermittent dosing of an ICS KQ1c: ICS+LABA used as both controller and quick relief therapy KQ2a-b: ICS+LAMA controller therapy KQ2c: ICS+LABA+LAMA controller therapy Therapies considered an ICS, LABA or LAMA that are not FDA approved but used outside of the United States will be included as identified.	KQ1c: ICS+LABA used as controller therapy but not quick relief therapy All KQs: All other interventions outside of pharmacologic therapies listed in PICOTS; Combinations of interventions other than those listed in the PICOTS
Comparator	KQ1a: No treatment <b>OR</b> pharmacologic therapy <b>OR</b> non-pharmacologic therapy. Therapies are further defined according to PICOTS above. KQ1b: ICS controller therapy KQ1c: ICS+LABA controller therapy KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or higher than in the intervention arm KQ2b: ICS+ another controller therapy as defined in PICOTS KQ2c: ICS+LABA controller therapy Therapies considered an ICS, LABA or LAMA that are not FDA approved but used outside of the United States will be included as identified.	KQ1c: ICS+LABA used as both controller and quick relief therapy All KQs: All other comparators outside of those specified in PICOTS; Combinations of comparators other than those listed in the PICOTS
Outcomes	As defined in the PICOTS criteria	Studies that do not include at least one of the outcomes listed in the PICOTS
Timing	All study durations and follow-up lengths will be included	None

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Category	Inclusion Criteria	Exclusion Criteria
Setting	All settings will be included	None
Study Design	Randomized-controlled trials, cross-over trials*, prospective or retrospective observational cohort studies, case-controlled studies	Case series, case reports, nonsystematic reviews, systematic reviews with or without meta-analysis <sup>†</sup>
Publication Language and Dates	English language publications <sup>‡</sup> with no limits on date of publication	Non-English language publications

\*Cross-over trials will be included if the outcomes data can be abstracted after the first period. If data cannot be abstracted after the first period, the trial will be included based on the following criteria, to minimize carry-over effects: for ICS-if the washout period is at least 6 weeks<sup>11</sup>, for LABA or LAMA- if the washout period is at least 4 weeks<sup>12</sup>.

† Systematic reviews with meta-analysis will be flagged for purposes of backwards citation tracking but will not be included in this review.

‡ This is consistent with the Expert Panel Report-3. English language abstracts of non-English language articles will be reviewed at the abstract stage consistent with the process described by the Methods Guide.<sup>10</sup>

FDA=Food and Drug Administration; KQ=key question; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic antagonist

**Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions -** To identify relevant published literature, we will search the following databases: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials via OVID, and Cochrane Database of Systematic Reviews via OVID, limiting the search to human subjects (consistent with EPR-3). We will search [clinicaltrials.gov](http://clinicaltrials.gov) and the World Health Organization International Controlled Trials Registry Platform (ICTRP) for ongoing studies as well as those completed with results, when available. Drug manufacturers will be notified by the Scientific Resource Center of the opportunity to submit scientific information packets for this review.

Two search strategies will be implemented, one for KQ1 and a second for KQ 2. The preliminary search strategies formatted for MEDLINE are shown in the Appendix and are comprised of medical subject heading (MeSH) terms and natural language terms reflective of asthma and the drug therapies of interest. The search strategy will be adapted for the other databases as needed. The reference list of key articles and systematic reviews or guidelines identified during the article screening process will be reviewed for additional eligible studies. The literature search will be updated during public/peer review of the draft report.

Articles retrieved through electronic database searching will be screened for inclusion in this review against the established PICOTS framework and inclusion/exclusion criteria. The title and abstract of each article will be reviewed by two independent investigators and the article will be excluded if both reviewers agree that it meets one or more exclusion criteria. Articles identified for inclusion will advance to the full-text screening. Two independent reviewers will screen each article and agree upon the inclusion/exclusion decision. Disagreements will be resolved through consensus adjudication in consultation with a third reviewer. Articles that meet



inclusion/exclusion criteria will be eligible for data abstraction. When necessary, we may contact authors of candidate articles for clarification of reported study details in order to assess for inclusion/exclusion. For articles excluded at the full-text level, we will record the reason for exclusion and present a list of such studies in the review.

Abstracts and meeting presentations will be considered for inclusion into the review under two conditions: 1) if they are a source of a unique study that meets inclusion criteria and provides enough methodologic detail to assess risk of bias or 2) if the abstract or presentation can be matched to an original publication that has been included into the review when the abstract or presentation reports data on an outcome that was not provided by the original publication.

All results retrieved through database searches will be imported into an electronic bibliographic database (RefWorks). Results from other searches will be recorded in a Microsoft Excel database, as will the screening and selection of citations.

Data Abstraction and Data Management - Data will be abstracted using a standardized tool in Microsoft Word and Excel. Data will be abstracted by two trained researchers. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. A third reviewer will audit a random sample of articles to ensure consistency of the process.

Articles referring to the same study will be abstracted on a single review form, assuming the populations are the same. Authors of individual studies may be contacted either for clarification or to request additional data, if necessary.

For all included studies, reviewers will extract data on study characteristics (e.g. study design, duration of follow-up), eligibility criteria, study population (e.g. age, gender, race/ethnicity, mean asthma duration, severity of condition, baseline lung function, comorbidities), interventions (e.g. intervention drug(s), comparison, dose, frequency, concomitant medications), outcome measures, and the results of each outcome, including measures of variability.

Assessment of Methodological Risk of Bias of Individual Studies - The assessment of risk of bias for included RCTs of pharmacologic interventions will be performed using the Cochrane Collaboration's Risk of Bias Tool.<sup>13</sup> For non-randomized studies, we will use the ROBINS-I tool for risk of bias assessment.<sup>14</sup>

Two reviewers will independently assess the risk of bias of each included study, with disagreements resolved by either discussion or consultation with a third team member. The overall risk of bias for each study will be classified as low, moderate or high, according to the collective risk of bias per evaluated domain and the investigator's confidence in the study results given the identified limitations.<sup>15</sup>

Data Synthesis – For each Key Question, we will create a set of detailed evidence tables containing all information extracted from included studies. Synthesis of data will be based on the pharmacologic class named as the intervention and comparator,

not on the individual drug level, unless there is evidence to support a differential effect exists between therapies within a given class in which case an individual drug therapy could be considered separately. We will perform random-effects meta-analysis using the Hartung-Knapp method when sufficient data for a given outcome is available from at least three studies that are sufficiently homogenous with respect to key clinical (population characteristics, study duration, and intervention) and methodologic (based on risk of bias assessment) variables. Statistical significance will be set at a two sided alpha of 0.05. All studies, including those that are not amenable to pooling, will be qualitatively summarized.

When quantitative pooling of studies is possible, we will evaluate for statistical heterogeneity using the Cochrane chi-square p-value and the  $I^2$  statistic. A Cochrane p-value of <0.10 suggests the presence of statistical heterogeneity. The  $I^2$  statistic assesses the degree of inconsistency across studies and ranges from 0-100% with the higher percentage representing a higher likelihood of the existence of true heterogeneity as opposed to chance.<sup>16</sup> An  $I^2$  value of greater than 50% will be considered substantial heterogeneity. We will attempt to determine potential reasons by conducting relevant subgroup analyses and/or meta-regression if pertinent covariate information in a sufficient number of studies is available. The Technical Expert Panel (TEP) was consulted for the stratifications or categories to consider for subgroup analyses and they include asthma severity, asthma control, age, ICS dose, onset of asthma, obesity, atopy, smoking history, race, pulmonary function, LAMA dose/delivery device, the determinant of ICS use with intermittent ICS dosing and concomitant asthma medications.

To assess for the presence of publication bias, visual inspection of funnel plots will be considered for pooled analyses with 10 or greater studies as well as consideration of Egger's weighted regression tests.<sup>17</sup> All meta-analyses will be conducted using Comprehensive Meta-Analysis, Version 3 (Biostat, Englewood, NJ, USA).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes- We will grade the SOE based on the guidance established for the EPC program.<sup>18</sup> At the completion of the review, two reviewers will independently grade the SOE for critical outcomes which are expected to include asthma control composite scores, spirometry, asthma exacerbations, mortality, asthma-specific quality of life and healthcare utilization. Conflicts will be resolved either through consensus or third-party adjudication. The SOE approach incorporates five key domains: study limitations, directness, consistency, precision, and reporting bias of the evidence body. Additional domains (plausible confounding, dose-response, and magnitude of effect) will be considered when applicable. The SOE pertaining to each KQ will be classified into four categories:

- 1) High – We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- 2) Moderate – We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some

deficiencies. We believe the findings are likely to be stable, but some doubt remains.

- 3) Low – We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- 4) Insufficient – We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available of the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Assessing Applicability – We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Questions as recommended by the EPC methods guide.<sup>19</sup> We will consider how important population characteristics (e.g. age, gender, race, ethnicity, and severity of asthma), and intervention features (co-interventions) may cause heterogeneity of treatment effects and affect generalizability of the findings.

## V. References

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Rockville, MD: Agency for Healthcare Research and Quality; 2014. Chapters available at [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).

## VI. Definition of Terms

**Asthma control:** The degree to which the manifestations of asthma (symptoms, functional impairments, exacerbations) are minimized. Asthma control is determined by assessing the domains of impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and risk (exacerbations requiring oral systemic corticosteroids).

**Asthma severity:** The intrinsic intensity of the disease process. Asthma severity is assessed in a patient who is not currently receiving controller therapy using the domains of impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and risk (exacerbations requiring oral systemic corticosteroids) or it is inferred from the least amount of treatment required to maintain control. Asthma severity is classified as “intermittent”, “mild persistent”, “moderate persistent”, or “severe persistent”.

**Controlled asthma:** Minimal manifestations of asthma symptoms and functional impairments, as determined by assessment of the impairment and risk domains.

**Intermittent dosing:** The prescribed use of ICS that is not the same on a daily basis. As prescribed, intermittent ICS dosing may specify variations in the dose or frequency of administration of ICS. The determinant of ICS use with intermittent ICS dosing may be a patient decision (based on need), an index of worsening asthma, or some other pre-defined criteria.

**Controller therapy:** Medications recommended to be taken daily on a long-term basis to achieve and maintain control of persistent asthma. Long-term controller medications include inhaled corticosteroids, inhaled long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, immunomodulators, and oral systemic corticosteroids.

**Persistent asthma:** A classification of asthma severity defined either by the assessment of the impairment (patient self-reported symptoms, nighttime awakenings, rescue SABA use, interference with normal activities; objective measures of lung function) and/or risk (exacerbations requiring oral systemic corticosteroids) domains in a patient not taking controller therapy or use of controller therapy to achieve and maintain asthma control. Persistent asthma is further sub-divided as “mild persistent”, “moderate persistent”, and “severe persistent”.

**Quick-relief therapy:** Medication to be used as-needed for acute symptom relief.

**Uncontrolled asthma:** A lack of asthma control, as determined by assessment of the impairment and/or risk domains.

## VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
11/18/16	IV. Methods	For non-randomized studies, we will use the ROBINS-I tool for risk of bias assessment.	For non-randomized studies, we will use the Newcastle-Ottawa scale for risk of bias assessment.	To be consistent across the 4 simultaneous systemic reviews of asthma treatment topics, we will change the tool used for assessment of risk of bias for non-randomized studies.

## VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

## IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do



they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

#### XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

#### XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

#### XIII. Role of the Funder

This project was funded under Contract No. HHS 290-201-500012I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.



## Appendix

**Appendix Table 1. Drug therapies either as individual or combination products of inhaled corticosteroids, long-acting beta-agonists, and long-acting muscarinic antagonists**

<b>Class Registered/Trademark (chemical name)</b>	<b>Regulatory Agency Approved Indication</b>
<b>ICS</b>	
Aerospan (flunisolide)	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 6 years of age and older; Asthma patients requiring oral corticosteroid therapy, where adding Aerospan inhalation aerosol may reduce or eliminate the need for oral corticosteroids
Alvesco (ciclesonide)	Maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older
Arnuity Ellipta (fluticasone furoate)	Once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older
Asmanex HFA (mometasone furoate)	Maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older
Asmanex Twisthaler (mometasone furoate)	Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older
Azmacort (triamcinolone acetonide)	Maintenance treatment of asthma as prophylactic therapy; Asthma patients who require systemic corticosteroid administration, where adding Azmacort may reduce or eliminate the need for the systemic corticosteroids*
Flovent Diskus (fluticasone propionate)	Maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older; Treatment of asthma in patients requiring oral corticosteroid therapy
Flovent HFA (fluticasone propionate)	Maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older; Treatment of asthma in patients requiring oral corticosteroid therapy
Pulmicort Flexhaler (budesonide)	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 6 years of age or older
Pulmicort Respules (budesonide)	Maintenance treatment of asthma as prophylactic therapy in children 12 months to 8 years of age
Qvar (beclomethasone dipropionate)	Maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older; Treatment of asthma in patients who require oral corticosteroid therapy. Qvar may reduce or eliminate the need for the systemic corticosteroids
<b>LABA</b>	
Arcapta Neohaler (indacaterol)	Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
Brovana (arformoterol tartrate)	Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema
Foradil Aerolizer (formoterol fumarate)	Treatment of asthma in patients $\geq 5$ years as an add-on to a long-term asthma control medication such as an inhaled corticosteroid; Prevention of EIB in patients $\geq 5$ years; Maintenance treatment of bronchoconstriction in patients with COPD
Perforomist (formoterol fumarate)	Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema
Serevent Diskus (salmeterol xinafoate)	Treatment of asthma in patients aged 4 years and older; Prevention of EIB in patients aged 4 years and older; Maintenance treatment of bronchospasm associated with COPD

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

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<b>Class Registered/Trademark (chemical name)</b>	<b>Indication</b>
Striverdi Respimat (olodaterol)	Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
<b>LAMA</b>	
Incruse Ellipta (umeclidinium)	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD
Seebri Neohaler (glycopyrrolate)	Long-term, maintenance treatment of airflow obstruction in patients with COPD
Spiriva Handihaler (tiotropium bromide)	Long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations
Spiriva Respimat (tiotropium bromide)	Long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations; Long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older
Tudorza Pressair (aclidinium bromide)	Long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema
<b>ICS+LABA</b>	
Advair Diskus (fluticasone propionate/salmeterol)	Treatment of asthma in patients aged 4 years and older; Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD
Advair HFA (fluticasone propionate/salmeterol)	Treatment of asthma in patients aged 12 years and older
Breo Ellipta (fluticasone furoate/vilanterol)	Long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD; Once-daily treatment of asthma in patients aged 18 years and older
Dulera (mometasone furoate/formoterol fumarate dihydrate)	Treatment of asthma in patients 12 years of age and older
Flutiform, Iffeza or other associated names (fluticasone propionate/formoterol fumarate dihydrate)	Regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting $\beta_2$ agonist) is appropriate: for patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting $\beta_2$ agonist or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting $\beta_2$ agonist in adult and adolescents aged 12 years and above <sup>†</sup>
Fostair, Kantos Master or other associated names (beclometasone dipropionate/formoterol fumarate dihydrate)	Regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $\beta_2$ -agonist is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting $\beta_2$ -agonist or patients already adequately controlled on both inhaled corticosteroids and long-acting $\beta_2$ -agonists; Symptomatic treatment of patients with severe COPD (FEV <sub>1</sub> <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators <sup>†</sup>
Fostair Nexthaler or other associated names (beclometasone dipropionate anhydrous/formoterol fumarate dihydrate)	Regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $\beta_2$ -agonist) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting $\beta_2$ -agonist or patient already adequately controlled on both inhaled corticosteroids and long-acting $\beta_2$ -agonists in adults; Symptomatic treatment of patients with severe COPD (FEV <sub>1</sub> <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators <sup>†</sup>
Symbicort (budesonide/formoterol fumarate dihydrate)	Treatment of asthma in patients 12 years of age and older; Maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema
<b>LABA+LAMA</b>	

Anoro Ellipta (umeclidinium/vilanterol)	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Duaklir Genuair, Brimica Genuair or other associated names (aclidinium/formoterol fumarate dihydrate)	Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) <sup>‡</sup>
Stiolto Respimat (tiotropium bromide/olodaterol)	Long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Utibron Neohaler (indacaterol/glycopyrrolate)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)

\* discontinued by the United States Food and Drug Administration (FDA) in 2010

† approved by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA)

‡ approved by the European Medicines Agency (EMA)

COPD=chronic obstructive pulmonary disorder; EIB=exercise-induced bronchospasm; FEV<sub>1</sub>=forced expiratory volume in one second

### Search for KQ 1

1. Asthma.mp or Asthma/
2. Wheez\$.mp.
3. Bronchial spasm/ or bronchospas\$.mp.
4. Bronchoconstriction/ or bronchoconstrict\$.mp.
5. Bronchial hyperreactivity/
6. Reactive airway disease.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Inhaled corticosteroid.mp.
9. Inhal\$.mp.
10. Ciclesonide.mp.
11. Fluticasone/ or fluticasone.mp.
12. Flunisolide.mp.
13. Beclomethasone/ or beclomethasone.mp.
14. Budesonide/ or budesonide.mp.
15. Mometasone furoate/ or mometasone.mp.
16. Triamcinolone/ or triamcinolone.mp.
17. 9 AND (10 or 11 or 12 or 13 or 14 or 15 or 16)
18. "Single inhaler".mp. OR "single maintenance and reliever therapy".mp. OR SMART
19. 8 or 17 or 18
20. 7 and 19
21. Limit 20 to humans

### Search for KQ 2

1. Asthma.mp or Asthma/
2. Wheez\$.mp.
3. Bronchial spasm/ or bronchospas\$.mp.
4. Bronchoconstriction/ or bronchoconstrict\$.mp.
5. Bronchial hyperreactivity/
6. Reactive airway disease.mp.

7. 1 or 2 or 3 or 4 or 5 or 6
8. Long acting muscarinic antagonist.mp.
9. Tiotropium bromide/ or tiotropium.mp.
10. Aclidinium.mp.
11. Glycopyrronium.mp. or glycopyrrolate/ or glycopyrrolate.mp.
12. Umeclidinium.mp.
13. 9 or 10 or 11 or 12
14. 8 or 13
15. 7 and 14
16. Limit 15 to humans