Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:
Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Draft review available for public comment from March 21, 2017 to April 18, 2017.

Research Review Citation: Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma. Comparative Effectiveness Review No. 194. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012-I.) AHRQ Publication No. 17(18)-EHC027-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2018. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER194

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #1	Abstract	My only comment is to define “ICS controller” in the abstract	As suggested, we have added the definition of “controller”
TEP reviewer #2		Structured Abstract, pg vi, Ln 37: Here you state exacerbation requiring oral corticosteroids and then after that in the abstract you just say exacerbations but you have may definitions for exacerbations. Be explicit by either defining exacerbations as those requiring oral corticosteroids or whatever. On page vii, Ln 16-17 you say requiring systemic corticosteroids (which is better than oral corticosteroids) please just be explicit.	We have more specifically identified the exact exacerbation type throughout the abstract, as suggested.
TEP reviewer #2		pg vii, Ln 37-38: I think you want to say improves "some" outcomes. Based on line 25.	We have made this change as suggested.
TEP reviewer #2		pg vii, Ln 40: Change to "...produced no difference in outcomes."	We have made this change as suggested
Public Reviewer #1, Anonymous		This wording of KQ1c doesn't correlate with that laid out in the objectives (i.e., LABA not mentioned). Thus, it is initially confusing to read.	We revised the objective to point out KQ1c is with or without LABA, as suggested.
TEP reviewer #1	Introduction	No comments	NA
TEP reviewer #2		The rationale is concise and well written and the division of the Key Questions into specific sub-questions is appropriate and quite helpful for viewing and assessing the data.	Thank you.
TEP reviewer #3		No specific comments on this section.	NA

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1		The introduction in quite perfunctory and uninformative. The most glaring omission: adherence to daily medication goes entirely unmentioned. Lack of adherence is one of the most (if not the most) important barriers to success in reaching asthma control in perhaps 90% of patients. If all patients adhered 100% to therapy, intermittent therapy and the need to add more and more controllers would probably be much less important issues. In other words: the introduction should at least briefly explain why intermittent therapy is even an issue and why a new, rather expensive type of long-acting bronchodilator (LAMAs) could find a place in asthma therapy.	Thank you for this comment. We have added context regarding barriers to clinical management, including adherence.
Peer reviewer #2		Clearly laid out with questions well identified.	Thank you.
Peer reviewer #3		No comments.	NA

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Anonymous		It is better to report increases in prevalence in percentages (because numbers could just reflect population growth rather than a real increase). However, if it is not easy to find a source that combines the adult and pediatric estimates, you could change this sentence to "In the US, the number of persons with asthma has increased over the past decade, from..."	Our purpose is to describe how many Americans are affected as well as the trend in prevalence (which has increased whether you use the number affected or the percentage in this case). While the reviewer's point is understood, it is more straightforward to use the number affected to describe the trend, because the number affected has increased steadily whereas percentage has not consistently increased. Nonetheless the overall ***trend*** is increasing (despite year to year differences in direction and amount of change) according to CDC reports, whichever measure of prevalence you use. The reference (link) used does have prevalence by adult and children and using percentages and the number of Americans affected.
Public Reviewer #1, Anonymous		Here, it may be more meaningful to cite the number of deaths (3,651 in 2015). Without comparison to death rates from other causes, it is difficult to gauge the significance of the asthma death rate.	The selected data provides an indication of proportion of deaths that asthma accounts for (i.e., 99,999 deaths of every 100,000 are from other causes. Citing the number of deaths from asthma provides no comparison to the death rates (or numbers) from any cause. However, we can keep the proportion of deaths attributed to asthma and add the absolute number as well.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Anonymous		Somewhere in this section, it would be good to define what is meant by the treatment terms. e.g., What is "intermittent ICS?" What type of usage schedule and/or time duration of treatment differentiates LABA as quick relief versus controller?	The term “intermittent” and “controller therapy” are defined within the glossary of the report.
Public Reviewer #2, Tami Kochan		It appears that as though some studies were limited I came to almost the same conclusion as the reviewers.	Thank you.
Public Reviewer #3, Veronica Mansfiled, DNP, APRN, PPNP-BC, AE-C; National Association of Pediatric Nurse Practitioners		The background and content are clear and understandable. The argument presented identify why a systematic review is necessary at this time. I felt that the questions asked throughout the review were clearly stated in the introduction.	Thank you.
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network		No comment	NA
TEP reviewer #1	Methods	No comments	NA

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #2		The inclusion and exclusion criteria are justifiable and the search strategies are clearly stated and logical with the outcome measures being highly appropriate. I will reserve the statistical review to statisticians but seem to be the standard for systemic reviews. I have on concern about methods that is prevalent across many systematic reviews and the is the ignoring doses. Specifically, I am referring to intermittent ICS dosing on top of ICS control Pg 16 &17 Table 8. There were two trials of quadrupling the dose of the intermittent dose that should have been looked at separately from the doubling the ICS dose (Refs 48, 54) pg 6, Lns 41-42: What if the different dose produced different results?	Per the protocol 3 or more trials were one criterion for meta-analysis, including subgroup analyses. Thus, we were unable to conduct subgroup analyses by dose (i.e doubling, quadrupling). We have added this as a limitation to the meta-analysis and interpretation of the data for this KQ, in the discussion.
TEP reviewer #2		Pg 7, Ln 47: Define PICOTS on first use.	We have made this suggested revision.
TEP reviewer #2		Pg 21, KQ1c: How did you sort out rescue medication use with SABA as it was used for exacerbations. The ICS/LABA was used for exacerbations as well and the formoterol has a 8-12 hour duration but the albuterol or terbutaline has a two to six hour duration depending on the level of bronchoconstriction. Did you subtract the number or as needed ICS/formoterol prn from the albuterol or terbutaline prn to get a reasonable comparison?	We collected data from the included studies as it was defined. Studies reported number of puffs of rescue medication use per 24h or per week most commonly and reported this as a mean and SD. We did no further manipulation of the values.
TEP reviewer #3		I am glad you discussed the strength of evidence categories and how they were defined. However, in the text, it does not give specific reasons why some studies were graded as low or moderate evidence. That would be helpful, especially to the Expert Panel.	The specific domains which contributed to the downgrading of all outcomes, organized per KQ, appear in the Appendix of the report.
Peer reviewer #1		Methods and selection strategies are outstanding. Definitions of outcomes are well outlined and statistical methods appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2		Well described.	Thank you.
Peer reviewer #3		Very detailed and described the entire process - well done. It may be more specific to state that the intermittent dosing is defined as a change in dosing with a change in condition or seasonal variability for expected change in condition instead of not the same each day? There are people that will argue that the dose is the same each day as long as their condition does not change, once they have symptoms of UTI the does changes. It is not a random daily difference as baseline. Not the same on a daily basis seems too general for the meaning behind the review.	Thank you for this suggestion. The definitions used throughout this report were determined during the protocol developed by the EPC with input for the Technical Expert Panel.
Eisenberg Center		The background section indicates that the current systematic review was conducted with the aim of updating the National Asthma Education and Prevention Program Expert Panel Report (EPR) guidelines. However, additional detail regarding the current guidelines and treatment algorithm, and how current practice is directed by guidelines would be very helpful. Clinicians and guideline developers might seek information on what new insights come from this systematic review and how the findings align or do not align with current recommendations.	Information is presented within the introduction to state what the position of the EPR-3 was regarding intermittent ICS dosing when those guidelines were written. LAMA were not yet approved at the time of writing EPR3 thus they are not incorporated into the guidelines. This is stated within the introduction as well.

Commentator & Affiliation	Section	Comment	Response
Eisenberg Center		The currently-available guidelines appear to have been published in 2007 (https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthmaguidelines/summary-report-2007) and this systematic review and the guidelines have some divergence or areas where new evidence is anticipated, for example: -The guidelines do NOT contain recommendations regarding LAMA. -They support using controlling ICS for moderate persistent asthma symptoms -The guidelines mention the use of leukotriene antagonists, which this review does not address	Thank you for this comment. This review is an effort to update the 2007 guidelines that are cited in this reviewer's comment and the scope of the review is limited to the two distinct topics: intermittent ICS and LAMA in asthma.
Eisenberg Center		While the background section briefly describes inhaled corticosteroids and LAMA used in the treatment of asthma, the different types of inhaled corticosteroids and LAMA, as well as long-acting (LABA) and short-acting β2-agonists (SABA) are not clearly described. In addition the mechanisms of action of these various drugs are not described. Given the large number of inhaled corticosteroids, LAMA, LABA, and SABA available, including newly-approved medications, clinicians (and patients), might find information on the types of medications and their mechanisms of action helpful.	This review is focused on the class comparison of these therapies. The protocol contains a detailed table of ICS, LABA and LAMA drugs and the reader is referred to the protocol at the start of the methods section to review the entire document.
Eisenberg Center		Table 1 on page 3 of the draft report lists the currently-available ICS, LAMA and LABA, as well as their FDA approval status. Clinicians (and patients) might find a list of available SABA and their FDA approval status useful, particularly in light of the recent changes in the available SABA in clinical practice (and the varying coverage by insurers).	The KQ in this report do not focus on SABA, thus SABA was not included in that table.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Veronica Mansfield, DNP, APRN, PPNP-BC, AE-C; National Association of Pediatric Nurse Practitioners		The methods section was thoroughly comprehensive. Utilizing multiple databases was key to identification of appropriate articles for review. Inclusion and Exclusion criterion of patients was easily identified. Having the tables throughout the review was helpful to understand and be able to summarize each question being asked. The only comment I had was on the sources of evidence-high, moderate, low and insufficient wasn t based on type of study, statistical significance of study or size of participants.	The standard methodology for assessing the SOE as per the AHRQ methods guide was approved for this review during the protocol stage and was consistently applied throughout the document. Further description as to the domains that led to downgrading a given outcome are provided in the Appendix tables.
Public Reviewer #5, Thomas Seck, Boehringer Ingelheim Pharmaceuticals, Inc.		Expand the assessment of LAMA to include patients 6 years old and above BI appreciates AHRQ's thorough review of currently available therapeutic options ("Table 1: Included pharmacologic classes and representative drug moieties" as indicated in the report) for the treatment of asthma. BI agrees that examining studies on a wide range of available products provides a comprehensive overview for providers, patients, and others who may use the findings to inform healthcare decisions. However, we are concerned that the draft report does not include all FDA-approved indications for these products. Critically, while the report acknowledges that tiotropium bromide has been approved for the long-term maintenance treatment of asthma in patients ≥12 years old, it does not examine the recent approval for its use in patients ≥6 years old.1 BI would recommend AHRQ consider updating the report's language to acknowledge this approval and update the scope of the report to consider the evidence for this member of the LAMA class in patients ≥6 years old as part of this assessment.	The scope of this review was determined during the protocol development period at which time it was determined to address evidence in patients 12 years of age and older. We recognize that during the later stages of this review the FDA approved tiptropium for use in as young as 6 years of age and since this report does not address that evidence we have added this as a limitation in the discussion section.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network		No comment	NA
TEP reviewer #1	Results	No comments	NA
TEP reviewer #2		The Result Tables followed by further discussion is a good format and provides adequate detail. One can then find more detail in the appendices Tables and figures. I am not aware that they missed any studies or used studies inappropriately although I do believe that the few cohort (non-RCTs) that they included were worthless and could have been left off. Pg 13, Table 5: Asthma Acute Care visits? What if they didn't result in patient receiving systemic corticosteroids?	Asthma-related acute care visits were listed as such within the trials-separately from the reporting of distinct exacerbations requiring steroid. Thus, these outcomes were reported and analyzed separately since whether or not a steroid was given or whether or not an exacerbation was diagnosed was not known.
TEP reviewer #2		Pg 14, Ln 22: "...was not different..."	This revision has been made as suggested.
TEP reviewer #2		pg 17, Table 8: I didn't find a reference 48 in the table.	We have corrected this omission. The only outcome in which study 48 contributed was a study defined exacerbation as fall in PEF to <70% from baseline and we have added this to the table as well as associated appendices.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #2		Pg 24, Table 11: I would like to go on a little rant about the O'Byrne (ref 75) Bisgaard (ref 67) that incorporates my issue about lack of awareness of dosing. The Bisgaard paper is a prespecified subset (children 4-11 years) of the original O'Byrne paper. A major problem with the dosing in that subset is that the baseline dosing for BUD/Form was 80mcg/4.5mcg daily at night a dose that is not indicated for the treatment of persistent asthma in children and I am unaware of any efficacy data. The PI recommended starting dose for BUD by itself in children 6-17 yrs is 180 mcg/day. The combination of BUD/Form is not approved for children under 12 but efficacy and safety studies discussed in the PI used twice daily dosing. From the reference 67 and pg C-28 Table 11 the children receiving maintenance and reliever therapy received a mean dose of 126 mcg/day of BUD, or about 80% of an appropriate twice daily dose. I think that the only thing that can be concluded from this study is that once daily dosing of a drug that is indicated for twice daily dosing provides inadequate control of asthma and so many of the patients ended up taking it twice daily.	We have denoted that this is also a reason that the SOE has been downgraded for indirectness within the main report.
TEP reviewer #2		Pg 24, ln 44 superscript b: 2 consecutive what?	This has been corrected, the word "days" was missing.
TEP reviewer #2		Pg 24, Table 11: I don't see a superscript c in the table. This goes for the results for Table 12 as well.	This has been corrected, as the SOE for mild exacerbations in patients 4-11 should have listed C "superscript".

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #3		This is well described in terms of article sorting. A few general comments: It would be useful to give specific information on why a study was considered low or moderate SOE, for example, Table 12.	The standard methodology for assessing the SOE as per the AHRQ methods guide was approved for this review during the protocol stage and was consistently applied throughout the document. Further description as to the domains that led to downgrading a given outcome within each intervention/comparator are provided in the Appendix tables. We have added text into the "organization of the report" to specify the types of tables available in the appendix. SOE is not graded per study rather per outcome, for each unique intervention/comparator pair.
TEP reviewer #3		It would also be useful to give a summary of the outcome variable and the SOE based on the total number of studies that were assessed along with the individual studies, for example what is the strength of evidence on effect of the strategy on exacerbations as in Table 12.	The standard methodology for assessing the SOE as per the AHRQ methods guide was approved for this review during the protocol stage and was consistently applied throughout the document. Further description as to the domains that led to downgrading a given outcome within each intervention/comparator are provided in the Appendix tables. SOE is not graded overall for multiple types of an outcome (i.e. combining different definitions of exacerbations).

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #3		It would be useful to have a conclusion at the end of each question or better yet each section of a question that was evaluated.	The key points that begin each section are synonymous with the conclusion and are formulated on the objective data that is presented in the following table and text.
TEP reviewer #3		It would be useful to have subtopics within a long discussion in order to be able to easily identify the area that is being evaluated. Some of the text is very lengthy and challenging to follow, for example, pp. 27 to 29.	We have added subheaders throughout the results to indicate “study overview”, “results” and “subgroup data”.
TEP reviewer #3		More definitive conclusions regarding the literature would be helpful. Some seem vague or soft.	The concluding statements are based solely on the objective data that is presented per KQ in the overview table and text.
TEP reviewer #3		In some areas the SOE is labeled as being ”indirect”, for example page 24, but it is not clear what that means.	Superscript “d” was added to define why the SOE was downgraded for indirectness, to be consistent with other area of the report. We have also added this information to the text, also for consistency.
TEP reviewer #3		It would be helpful to include the short names of the studies in the reference tables, if they are available, for example TALC, for the ACRN tiotropium study. That would make it easier for the reader, especially for finding some major studies to determine how they were evaluated.	We have added study acronyms to the appendix Tables when individual studies are listed in a given table.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1		The results are presented in a clear, comprehensive way. Each study has clearly been analyzed extensively, including requests of further data from authors. Summaries of results are concise but accurate. Conclusions are always solidly based on the specific KQs and on an objective assessment of the data at hand. The second set of 830 references presents details of every study that was assessed and excluded, with the reasons for exclusion explained. In summary, phenomenal job.	Thank you.
Peer reviewer #2		I did not see any key study that was overlooked. The summaries, tables and descriptions of the study populations and their diversity were clearly defined.	Thank you.
Peer reviewer #3		yes - the details are necessary as those looking to use this document as a guide for EBP will need to be able to justify the results and this spells it out nicely so they do not have to go back to the original documents, which they may not have access to.	Thank you.
Peer reviewer #3		The tables for each section are good to assist in detailing the rationale behind the results and points to the specific biographies for each question and section if they need them.	Thank you.
Public reviewer #1, Anonymous		Time frame of the study (weeks, time of year) would also be informative to see in the tables throughout. This may also speak to the "application" of intermittent ICS. For example, is this use of ICS just as effective in allergy season (perhaps not applicable as much to this age group in this example) as during respiratory season? If it is indeed beyond the scope of this assessment or the studies are inadequate to evaluate this question, perhaps seasonality and duration of effect can be proposed as future key questions to be studied.	Thank you for this comment. If the studies provided any explicit inclusion or exclusion criteria regarding seasonality, they would be listed in the appendix tables although this was rare if ever reported. Seasonality was not a prespecified subgroup of interest and thus was not further evaluated in this review.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1, Anonymous		Are the numbers in the parentheses after the RR the 95% confidence interval? This should be indicated more clearly, and if CI, a comma rather than "to" should be used (e.g., (0.46, 0.98).	We have include information in the column header to denote that the values are the effect estimate and 95% confidence interval.
Public reviewer #1, Anonymous		KQ1b It may be worth summarizing here that this approach of adding ICS intermittent therapy is akin to increasing the dose (as opposed to changing the schedule from daily preventive to prn or intermittent).	Thank you for this suggestion. The definitions used throughout this report were determined during the protocol developed by the EPC with input for the Technical Expert Panel.
Public reviewer #1, Anonymous		When the result is "no difference," how does this compare to "noninferior?" That is, can one conclude that the lower cumulative dose option is noninferior and thus perhaps preferred in terms of minimizing dosage?	The results "no difference" means that statistically, there was no difference in the two therapies being compared just like one would conclude from a test of superiority in a typical RCT. This review did not test for inferiority or equivalence, thus no conclusions on non-inferiority or equivalence can be made based on the methods used.
Public reviewer #1, Anonymous		KQ1c A description of how dosing (frequency and cumulative dose) differs between controller/quick relief ICS/LABA and ICS controller with/without LABA would be helpful.	Consistent with the terms in the glossary, as used throughout the report, "quick relief" is defined as " Medication to be used as-needed for acute symptom relief " and "controller therapy" is defined as "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".

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1, Anonymous		Table 15 The terminology here “lower with LAMA” differs from elsewhere (favors LAMA).	We have revised this statement as suggested.
Public reviewer #1, Anonymous		Is there a word missing in this sentence? (“required to BE at least 18y”), KQ2a	This edit has been made as requested.
Public reviewer #1, Anonymous		KQ2b Very short duration (15d) seems like it could be a criterion for low SOE.	The standard methodology for assessing the SOE as per the AHRQ methods guide was approved for this review during the protocol stage and was consistently applied throughout the document. The five contributing domains include risk of bias, consistency, directness, precision and publication bias. SOE is graded on an outcomes basis, not for a given study, and thus the totality of evidence contributing to the outcome is considered. Although the duration of a trial is not specifically considered as a domain, the duration could contribute to multiple domains graded such as precision, consistency, directness and would be considered appropriately when grading those domains. In addition, there was no limitation of duration set within the inclusion criteria for this review.

Commentator & Affiliation	Section	Comment	Response
Eisenberg Center		The key outcomes assessed in the systematic review are defined on page 4 of the report. Several other outcomes from individual studies have been included in the findings tables throughout the report. For a given key question, since the outcomes assessed do not appear to be consistent across the various interventions evaluated, readers might find it challenging to interpret the results and apply them to their practice. Additional clarity here would be helpful to readers in assessing applicability.	All of the outcomes collected and reported fall into one of the 6 categories of outcomes defined on Page 4. Since in addition to specific types of exacerbations we also collected study defined exacerbations, definitions vary from one KQ to another. In addition, there are different versions of the exact tools that are listed o page 4, for example ACQ has the 5, 6 and 7 question version (noted as ACQ-5, ACQ-6 etc.) and similarly with the AQLQ.
Eisenberg Center		Both key questions 1b and 1c focused on two of the three EPR-3 age categories (5 to 11y and >12 years). For both key questions, a few studies were included that had enrolled patients as young as 4 years of age. Our readers might be interested in learning what percentage of patients in the studies were <5 years of age, and what percentage of patients are 5-11 years of age, and if the findings are applicable to these patients.	We have added the requested details to the extent that they were available in the primary publications.

Commentator & Affiliation	Section	Comment	Response
Eisenberg Center		Several findings in the review are based on a single RCT and have a Moderate SOE rating assigned to them. A percentage of these studies are industry-sponsored. Clinicians might wish a better understanding of the assignment of Moderate SOE for these findings from the single RCT in light of the definition of Moderate SOE provided in the report (*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*).	The standard methodology for assessing the SOE as per the AHRQ methods guide was approved for this review during the protocol stage and was consistently applied throughout the document. In the presence of one domain that is downgraded, moderate SOE is assigned. Each study included in this review was evaluated for risk of bias (ROB) using tools approved in the protocol and commonly applied in this field. ROB was taken into account when SOE was graded, as one of the domains. In addition, the number of industry reported studies is clearly stated in the results section of each KQ with citations so that the reader can learn this information and apply their own judgement as to how this may or may not impact their interpretation of the data presented. Reporting bias was also evaluated when a trial was matched with a published protocol on clincitaltrials.gov.
Eisenberg Center		In key question 1c, conventional best practice (CBP) is used as a comparator, but CBP is not clearly defined. Our readers might be interested in knowing what CBP is. Additionally, since CBP might vary in studies, readers might wish to have clarity where that can be provided	We have added a definition to the results of KQ1c for CBP as suggested.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Veronica Mansfield, DNP, APRM, PPNP-BC, AE-C; National Association of Pediatric Nurse Practitioners		The results of the review were well organized by each key question being asked. I thought the first question is quite pertinent to daily primary care practices for pediatric providers. In my opinion the literature is inconclusive on whether it is best to treat patients with intermittent versus maintenance corticosteroids for this population, however it showed that it may be beneficial with children 0-4 years of age with a RTI. As I look at the results on use of the key question 1b I found it confusing when it is supposed to address the age group of 5-11 years and the studies are addressing mostly 12 years and older. So I took it to mean that the result of using inhaled corticosteroids intermittently with the 5-11 years of age population is not beneficial. Sources of evidence strongly support the use ICS and LABA and short acting beta agonist in compared to ICS alone in the population age of 12 or greater. Unfortunately comparing it to high dose corticosteroid the evidence is week that it is a better choice in 5-11 year olds or patients 12 or greater. Not surprisingly ICS and LABA along with adding a quick relief showed reduction in requiring oral corticosteroids, ED visits or hospitalizations. In regards to the addition of LAMA to ICS in patients 12 or greater the results have some promise in reducing need for systemic corticosteroids and reducing asthma symptoms. However as a pediatric provider I am not sure that these studies are pertinent to daily practice.	KQ1b addresses intermittent ICS use in patients 5 years of age and older, not only 5 to 11 years of age. However, it is in fact correct that the majority of evidence found for KQ1b was in patients 12 years of age and older, very little is published in patients 5 to 11 years old. Lack of published evidence or a relatively smaller amount of published evidence should not be misinterpreted to mean there is no effect or no benefit.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network		We would recommend changes to key messages reflecting the following: Intermittent use of ICS during an upper respiratory tract infection in children less than 5 years old with recurrent wheezing decreases asthma exacerbations. Intermittent ICS use in patients 12 years and older with persistent asthma may be similar to ICS controller use. There is low strength of evidence for this statement, and we would prefer it be deleted or it read Intermittent ICS and adding Intermittent ICS to Controller ICS does not reduce risk of exacerbation. Using ICS and long-acting beta-agonist (LABA) together as controller and quick relief therapy reduces exacerbations compared to using ICS alone or with LABA as a controller only. In patients at least 12 years old with uncontrolled, persistent asthma adding LAMA to ICS reduces exacerbations and improves lung function while adding LAMA to ICS and LABA controller improves asthma control and lung function. Adding LAMA to ICS instead of adding LABA impacts outcomes similarly.	We have revised the key messages to make it more clear that for KQ1c the benefit is in reducing exacerbations and for KQ2b LAMA vs LABA when added to ICS did not differ in outcomes. Although in fact the strength of evidence is low, data synthesized in this report does support the original key messages made "Using inhaled corticosteroids intermittently in patients 12 years and older with persistent asthma may be as effective as using them as a controller medication" and thus no changes to those statements have been made.
TEP reviewer #1	Discussion	No comments	NA
TEP reviewer #2		All the implications are clearly stated. If they add some discussion of limitation of the Bisgaard (67) paper it would be nice. Nothing was omitted that I could see.	We have added discussion to the limitations of this data.
TEP reviewer #3		This section in particular would benefit from some labels for subtopics to specially address each question and give a firm conclusion.	We have added subheadings throughout the discussion.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #3		Overall, I agree with the conclusions but it would be good to be more direct and conclusive. To me, that is the purpose of this review. It would be important to have a medical reviewer look at each one to see if they will be helpful to the expert panel.	The concluding statements are based solely on the objective data that is presented per KQ in the overview table and text. No further conclusions or recommendations are made, standard to these reports.
TEP reviewer #3		In the tiotropium literature, I was under the impression that the 5 mcg dose was more consistently effective than the 2.5 mcg dose. Also, the parameters for these studies were not discussed in regards to 3 hour peak.	When possible in this review, we conducted subgroup analysis based on tiotropium dose. This was only possible in KQ2a and results of the subgroups were consistent with overall results, as described in the report and appendix table. There was no statistically significant difference between 2.5mcg and 5mcg (Appendix Table 23), including peak values for FEV1 and FVC, which in all of the tiotropium studies were measured at 0-3h.
TEP reviewer #3		In addition, there is a manuscript on-line with JACI on tiotropium in children ages 5 to 11 years that I believe is available for the public. See attachment to this review.	Studies for KQ 2 required the population to be 12y of age and older for inclusion. Thus, studies evaluating a younger population were outside of the scope if this review.
TEP reviewer #3		I believe you have requested data on another study that was recently published in the December 2016 issue of the JACI by Fitzpatrick et al on intermittent ICS in young children. I have attached a copy as well.	This study has been reviewed for inclusion into this review as it was identified in the updated literature search.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1		As explained in general comments, here is where the authors have not been up to the task. The discussion reiterates (perhaps one too many times) the conclusions already detailed in several other sections. What is missing is en explanation of where these results fit in the general framework of asthma therapy, and why is it that they cannot be interpreted without considering the obvious biases created by the financial interests that have focused on LABA and LAMA and avoided almost completely studies of intermittent ICS+SABA. It could be argued that that was not the scope or purpose of the report, but I disagree. An aseptic presentation of the strength of the evidence for the different approaches assessed (i.e., KQ1, KQ2 and KQ3) could lead to the wrong conclusions regarding the relative strength of such evidence. In this same sense, I urge the authors to explain why assessing each these 3 approaches is important today (see general comments)	Consistent with a similar comment made, we have added more emphasis to the SOE particularly when discussing KQ1 a and b where the SOE was relatively lower than other KQ in this report. Each study included in this review was evaluated for ROB using tools approved in the protocol and commonly applied in this field. ROB was taken into account when SOE was graded, as one of the domains. In addition, the number of industry reported studies is clearly stated in the results section of each KQ with citations so that the reader can learn this information and apply their own judgement as to how this may or may not impact their interpretation of the data presented.
Peer reviewer #2		The data to address the key questions are well-described and conclusions can be reached based upon the data reviewed and discussion of the data. Future research is acceptable.	Thank you.
Peer reviewer #3		It would be good to have a table or list with the main takeaways in the discussion. Again this is a large document and most may look for those key points and tables to provide the most important info to relay or to post/send to others	Key points are published with this report, which are a plan language summary of the most salient points to take away from the report.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1, Anonymous		The different definitions of intermittent ICS are not clear above. Perhaps one way to highlight these differences are in boxes defining interventions and comparisons for each KQ throughout the document.	The term "intermittent" and "controller therapy" are defined in the glossary and in the introduction and used consistently throughout the report. The exact dosing of drug per study can be found in the Study and Population characteristics tables within the Appendix.
Public reviewer #1, Anonymous		This summary is a little confusing in that it isn't clear if "ICS controller" (the comparator) involved a similar response to yellow zone or other increase in severity.	The term "intermittent" and "controller therapy" are defined in the glossary and in the introduction and used consistently throughout the report. The exact dosing of drug per study can be found in the Study and Population characteristics tables within the Appendix. We avoid using terms such as "similar" so as not to convey equivalence of therapies. Conclusions either state a difference was found or no difference was found. When no difference was found, this does not imply similarity.

Commentator & Affiliation	Section	Comment	Response
Eisenberg Center		While the systematic review provides findings on the effectiveness of ICS, LABA, SABA, and LAMA in various populations, it does not discuss the potential adverse effects associated with these medications. Clinicians and patients might find it very helpful to know the adverse effects associated with these medications when making decisions about their use. One of our Primary Care Physician reviewers pointed out the following: *"One of the most common questions PCP's receive are about the adverse effects of ICS's, especially on children (in particular, the influence on growth). Clinicians also are aware of concerns about LABA use and risk of death, but have no perspective about this risk. Addressing these 2 questions would be very helpful. Lastly, the use of LAMA in COPD is slowly being adopted but I am unaware if these agents have adverse effects in children and would not use them without knowing this."*	The KQ addressed in this review were determined during the protocol and did not include specific drug harms. We have added this as a limitation in the limitations section of the discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Deborah Hickman, DNP, APRN, CPNP-PC, NNP-BC; National Association of Pediatric Nurse Practitioners		In patients 0-4 years with recurrent wheezing, the initiation of intermittent ICS with rescue SABA appears to be beneficial within the setting of respiratory tract infection. From a clinical perspective, the research questions are quite pertinent to practical issues. In reviewing individual studies, the evidence is seems inconclusive but through the meta-analysis there appears to be some evidence to support intermittent is therapy in young children (0-4 years). Inhaled corticosteroids are generally safe to use but not without some risk of side effects, intermittent dosing would be an appealing treatment strategy. Limitations in translating the data to clinical recommendations would be lack of a conclusion of specific dosing in this age group to achieve the described outcomes. As a clinician, I would be interested in a discussion this type of information.	This limitation has been added to the discussion.
Public Reviewer #3, Veronica Mansfield, DNP, APRN, PPNP-BC, AE-C; National Association of Pediatric Nurse Practitioners		As a pediatric provider I am looking forward to possibly using ICS for young patients with wheezing and RTI. However, at this time I am not comfortable using LAMA s in the adolescent population. In general I find it unfortunate that many of the studies included mostly adults. Lastly as a provider and educator I wish that the studies reviewed identified race and ethnicity as well as environmental factors all of which contribute to control or poorly controlled asthma for that matter.	These limitations are within the discussion of the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Thomas Seck, Boehringer Ingelheim Pharmaceuticals, Inc.		Ensure homogeneity of patient populations included in meta-analyses. Combining studies via meta-analysis should only be considered if they are clinically and methodologically similar.2,3 In the clinical trials included in this review, the methodological similarity criterion is broadly met through the availability of data from good quality randomized controlled studies of the treatments of interest. However, there is heterogeneity in the patient populations enrolled in these trials, in relation to characteristics which are known to have an impact on the magnitude of treatment effects, such as disease severity. BI recommends that AHRQ reports subgroup analyses for clinically relevant subpopulations, e.g. disease severity, in order to ensure that its conclusions are valid. If this is not possible, AHRQ should note the limitations associated with the pooling of data from heterogeneous populations.	For purposes of each KQ2a, b, and c, the populations were considered homogeneous enough for meta-analysis. In addition, statistical evaluation of heterogeneity revealed no concerns for the analysis. Disease severity was an a prioir subgroup of interest although due to the small number of studies per subgroup, analysis was not possible. We have noted this as a limitation within the discussion.
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network		We certainly agree.... Future research is needed to further explore the impact of intermittent ICS dosing on asthma outcomes in addition to studies more explicitly defining asthma severity and control, including reasons for a lack of control.	Thank you.
TEP reviewer #3	Conclusion	The conclusions should state specific answers to each of the questions.	The concluding statements are based solely on the objective data that is presented per KQ in the overview table and text. No further conclusions or recommendations are made, standard to these reports.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Deborah Hickman, DNP, APRN, CPNP-PC, NNP-BC; National Association of Pediatric Nurse Practitioners		In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected (low strength of evidence). This conclusion was primarily based on adults with mean ages 30-50 years old so would be difficult to translate into clinically relevant practice in the majority of pediatric patients.	This limitation is addressed in the discussion of the report.
Public Reviewer #5, Thomas Seck, Boehringer Ingelheim Pharmaceuticals, Inc.		**Revise concluding language to avoid confusion over efficacy of treatments** BI is concerned about AHRQ's phrasing regarding the efficacy of adding LABA to ICS versus adding LAMA to ICS on page vii and 49. Specifically, it may be inferred by some readers that the phrase "adding LAMA to ICS controller compared to adding LABA to ICS controller was no different in outcomes" suggests that these treatments are not beneficial to patients seeking to control their asthma. For this reason, BI recommends ARHQ revise the statement to read "Adding LAMA to ICS has similar efficacy to adding LABA to ICS" to avoid any potential misinterpretation of the statement.	We have revised the statement as it is not our intention to convey "no efficacy" rather there was not difference in efficacy detected.
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network	Figures	No comment	NA
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network	References	NA	NA

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network	Appendix	No comment	NA
TEP reviewer #1	General	I think this information will be extremely valuable for the updated guidelines process	Thank you.
TEP reviewer #2		This is an excellent systematic review of the questions provided to the AHRQ for the update of the EPR-3. I like the way that they divided the key questions into subsets that made digesting the reams of data more manageable. They results are clinically meaningful and all necessary information for evaluating the conclusions is available. I have a few specific questions and comments below but have one general procedural/methods questions that covers all the Key Questions. Why were hospitalizations and ED/Urgent Care visits part of exacerbations as opposed to Healthcare Utilization as they are often listed in clinical studies and other systematic reviews? It makes it easier to combine all the exacerbations which may or may not be appropriate if the outpatient visit did not require systemic corticosteroids to resolve.	We recognize that outcomes such as emergency visits or hospitalizations for asthma can be considered as a healthcare utilization or as an exacerbation given most likely this is the case. However, because it is not certain, we did not statistically pool such outcomes with definitive reporting of exacerbations requiring hospitalization or ER visit.
TEP reviewer #3		Overall, the questions are well summarized and the literature review is comprehensive. I think the sections in the discussion could be better highlighted and summarized to make it easier to find specific sections and also to identify the conclusions to the various questions.	We have added subheading to break up the lengthy discussion to identify specific KQ.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #3		Overall, the report is well structured in its content and organization. Where it falls short is in the area of definitive conclusions based on this careful review of the literature. I would like to see each question specifically addressed with a mention of the key articles that answer the question. That would help wrap things up and make it more useful for the Expert Panel when it is passed on to them. They will want to get to work on writing the final document as quickly as possible rather than going back to review the literature again.	The key points that begin each KQ are summative statements of the findings of this review. The overview tables are all labeled with the exact studies that contributed to the given outcome/conclusion.
TEP reviewer #3		The limitations should specifically say what would make a study with low to moderate evidence reach a level of high strength. The NHLBI often uses the guidelines to point out gaps in information and then supports studies to fill those gaps. Assisting the panel with this information would be valuable.	Where data was primarily of low SOE, we have added more discussion as to the common reasons for this SOE rating and what may possibly lead to improved SOE rating in the future.

Peer reviewer #1		This is technically one of the best studies I have read of its type. The key questions were explicitly defined, and the target audience appears to be practitioners caring for asthma patients. The literature has been exhaustively and objectively evaluated. The conclusions of this "technical" analysis are soundly based on the data available. My main qualm is thus not with the professionalism and skills of the analysts, who have fulfilled the task assigned to them in an unassailable manner. My concern has to do with the arms-length flavor of the "practical" conclusions of the report. The authors have accepted as a given the universe of studies available in the literature. Only perfunctorily have they noticed that there could be what I would call a global bias in the studies available in the literature in favor of certain strategies and not others. Obviously, the strength of any conclusions will depend not only on the strength of the effects observed but also on the number of subjects enrolled in each study and on the number of studies available for each KQ. Just a perfunctory review of tables 5 to 17 in the text and the forest plots in appendix F reveals that studies of intermittent use of ICS are scanty in number and include, at most, participants in the low-mid-hundreds. Studies of add-on LAMA and intermittent LABA are abundant and include participants in the thousands. It is thus non surprising that conclusions about intermittent ICS are tentative and most often inhabited by "unknown consistencies", whilst those on LABA and LAMA tend to be clearly more assured. Technically, this is indisputable, but might lead practitioners to wrongly conclude, for example, that intermittent ICS+SABA is less effective and intermittent ICS+LABA because the evidence for the first is scanty and that for the second-third abundant. There is no evidence presented herein	We have added a section to the discussion to elaborate on this limitation particularly emphasizing the SOE grading and the meaning of "low" SOE so as not to convey the wrong impression to the reader. More emphasis has been added regarding the need for future research on intermittent ICS in the Future Research Needs section of the discussion.

Commentator & Affiliation	Section	Comment	Response
		to support that conclusion, and that should be made explicitly clear.	
Peer reviewer #1		As can be elucidated from my previous comments, I found he methodologies used and the presentation of the results an outstanding example of this type of evaluation. This is extremely useful new information. Usability and understanding are hampered by the less than stellar way in which this great work was put into context.	We have made changes to the discussion based on specific comments received from the reviewers.
Peer reviewer #2		The report is clinically meaningful and will be very helpful, and comprehensive, to address questions for NAEPP updates. It directly addresses the key questions of intermittent (1) ICS treatment and (2) addition of anticholinergics to ICS. The report describes, clearly, the trials, their design, the identified outcomes, and strength of evidence as well as ages of subjects to which the data can be judged for determining specific outcomes.	Thank you.
Peer reviewer #2		The report is well-structured, organized and supported by appropriate tables.	Thank you.
Peer review #3		I think this review is excellent, is does a great job separating out the individual questions and giving the key points for each section for people that do not have the time to read the entire document to get the necessary information for each section.	Thank you.
Peer review #3		It is outlined great and all the components of what people are looking for in each section are present	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1, Anonymous		My comments are embedded in the attached document. In general, the report is well laid out and clear. However, there is a lot of text, table and chart space devoted to laying out the evaluation strategy. The space could be used instead to more clearly map out similarities and differences in studies being compared. For example, differences in doses, duration, baseline symptoms and severity, race/ethnicity and age could be better highlighted. In particular, varying duration of the evaluated interventions could have a large impact on how the strength of their findings are weighed.	Each KQ results section begins with a comparison of studies in regards to interventions, age, race, asthma severity and control, sponsorship, and other notable characteristics that are important for data interpretation that may be KQ specific. Further details are provided on an individual study basis within the appendix tables "study and population characteristics", including duration of studies. Of note, per the protocol there were no restrictions on the duration of study for inclusion or exclusion into the review.
Public Reviewer #6, Deborah Hickman, DNP, APRN, CPNP-PC, NNP-BC; National Association of Pediatric Nurse Practitioners		In patients 12 years and older, using ICS and LABA as both a controller and quick relief therapy showed benefits over use as a controller medication alone.	NA
Public Reviewer #6, Deborah Hickman, DNP, APRN, CPNP-PC, NNP-BC; National Association of Pediatric Nurse Practitioners		For patients 12 years old and greater with uncontrolled persistent asthma, addition of LAMA to ICS controller or adding LAMA to ICS plus LABA compared to ICS or ICS plus LABA alone improves outcomes. Adding LAMA to ICS controller compared to adding LABA to ICS controller was no different in outcomes. Again, from a pediatric clinician perspective, this key question has limited applicability to the pediatric population with only one study including children under the age of 18 years.	NA

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Deborah Hickman, DNP, APRN, CPNP-PC, NNP-BC; National Association of Pediatric Nurse Practitioners		Recommendations: I have the following discretionary comments on the report- This was a well planned and executed systematic review of intermittent ICS and LAMA dosing strategies for asthma exacerbations. As a pediatric asthma clinician, I found the discussion on the 0-4 year old use of intermittent ICS to be a promising treatment option but would be interested in discussion on dosing strategies that were employed if possible. In the other key questions, I found it difficult to understand whether there were sufficient numbers and evidence in the 12-17 year age group to fully translate the findings down to this particular population	Exact dosing strategies for each included study are part of the Study and Population Characteristics tables in the Appendix. We have added a limitation that this review was focused on class effects and comparing specific dosing was outside of the scope. The inclusion criteria for each KQ determined the age groups evaluated and the totally of evidence summarized for, consistent with thresholds used in the current EPR-3 guidelines. When subgroups were possible based on these EPR-3 categories, they were presented separately for the given KQ.
Public Reviewer #7, Gayle Higgins, CRNP; National Association of Pediatric Nurse Practitioners		Felt that the data may be skewed(sp) due to the many of the studies using only Caucasians in the studies.	This has been added as a limitation to the review.
Public Reviewer #7, Gayle Higgins, CRNP; National Association of Pediatric Nurse Practitioners		Interesting to see that many of the reports showed there was no improvement in using ICS intermittently with illness. They found that using ICS along with SABA worked better for most of the patients studied.	NA

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, Gayle Higgins, CRNP; National Association of Pediatric Nurse Practitioners		Despite all of the studies that were reviewed many were not placed in the high category (meaning they were of relevance)	NA
Public Reviewer #7, Gayle Higgins, CRNP; National Association of Pediatric Nurse Practitioners		I will not change my practice based on the findings of this study.	NA
Public Reviewer #4, Tonya Winders, Asthma & Allergy Network		We are not sure of this report's potential impact in patient management but the fact that the SOE is low for intermittent use of ICS with URI means that it would be a shame for a major change in recommendations based on this report. We are also concerned if one would misconstrue their statements about using ICS/LABA for quick relief or intermittent use. for example, Spiriva is approved for 6 yo and older and may provide benefit in uncontrolled asthma in children already on ICS & maybe ICS/LABA, although the SOE was only low to moderate. Although there is data supporting adding LAMA to ICS instead of LABA, there aren t any LAMA/ICS for children and there is benefit in using single inhaler device. We would also like to see a plain language summary document prepared for primary care providers with key messages and clinical impact for ease of implementation and to reduce confusion.	The KQ evaluating LAMA were limited to patients 12y of age and older, thus no data was included for younger patients and no statements were made regarding younger patients. Please see the key messages that are published with this report which provide a plain language summary as requested.