*Comparative Effectiveness Review Disposition of Comments Report*

**Research Review Title:** *The Role of Immunotherapy in the Treatment of Asthma*

Draft review available for public comment from April 27, 2017 to May 26, 2017.

**Research Review Citation:** Lin SY, Azar A, Suarez-Cuervo C, Diette GB, Brigham E, Rice J, Ramanathan M, Gayleard J, Robinson KA. The Role of Immunotherapy in the Treatment of Asthma. Comparative Effectiveness Review No. 196 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2015-00006-I). AHRQ Publication No. 17(18)-EHC029-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/AHRQEPCCER196.

## 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 EHC Program 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 |
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| | Executive Summary | Not applicable. No comments submitted. | |
| **Peer Reviewer #1** | Introduction | The Introduction is clearly written and thorough. It provides an important overview of the topic and the relevance of this analysis for clinical care. | Thank you for your comment. |
| **Peer Reviewer #2** | Introduction | On page 12 line 10---Perhaps further definition/elaboration on what is considered "standard of care" would be helpful here. | This is a practice parameter for all allergic conditions (allergic rhinitis, allergic rhinoconjunctivitis, and allergic asthma). Practice parameters are specific for each condition. We define treatments in appendix B. This refers to standards of care for asthma management. Medical management of asthma per standards of care (describing the detailed medical management of asthma is beyond the scope here) |
| **Peer Reviewer #2** | Introduction | Also some background on the GINA classification/severity grade might be helpful in the introduction | Thank you. We have added information to the introduction on last paragraph of the introduction "Current asthma guidelines recommend assessment of asthma control and severity, in order to guide treatment. These assessments include factors such as symptom frequency, use of medications, acute care visits and other indicators of asthma health." |
| **Peer Reviewer #3** | Introduction | The introduction is well structured and lays out the relevance of the study questions. The inclusion of the prior reviews on this topic are especially useful to understand the added value of this report. | Thank you for your comment. |
| **Peer Reviewer #3** | Introduction | Definitions of each of the types of therapies are provided, though some of the detailed descriptions of the various schedules of AIT could be condensed. | We think that definitions and descriptions of the types of therapies can be helpful for readers who might not be very familiar with all those terms, as many other reviewers have already acknowledged. Therefore, we prefer to leave these definitions as they are now. |
| **TEP #1** | Introduction | Page 2 line 36: Subcutaneous immunotherapy (SCIT) injections are not “into the skin”, as indicated by subcutaneous they are into the fatty tissue beneath the skin. | Thanks for your suggestion. We have changed this to "under the skin”. |

| Commentator & Affiliation | Section | Comment | Response |
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| **TEP #1** | Introduction | Page 3 line 1: Here and elsewhere in the report there is an inappropriate emphasis on anaphylaxis. As reported by Jean Bouquet (Bousquet J, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989;83:797-802) the asthmatic reactions are much more common systemic reactions in asthmatics than is anaphylaxis. Also, the reports from the Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology (Reid MJ, et al. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993;92:6-15 & Bernstein DI, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing 1990-2001. J Allergy Clin Immunol 2004;113:1129-36) clearly indicate that asthma, poorly controlled asthma and severe asthma are the predominant risk factors for death from SCIT strongly suggesting that bronchoconstriction rather than anaphylaxis is the leading cause of fatal reactions. This misplaced emphasis is seen again in Figure 1, breakdown of adverse events. | Anaphylaxis was pre-specified in our protocol as a critical outcome, that is, an outcome for which we would grade the body of evidence. We have added specific data on bronchoconstriction in systemic reactions both for RCTs and non RCTs (page 24 and 26). Bronchoconstriction was reported in patients receiving SCIT as follows: “Bronchospasm”, “wheezing”, “asthma”, and “pulmonary reactions” were specifically reported in 15 patients receiving SCIT in seven RCTs: 1/37[53], 2/18 [56], 2/17[40], 1/15[61], 3/30 (two receiving cluster and one in the conventional arm)[62], 4/18[63] and 2/36.[19] Only one study reported pulmonary reactions in the control arm; 3/17. [63] Non-RCTs; Bronchoconstriction was reported in patients receiving SCIT as follows. One case series reported of one participant out of 18 presenting “Bronchospasm grade 2”, after receiving treatment with dust mite SCIT.[67] Another study reported one case of shortness of breath and hypotension during buildup, out of 144 patients who received SCIT.[73] |
| **TEP #3** | Introduction | Generally well written. Introduces asthma, allergy, and AIT appropriately. The reason for performing this review is nicely discussed. | Thank you for your comment. |

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| **TEP #3** | Introduction | One major concern – there is much more background information given on SCIT, as compared to SLIT. Similar to SCIT, suggest commenting on SLIT dosing, escalation, length of therapy, tablet vs. aqueous. Of course, many of these items are controversial, and that should be noted. | The suggested text has been added to the background section. It reads now:" Currently in the United States there are 2 forms of SLIT: tablet and “off-label” aqueous SLIT (using those allergens approved for SLIT in “off label” form of administration as there are no aqueous products specifically approved by the FDA for sublingual use). Typical regimens for SLIT include daily home administration, with dosing regimens such as year round or pre/co-seasonal for several years. The tablets approved for use in the United States do not involve escalation, and for aqueous formulations there have been studies describing both the use of escalation and no escalation" |
| **TEP #3** | Introduction | Minor concerns:<br>Page 11, line 20: Need reference/citation for “62% of people with asthma have environmental allergies”. | We had provided data from two different references and presented slightly different information: the first provided percentage of people with environmental allergies in general population and the second provided data specific to those with asthma. We confirmed the numbers and since the data may seem contradictory we decided to use only the second number and reference. |
| **TEP #3** | Introduction | Page 11, second paragraph: Second sentence says 62% of people have environmental allergies. Last sentence says 78% of asthmatic children and 75% of middle-aged asthmatic adults are allergic to one or more inhalant allergens by skin testing. These numbers seem contradictory… or at least not entirely similar. Suggest better specification/explanation of these statistics. | We had provided data from two different references and presented slightly different information: the first provided percentage of people with environmental allergies in general population and the second provided data specific to those with asthma. We confirmed the numbers and since the data may seem contradictory we decided to use only the second number and reference. |
| **TEP #3** | Introduction | Page 11, line 30: Change “Allergen immunotherapy” at the start of the sentence to “AIT”. | Per style guidelines, we do not start a sentence with an acronym. |

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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Introduction | Page 2:<br>Paragraph 2: It is noted that a better word for "swelling" would be "edema".<br>Paragraph 4: It is recommended that "subcutaneous" be added to the sentence, "One Form of AIT, …involves subcutaneous injections …" | Thanks for your comment, we made the changes suggested. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Introduction | Page 3:<br>It is recommended that the last sentence before the section "Key Questions" should read: "This systematic review focuses …to assess the efficacy and safety of SCIT and SLIT, the latter in aqueous and table forms …". | Thank you for the suggestion. We have chosen to not make this change. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Introduction | Page 4:<br>In Figure 1, regarding Adverse events, rather than "Anaphylactic reaction", it is suggested that the terminology should be "Anaphylaxis reaction." | Since the analytic framework underwent extensive review during protocol development we have chosen to not make this suggested change. |
| **Public comment #5 Karen Rance ALK Americas** | Introduction | Regarding the conclusion cited in the introduction (paragraph 6) from the 2011 Practice Parameters that "…certain patients with allergic asthma might benefit from SCIT after failure of standard care…", the Practice Parameters actually state that some patients may benefit from AIT in general, not just SCIT. Thus, the statement should replace "SCIT" with "AIT | Thanks for your comment, we made the changes suggested. |
| **Public comment #6 Susan Rappaport American Lung Association** | Introduction | With regard to the Introduction section of the draft report, subcutaneous immunotherapy (SCIT) guidelines do not support the use of SCIT at home. This may explain why there are no studies of SCIT at home. It might be beneficial to mention this as a possible reason why these studies do not exist and cannot be analyzed | Thank you for your suggestion, we have the guidelines as reference in the discussion. |
| **Peer Reviewer #1** | Methods | The Methods are described in a very thorough and detailed manner. The PICOTS framework and the attribution of specific measures to each area are well described. The method of article selection is clearly articulated. The statistical methods are well described and appropriate. The Methods section is appropriate and meets the necessary standards for robust systematic reviews. | Thank you for your comment. |

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| **Peer Reviewer #2** | Methods | The search strategy and study selection are well developed and explained in this section. The inclusion and exclusive criteria are justifiable. Appropriate statistical methods were used. The diagnostic criteria for the outcome measures are appropriate. | Thank you for your comment. |
| **Peer Reviewer #3** | Methods | The selection of studies included in this report is justifiable. Appropriately, both pediatric and adult populations were included, with attention to studies with single or mixed populations. A diversity of study types, including case reports was appropriately included. The authors followed the PICOTs framework, which clearly outlines the criteria used. The search strategy section is reasonably comprehensive, though the language could be condensed somewhat. Overall the approach seems to have been liberally inclusive, especially with respect to asthma severity and degrees of allergic phenotype. | Thank you for your comment. |
| **Peer Reviewer #3** | Methods | For the outcome measures, the table is most helpful, and all measures seem appropriate | Thank you for your comment. |
| **Peer Reviewer #3** | Methods | I would consider adding financial cost to the resource use point (page 6, line 38), as well as a short description about how compliance is measured within the table specifically, though it is described in the text (page 6, line 44). | We did not assess cost. For compliance, we considered however it was assessed by the studies and have, where reported, provided how compliance was measured by each study. |
| **Peer Reviewer #3** | Methods | One last suggestion would be to add whether asthma-specific visits are occurring at a subspecialty pulmonary vs. allergy clinic or general internist office if that information is available (page 6, line 37). The statistics seem appropriate given the heterogeneity in the sample. | There were no studies assessing healthcare utilization for SLIT. For SCIT, we did not extract this specific information. |
| **TEP #1** | Methods | It is difficult to understand how 88 RCTs of SCIT in patients with asthma were identified in the Cochrane review that ended, I believe, in 2005 (published in 2010) and only 31 in this systematic review. I have mentioned a couple that came to mind they seemed to have been missed, but I did not do a systematic review of the differences between criteria in this study and Abramson. | There are several differences in the scope of the Cochrane review and our review that mean that different studies were eligible or included for each. For instance, the Cochrane review considered symptoms scores, medication scores while we only included validated tools (ACT, ACQ and P-ACQ for asthma control) and medication usage (quick relief and long term control per EPR-3) as stated in our protocol and in the methods section. |

| Commentator & Affiliation | Section | Comment | Response |
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| **TEP #1** | Methods | The use of asthma control assessments as a surrogate for asthma symptoms in not appropriate. | The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |
| **TEP #2** | Methods | No explicit I/E criteria presented other than that included in Table 1 | We think table 1 presents in detail our eligibility criteria. |
| **TEP #3** | Methods | Nicely written, concise, and easy to read/interpret. | Thank you for your comment. |
| **TEP #3** | Methods | Minor concerns:<br>Page 17, line 16: Should “asthma specific ICU admissions/intubations” be a separate statement in parentheses, or separated by commas as part of the remainder of the list? | Thanks for catching this mistake, we corrected the error. |
| **TEP #3** | Methods | Minor concerns:<br>Page 20, line 7: Change “three on animal allergens” to “three used animal allergens”. | Thanks for the suggestion, we made the change. |

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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Methods | Page 6:<br>It is noted that “Methacholine” should not be capitalized.<br>At the Bottom of Table 1, it is recommended that the meaning of “Hypersensitivity reaction” be clarified. | Thanks for catching this mistake, we corrected the error.<br>We added the definition of hypersensitivity |
| **Peer Reviewer #1** | Results | The Results section is reported in a very detailed manner, and provides specific information on all studies and data. The summary tables are appropriate. | Thank you for your comment. |
| **Peer Reviewer #2** | Results | There is an appropriate amount of detail presented in this section. The characteristics of the studies are clearly described. The tables contain good detail. | Thank you for your comment. |
| **Peer Reviewer #2** | Results | Is page 30 line 32 and page 31 line 4 to read "uncontrolled on poorly controlled" or should it read "uncontrolled OR poorly controlled"? | Thanks for catching these mistakes. We corrected the mistakes and now it reads in both places "uncontrolled OR poorly controlled asthma". |
| **Peer Reviewer #2** | Results | Is page 38 line 38 really 100 micrograms of "Bet v 1" or is it Phl p 5 or something else? | Thank you for catching this, we added the correct dose and allergen. |
| **Peer Reviewer #2** | Results | There are a few typos in this section: Page 32 line 3 has two ")" at end of first sentence. Page 33 line 40 "Non" should not be capitalized. Page 34 line 36, there should be a space between "D" and "pter". Page 35 line 28--the sentence should be clarified perhaps with "()" around the 5264 doses information. Page 37 line 12 should have a period at the end of the sentence not ",". Page 38 line 32 should read "measured" not "measure". | Thanks for your edits. We made the corrections. |
| **Peer Reviewer #3** | Results | Reporting of results by key question allows for easy readability. Results are presented clearly as they pertain to each of the outcomes. Discussions within these seem comprehensive, and key messages are easy to extract. Comparisons were adequately detailed. | Thank you for your comment. |

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| **TEP #1** | Results | 3) Page 10, line 1: The Abrahamson Cochrane systematic review included 88 articles on SCIT treatment of asthma. There is a problem when a decade later you include only 31 RCTs. | There are several differences in the scope of the Cochrane review and our review that mean that different studies were eligible or included for each. For instance, the Cochrane review considered symptoms scores, medication scores while we only included validated tools (ACT, ACQ and P-ACQ for asthma control) and medication usage (quick relief and long term control per EPR-3) as stated in our protocol and in the methods section. |
| **TEP #1** | Results | 4) Page 11, line 46: "There was insufficient evidence regarding effect of SCIT on asthma symptom control." This is because you set up an artificial and inaccurate design for assessing asthma symptoms. You only accepted ACT, ACQ or P-ACT for assessing symptoms. There were two problems with this approach, first these tools were not invented at the time some of your SCIT studies were conducted and, more importantly, these tools assess asthma control, not asthma symptoms. | The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |

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| **TEP #1** | Results | 5) Page 13, line 31: “Overall there was moderate strength of evidence that SCIT reduces use of long term control medications”. Why is it only moderate strength when all of the cited studies show significant reduction and two have p values of <0.001 and =0.002? | The strength of evidence considers several domains and is not based solely on statistically significance. We graded the evidence for long term control medications as moderate based on a body of evidence with studies that were direct, consistent and had medium risk of bias. |
| **TEP #1** | Results | 6) Page 16, Line 1: You seem to have missed the following studies of cat/dog immunotherapy in patients with asthma (Hedlin G. et al. Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. J Allergy Clin Immunol 1991;87:955-64 & Hedlin G, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol 1995;96:879-85). She reported reduction in both specific and non-specific bronchial hyperresponsiveness. | We reviewed the suggested studies. The Hedlin studies do not meet our inclusion criteria, because they compare cat versus dog allergen. |
| **TEP #1** | Results | 7) Page 17, line 9: “reduction” must be a mistake. | Thanks for your edit. We corrected the mistake. |
| **TEP #1** | Results | 8) Page 17, line 43: The paper by Olsen et al clearly states in the title and abstract that treatment was of one-year duration. | Thanks for catching this mistake. We reworded accordingly. |
| **TEP #1** | Results | 9) Page 20, line49-51: “Systemic reactions did not appear to occur more commonly in patients receiving an accelerated SCIT protocol compared to conventional SCIT protocols.” This is contrary to all conventional wisdom regarding “rush protocols”. Granted many are with allergic rhinitis, but that is probably irrelevant. Also see the studies on systemic reactions as the Bousquet group modified their protocol, eventually going to only a partial build-up by rush and then weekly injections (Hejjaoui A, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. IV. Systemic reactions according to the immunotherapy schedule J Allergy Clin Immunol 1990;85:473-9). | We agree with the reviewer that accelerated SCIT protocols are typically associated with a higher risk of systemic reactions. However, the general trend of the studies included in this report did not suggest that accelerated protocols had a higher incidence of systemic reactions. We did not set out to assess this comparison separately (i.e., not outlined in our protocol), and did not identify any studies providing this comparison. We have thus removed this statement from the key points. |
| **TEP #1** | Results | 10) Page 25, lines 50-54: “We are unable to draw conclusions on whether SCIT increased risk of anaphylaxis”. This is a remarkable statement, having just said that SCIT caused up to 15 additional cases of anaphylaxis per 100 people treated with SCIT!! | Effect size alone does not determine the ability to draw conclusions. As we stated: "We are unable to draw conclusions on whether SCIT increased risk of anaphylaxis primarily because the RCTs did not directly measure or report anaphylaxis (indirectness), and were not powered to assess such effects (imprecision)." |

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| **TEP #1** | Results | Page 28, line 34: “The second RCT found statistically significant improvement in asthma symptoms with a decrease of 0.41 in ACQ score.”. Line 41: “the Asthma Control Test to assess asthma symptoms outcomes” As noted before, these are measurements of asthma control, not asthma symptoms. | The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |
| **TEP #2** | Results | As stated on pg. 10, line 40, no consistent criteria were applied to establish asthma diagnosis. This is a substantial limitation when asthma-related outcomes are the relevant endpoints | We point in our discussion: "There was much variability across studies in methods and criteria used for asthma diagnosis, as well as grading of asthma severity and control status. Also, some studies did not provide information about baseline asthma severity or control. These issues may affect the ability to generalize the findings to certain patients with asthma, and limited with our ability to determine whether asthma health status at the beginning of treatment affects the observed outcomes." |

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| **TEP #2** | Results | Furthermore, no consistent approach was applied to either establish baseline amount of controller therapy or how controllers were reduced. It is unclear how this substantial concern could result in a conclusion that there was moderate SOE that SCIT reduces long-term controller medication (pg13, lines 31-32). This is briefly noted in the Discussion. | Thanks for your comments. As explained in the report and shown in the appendix, the studies measured the controller medications in different ways. We abstracted baseline medications when provided (see appendices please). SOE grading is not based on homogeneity of comparators, or tools used. We graded this outcome as moderate based on the full body of evidence, which was consistent and precise and had medium risk of bias. As we say in the first sentence of the limitations " We found considerable heterogeneity in the outcomes reported, and in the measurement of outcomes, that precluded quantitative pooling of the data" this is applicable to many of our outcomes. |
| **TEP #3** | Results | Overall the Results are concise, to the point, and easy to read. The variation by population, etc. sections help to put the results into perspective. Tables and Appendices are nicely done and very informative. | Thank you for your comment. |
| **TEP #3** | Results | Page 19, lines 20-33: Please check the accuracy of the numbers in Table 2. Some of the numbers seem to be off and do not add up appropriately. Specifically… Age Group for KQ4, SLIT Safety. | Thanks for catching the errors. We have double-checked all of the numbers. |
| **TEP #3** | Results | Page 21, lines 5-9: There are literature citations for the studies discussed in this paragraph, but prior to this paragraph no other studies have been cited in this way when discussed. This actually occurs throughout the Result section – sometimes citations are provided, and other times they are not; this is confusing. | We have reviewed the report, and a copy editor has reviewed the report, to ensure consistency. |
| **TEP #3** | Results | Page 26, line 22: The Variation per Population section has an overall description of studies for children (on page 27, lines 43-53), but this is not included for adults. | Thanks for your comment. We reviewed all the sections to make sure we were consistent throughout. |
| **TEP #3** | Results | Abbreviations for antigens vary throughout the manuscript (i.e. Der p and Der f, compared to Dpter and Dfar. | Thank you for your comment. We reviewed the report and made sure we were consistent throughout with the use of abbreviations. |

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| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | The authors should consider a statement in Key points reinforcing that SCIT should be performed in a office with appropriate support available for potential anaphylaxis (reinforcing the Jt Task Force Practice Parameters Cox L., Nelson H., Lockey R., Calabria C., Chacko T., Finegold I., et al: Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127: pp. S1-S55) | Thanks for the suggestion. We do not think this is a key point as this is not a finding of our review. We do discuss the practice parameters statement in the Discussion. |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | Also may wish to comment about the fact that the majority of studies were in the mild to moderate class of asthma (as per AHRQ review) | Thanks for your suggestion, but as we say in the introduction of each key question and in our limitations section, not all studies provide these data, (in more than a third of the studies do not specify asthma severity at baseline) and we think that as we say in the limitations, studies should clearly report severity and control status of enrolled patients. |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | Compliance may wish to add (Kiel M., Roder E., Gerth van Wijk R., Al M., Hop W., and Ruttenvan Molken M.: Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013; 132: pp. 353-360) | Thank you for your suggestion, however this study did not meet inclusion criteria for our review. |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | The authors may wish to comment about the stratification of data regarding SLIT tablets and liquid SLIT as was note in the JT Task Force Practice Parameter Greenhawt et al Ann All Asthma Immunol 2017. There is no clinical data that suggests that multiple allergen SLIT drops is efficacy in asthma. In fact, there are no SLIT drops approved in the United States by the FDA. | We have clarified in the background that there are no SLIT drops in the United States approved by the FDA. It reads in the first paragraph of the introduction " Currently in the United States there are 2 forms of SLIT: tablet and “off-label” aqueous SLIT (using those allergens approved for SLIT in “off label” form of administration as there are no aqueous products specifically approved by the FDA for sublingual use)." |

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| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | Regarding safety of SLIT – the authors may wish to comment about the recommended prescription of an auto injectable epinephrine with SLIT use (Nolte et al. JACI in Practice 2017; 5: 84-89) | This has been added in the Discussion. We added at the end of the 4th paragraph of the introduction: "It is noted that the package insert for SLIT tablets approved by the FDA does recommend an epinephrine auto-injector device should be prescribed for patients taking SLIT tablets." |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | Key point: When mentioning the 3 reports of anaphylaxis to SLIT, all were receiving multiallergen SLIT. It is important to mention the lack of data regarding efficacy of SLIT with multiallergens. ( Nelson H. Multiallergen immunotherapy for allergic rhinitis and asthma. JACI 2009;123:763-9) | Thank you for your suggestion, we added this to the key points: "Although rates of anaphylaxis with SLIT compared to no treatment could not be determined (no cases reported in RCTs, insufficient evidence), 3 case reports suggest that rare cases may occur with SLIT treatment. All 3 reports of anaphylaxis secondary to SLIT were in patients who received multiallergen therapy." |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | Results | When discussing potential gains of SLIT, many presumed adherence would be better vs. SCIT. This may not be true and should be mentioned as noted in Key Question 3 (Kiel M., Roder E., Gerth van Wijk R., Al M., Hop W., and Rutten-van Molken M.: Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 2013; 132: pp. 353-360) | Thank you for your suggestion. This study did not meet inclusion criteria for our review. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 9:<br>Regarding Figure 2, the numbers are not added correctly. It is noted that, “we excluded an additional 410 articles (see Appendix D, List of excluded articles) that did not meet one or more of the inclusion criteria,” however the number of reasons for these exclusions does not equal 410. | The flow diagram has been updated to reflect the updated search results and we have checked all numbers. The number of studies excluded for each reason will not add up to the total number of studies excluded as the reviewers did not need to agree on reason excluded. This is noted in the footnote. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 10:<br>Regarding paragraph 2, it is recommended that the words “studies compared” be removed. The sentence would better read, “Thirty-four studies compared immunotherapy versus placebo, twelve versus immunotherapy, eleven immunotherapy versus immunotherapy …”. It is also recommended that this sentence be shortened due to its length. | Thanks for your suggestions. The final report has been reviewed by a copy editor. |

| Commentator & Affiliation | Section | Comment | Response |
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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 11:<br>It is noted that Alternaria and Cladosporium are species and should be capitalized and italicized throughout the paper. Likewise, Dpter may be a better abbreviation because Dermatophagoides is the genus and pteronyssinus is the species. Further, since few acronyms are used throughout the paper, it is noted that perhaps omission of all acronyms would be most effective | Thanks for your suggestion. We have corrected these through the report. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 12:<br>Further, an explanation of the authors' justification for limiting domain outcomes to only validated tools for asthma control would be insightful.<br>It is noted that this omission may bias outcome reporting for SLIT vs SCIT, based on year of publication and availability of such tools. It is further recommended that this omission should also be discussed carefully in the Discussion Section, noting it as an important difference compared to previous systematic review outcome choices | The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 14:<br>It is noted that two sentences begin with the same introduction, "Most of these studies …", while two others begin, "This study … ". A variation in word choice may improve the paper. Further, Cladosporium and Alternaria should be capitalized and italicized. | Thanks for your suggestions. The final report has been reviewed by a copy editor. |

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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 16:<br>It is suggested that the word choice “not” be changed to “no” in the sentence: “For the study of dog allergen challenge, there was no improvement …”. | We have corrected this text. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 20:<br>Key Points:<br>Second point: It is stated that only a “small number was consistent with anaphylaxis …”. To clarify, was this terminology used by the authors of the cited paper? | This Key Point does not specifically refer to one particular paper, but is a general summary regarding the frequency of reactions that are considered anaphylactic in nature, as compared to all systemic reactions. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 23:<br>Summary and Description of Events In RCTs<br>It is noted that in the sentence, “In four studies there were specifically no systemic reactions reported,” the word “specifically” should be deleted. It is further recommended that the word “allergic” be added to “systemic reaction”. Likewise, in the sentence, “Types of reactions included pruritus, urticaria, eczema, skin rash, rhinitis, conjunctivitis, nasal congestion, nasal obstruction, cough, asthma, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension,” the types of reactions probably included generalized pruritus and urticaria, not just pruritus and urticaria. It is noted that this would depend upon hat has been reported in the paper. | We removed the word "specifically" and added "systemic" allergic reactions. We agree that the description of the types of reactions was as reported in the original articles; many times the articles did not specifically describe whether the pruritus or urticaria were diffuse or localized. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Results | Page 26:<br>Regarding the reference to deaths with SCIT, it is noted that the authors conclude that the death described in the case report was not due to SCIT administration, based on timing, nature of reaction, and labs not being suggestive of hypersensitivity. While there may be no obvious link (such as a clear dosing error), given the amount of information provided, it is recommended that this be characterized as “unclear” rather than “unlikely.” Academy leadership would further observe that it seems that the authors themselves suggest that it may have in fact been due to some aspect of SCIT administration, and would therefore recommend that the authors of this draft report refer to this outcome as unclear, rather than make a determination without the medical records to fully review. | Thanks for catching this mistake. We reviewed our classification here and considered that we should change to possible because the event was related to the intervention but was not dose related. |

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| **Public comment #3<br>David Peden<br>American Academy of Allergy, Asthma & Immunology** | Results | Page 28 and 29:<br>It is recommended that the authors be mindful of the clinically important difference (MID) for ACQ and ACT when reporting improvements in asthma control. It is further noted that the authors report statistical significance for what may be clinically insignificant improvements. Also, it is recommended that the authors re-check reference 77, listed as showing statistical clinical improvement in asthma control, as this may be interpreted differently by others. | Thanks for your suggestion. Where possible, we have added information about clinically important differences (MCID). |
| **Public comment #5<br>Karen Rance<br>ALK Americas** | Results | As recognized in the limitations section, it is very difficult to compare efficacy and safety results among the trials due to heterogeneity in the products, doses, formulations, data reporting, and other study design variations. Furthermore, conclusions based on endpoints beyond the primary trial endpoint need to be made with caution. For example, the Virchow et al, 2016 trial (ref 73) did not use ACQ or AQLQ as the primary endpoint. Furthermore, the results for ACQ and AQLQ were controlled for ICS use and as such are not comparable to ACQ/AQLQ results from other trials. We recommend removing reference to the Virchow et al, 2016 trial from this section. | We assessed outcomes, pre-specified in our protocol, as reported in each study whether the outcomes were primary or secondary outcomes. |
| **Public comment #5<br>Karen Rance<br>ALK Americas** | Results | It would be relevant to report how AEs were collected in each study (ie, solicited via a questionnaire, spontaneous reporting, daily diary, according to International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] guidelines, etc). We realize many publications may not provide this information, but the method of AE collection can impact the results. For example, AEs collected by direct questioning for specific AEs may result in a higher reported incidence for that AE when compared with spontaneous reporting. (Wernicke JF, Faries D, Milton D, Weyrauch K. Detecting treatment emergent adverse events in clinical trials : a comparison of spontaneously reported and solicited collection methods. Drug Saf 2005; 28:1057-63) | As you note, this information is not usually available in the manuscripts. We did not extract this information. |

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| **Public comment #5<br>Karen Rance<br>ALK Americas** | Results | A grading system for AIT systemic allergic reactions (SAR) was developed by the World Allergy Organization in 2010. Based on the 2010 grading system, local reactions with SLIT such as lip pruritus would be considered a grade 1 systemic reaction. The WAO grading system was updated in 2017 and recognized that isolated local reactions in association with AIT were not indicative of a systemic reaction. The 2017 update states “Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after SLIT administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction… Gastrointestinal tract reactions after SLIT or oral immunotherapy (OIT) would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions.” Studies published before this 2017 update used the old grading system (or no formal grading system at all), which would lead to an overestimation of systemic reactions. This point should be recognized as a limitation of the analysis | Thanks for your suggestion. We added to our discussion 4th paragraph; "Recent alterations in grading of systemic versus local reactions, with a more liberal definition of systemic allergic reactions prior to the 2017 WAO update,[121] may lead to an overestimation of systemic allergic reactions." and to limitations " Studies reporting adverse events used different grading systems, no formal grading system at all, and in some cases not even descriptions of events, this made classification difficult for both SCIT and SLIT. All the studies included were published before the most recent WAO classification,[121] and even before the initial 2010 grading system,[124] therefore, classification of what was considered as local or systemic events and severity differed greatly, and might lead to overestimation or underestimation of events." |
| **Public comment #5<br>Karen Rance<br>ALK Americas** | Results | We disagree with the conclusion that systemic reactions with SLIT were common. In relation to the risk difference for SLIT local reactions and SCIT systemic reactions, the risk difference for systemic reactions with SLIT seems low. Furthermore, previous works have found the rate of SARs with SCIT to be 0.2% (Cox,2010) and with SLIT to be 0.06% (Cox,2006) , and in a 2013 AHRQ review of AIT, it was concluded that systemic reactions with SLIT were uncommon.(Lin, 2013) We propose eliminating the wording of “a common occurrence” throughout and simply report the risk differences. Please also revise the Conclusions accordingly | Thanks for your suggestion, but the rates we report reflect this wording. We consider adverse events presenting in up to a third of patients as common. We found that serious events (SARs) were low and we reported those accordingly. The review you mention included all allergic populations (Rhinitis, rhinoconjunctivitis and asthma), and not asthma specifically. |
| **Public comment #5<br>Karen Rance<br>ALK Americas** | Results | On page 30 for SLIT asthma exacerbations, the De Blay et al, 2014 (ref 74) should not be used since exacerbations were not reported. Therefore, the last sentence is misleading in its statement that there was no statistical difference in exacerbations between groups in this study. | De Blay, 2014 is the main reference for a study reported in three different manuscripts, reporting different outcomes, as we show in all the tables. De Blay, 2014 is the main reference but for asthma exacerbations, the data come from Mosbech, 2014. To avoid confusion, we now cite both references. |

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| **Public comment #5 Karen Rance ALK Americas** | Results | On page 35, the De Blay et al, 2014 (ref 74) was not adults only, the inclusion criteria was for patients aged 14 year and older, and did indeed include a limited number of adolescents. | As described in the Methods section, we defined our adult population as older than 12 years old, therefore, the DeBlay study, which as you say included only patients older than 14 years old, was classified as an adult study. |
| **Public comment #5 Karen Rance ALK Americas** | Results | On page 35, the Virchow et al, 2016 (ref 73) did not take place in a clinic setting, only the first dose was taken in the clinic | Thank you, you are correct. First dose only was in clinic, rest at home. We revised the text accordingly. |
| **Public comment #6 Susan Rappaport ALA - American Lung Association** | Results | On page 16 (Immunoglobulin E section), the Lung Association would recommend using "specific IgE" in the discussion, otherwise it is not clear if it is antigen specific or total IgE that is being discussed. The wording in the sublingual immunotherapy (SLIT) section (page 32) is properly phrased, and can be replicated in the SCIT section of the report | Thanks for your comment. We reworded, where applicable. |
| **Public comment #6 Susan Rappaport ALA - American Lung Association** | Results | On page 17 (immunoglobulin G4 section), the same issue as with the IgE section described in the above comment exists. The Lung Association would recommend using "specific IgG4" when discussing IgG4 levels. Again, the wording in the SLIT section (page 32) is properly phrased | Thanks for your comment. We reworded, where applicable. |
| **Public comment #6 Susan Rappaport ALA - American Lung Association** | Results | The report does not address the length of SCIT or SLIT treatment and the potential cost and inconvenience of these treatments. This should be added because it is important for practitioners to understand (and quite useful for the National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel Report). | Cost and measures of convenience were not included as outcomes for our review. |
| **Peer Reviewer #1** | Discussion/ Conclusion | The Discussion is well summarized and based on the results reported. The conclusions are appropriately stated based on the breadth and level of the evidence reviewed. The limitations are presented clearly. The section describing future research is clear and actionable. | Thank you for your comment. |
| **Peer Reviewer #2** | Discussion/ Conclusion | The limitations of the studies are well described. The investigators did not omit any important literature. | Thank you for your comment. |

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| **Peer Reviewer #2** | Discussion/ Conclusion | The future research section is clear. The gaps in knowledge are well defined. The investigators make suggestions regarding future needed research on the topic. | Thank you for your comment. |
| **Peer Reviewer #3** | Discussion/ Conclusion | The main criticism I have of the discussion section would be mainly in its organization. It is very difficult to read as it is and does not read as a discussion section, but rather a list of findings. The clinical applicability and the scientific significance should be highlighted up front. The recap of the findings should be more condensed, recapping the main messages. Much of the text is a repetition of individual findings, instead of synthesis within the context of its value as new medical research and translatability to clinical practice. | Thanks for your suggestion. We have reviewed and revised the Discussion section. |
| **Peer Reviewer #3** | Discussion/ Conclusion | The limitation section is out of proportion to the entire discussion section and needs to be similarly condensed. Overall, this entire section needs to be reorganized, with emphasis placed on the new interpretation and significance of the results of this updated meta-analysis | Thanks for your suggestion. We have reviewed and revised the Discussion section. |
| **TEP #1** | Discussion/ Conclusion | Page 43, lines 15-6: This supports the above suggestion that you are overemphasizing anaphylaxis, when bronchoconstriction is the more frequent and important adverse effect. | We added the data available on bronchospasm and pulmonary adverse events for both RCTs and Non-RCTs in the SCIT and SLIT sections. Bronchospasm was not specifically addressed in the studies included, though lower respiratory symptoms included asthma exacerbation or "aggravation" and chest tightness, which are often symptoms of bronchospasm. |

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| **TEP #1** | Discussion/ Conclusion | Page 43,9-10: "We found insufficient evidence to make conclusions about the effect fo SCIT on asthma symptoms." Anyone with any familiarity with the literature of SCIT will find this statement unbelievable. | The use of validated control measures for assessment of asthma was recommended by NHLBI guidelines published in 2007, and the availability of these instruments predated the guidelines. The measures were available for use in the time period of this review. The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clincal research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. |
| **TEP #1** | Discussion/ Conclusion | Page 43, lines 20-1: "An accelerated SCIT protocol did not appear that the risk of systemic reactions was higher with such protocols". This, again, would not find acceptance with those familiar with the SCIT literature. | We agree with the reviewer that accelerated SCIT protocols are typically associated with a higher risk of systemic reactions. However, the general trend of the studies included in this report did not suggest that accelerated protocols had a higher incidence of systemic reactions. We did not set out to assess this comparison separately (i.e., not outlined in our protocol), and did not identify any studies providing this comparison. We have thus removed this statement from the key points. |

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| **TEP #1** | Discussion/ Conclusion | Page 43, lines 41-2: "We could not draw conclusions about the effect of SCIT on asthma symptoms as we limited our review to studies that used validated tools to measure asthma symptoms and identified none." This is unacceptable!! You set up the arbitrary standard of using measures of asthma control as a surrogate for asthma symptoms, even though these are recent tools that antedate most of the articles of SCIT that you reviewed. | The use of validated control measures for assessment of asthma was recommended by NHLBI guidelines published in 2007, and the availability of these instruments predated the guidelines. The measures were available for use in the time period of this review. The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |

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| **TEP #2** | Discussion/ Conclusion | As noted in results: No analysis is presented by allergen. It seems as though HDM is most robust. Without a comment on specific allergens, how can providers determine which allergens should (or should not) be included in SCIT? | Even though there are more studies with HDM than with other specific allergens, we observed substantial variability between studies that prevented us from having confidence to perform allergen specific analyses. Variability included study population, level of control, use of other medications, and duration of treatment, among other factors. We would also point out that did not have an a priori study goal to determine which specific allergens do, or do not, have sufficient evidence, nor how to prioritize them. |
| **TEP #2** | Discussion/ Conclusion | No comment on standardized vs non-standardized allergens. Likely related to the previous comment as well. (add to pg 44, lines 18-20) | We added to limitations section in 3rd paragraph, page 52- "We found wide heterogeneity among studies in the allergens used, variability ranged from study to study in the use of standardized and non-standardized allergens, as well as the types of allergens utilized (seasonal and perennial, single and multiple allergens) and the sensitization status of patients. This variability may affect the generalizability of our findings and applicability of results." |
| **TEP #2** | Discussion/ Conclusion | SLIT studies performed in largely monosensitized populations - how to extend to poly-sensitized patients? And all used single allergens. | We have added following text to Discussion, Applicability section: "Almost all trials utilized a single allergen for immunotherapy, therefore we cannot comment on the comparative effectiveness of different allergen compositions." |
| **TEP #2** | Discussion/ Conclusion | Since the SLIT studies were using HDM and birch, the conclusion should be that SLIT with HDM and birch reduce asthma symptoms, not that SLIT reduces symptoms. Similar comment for QOL. | We added to limitations section in 3rd paragraph, page 52- " For some outcomes in this report, a limited number of allergens were studied. The applicability of results to allergens that have not been studied is unclear." |
| **TEP #3** | Discussion/ Conclusion | Discussion/ Conclusion: Discussion is well done. Limitations are appropriately described, as is the Future Research section. | Thank you for your comment. |

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| **Public comment #6 Susan Rappaport ALA - American Lung Association** | Discussion/ Conclusion | The conclusion section of the abstract states that anaphylaxis was observed rarely. In the discussion section this reaction is said to occur "in a small proportion" which is quite different. This is an important issue as immunotherapy has only modest beneficial effects. As a result, attention must be paid to even a small number of life-threatening events | We say in the abstract for SCIT "We are unable to draw conclusions on whether SCIT increased risk of anaphylaxis primarily because the RCTs did not directly measure and report anaphylaxis" and for SLIT we specify three cases reported. In the discussion we also specify numbers, we changed "small proportion" to "seldom" and we proceed to explain "of the total 180 systemic reactions reported in RCTs, we determined that six cases were consistent with anaphylaxis and there was one case reported from the 165 in the non-RCTs" |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Discussion/ Conclusion | Academy leadership would note that overall, the types of SCIT are used as if they are interchangeable (tablets vs. aqueous solutions), and would question this broad assumption. It is further noted that most discussion “lumps” SLIT, though the authors do carefully discuss the types of SLIT in individual paragraphs. It is recommended that the discussion should make mention of the different types of SLIT, since there is no reference to any direct head to head comparison of efficacy between those methods of administration, while there also appears to be different dosing between these methods as well. | We have added in future studies needs section: "There is a need of head to head comparison studies of SLIT tablet and aqueous formulations." |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Future Research | Academy leadership would note that the future needs were clearly identified and consistent with the limitations identified from the systematic review | Thank you for your comment. |
| **Peer Reviewer #3** | Figures and Tables | Figure 2 is useful to understand the analytic population. Characteristics of the studies are clearly described in the text and table 2. Appropriate categories corresponding to the key questions are well delineated in table 2 and figure 3. Summary tables at the end of each KQ are well layed-out and valuable to the reader. | Thank you for your comment. |

| Commentator & Affiliation | Section | Comment | Response |
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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Figures and Tables | Academy leadership would observe that the Tables are clearly presented and displayed. Further, it is recommended that the authors consider adding FEV1 % to Table A2, to assist readers in understanding this important aspect of risk associated with allergen immunotherapy. | Thanks for your suggestion. Table 2 includes studies per key question and subpopulations (age and setting) and we have not added additional details. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | Figures and Tables | Academy leadership noted one figure included wrong numbers, and would encourage the authors to ensure all the numbers utilized in the tables are correct. Academy leadership would note that it is common for readers to primarily review the introduction, the conclusion and the tables and figures, and that accuracy is appreciated | Thank you for your comment. We reviewed all the tables and figures to make sure that the numbers are correct. |
| **Peer Reviewer #2** | References | There are no studies that the investigators overlooked. | Thank you for your comment. |
| **Peer Reviewer #3** | References | I do not recognize any study that was inappropriately included or omitted. | Thank you for your comment, |
| **TEP #1** | References | It did not extensively check your retrieval, but I could not find any mention of the following articles:<br>*Johnstone DE, Crump I. Value of hyposensitization therapy for perennial bronchial asthma in children. Pediatrics 1961;27:39-44<br>*Reid MJ, et al. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol 1986;78:590-600. | We reviewed the studies suggested to evaluate if they meet our eligibility criteria: Johnstone does not meet our criteria because it does not report on any of our outcomes of interest (only reports on wheezing on exertion, wheezing at end of study and developing new allergies during study); Reid does not meet inclusion criteria as it included mixed population, it does not meet criteria for asthma control, it reports immunological outcomes and safety, but it does not report those separately for asthma. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | References | Academy leadership would comment that the paper is well referenced | Thank you for your comment. |

| Commentator & Affiliation | Section | Comment | Response |
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| **Peer Reviewer #1** | Clarity and Usability | The paper is very well done. Its structure is appropriate and it is organized logically. The information is clearly presented. The conclusions are relevant to clinical practice. They provide further support to data presented by the Cochrane Collaborative and others over the past several years. The manuscript will add appreciably to the current literature and will appropriately guide clinical practice. | Thank you for your comment. |
| **Peer Reviewer #2** | Clarity and Usability | The report is very well written. It is very well structured and organized. The main points are clearly presented. The conclusions are relevant to practice decisions and point out the need for future research. This report does contribute new information on the subject. | Thank you for your comment. |
| **Peer Reviewer #3** | Clarity and Usability | Specific comments pertaining to this section are highlighted throughout my comments above. While the rest of the paper is clearly organized, it is difficult to walk away with a sense that there are new insights based on the presentation of the discussion/conclusion sections that are supposed to tie everything together and demonstrate the added value of the work. | We revised the Discussion as suggested. |

| Commentator & Affiliation | Section | Comment | Response |
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| **TEP #1** | Clarity and Usability | Some of the conclusions, particularly in regard asthma symptoms, are not appropriate. | The use of validated asthma control measures was specified in the final study protocol that had undergone public review and comments, and was developed with input from Key Informants and the Technical Expert Panel. This approach to using validated instruments to assess symptoms is consistent with recommendations from the 2011 NHLBI workshop that convened asthma experts to recommend methods to assess outcomes in clinical research studies (Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology. 2012;129(3):S1-S8.). Furthermore, the NHLBI sponsors of this project specified that unvalidated symptom diaries and other similar measures not be included in this review. While asthma symptoms and asthma control are not identical, they are closely related. The control measures include questions about symptom frequency, nighttime awakening, use of demand medication, emergency visits among others. |
| **TEP #2** | Clarity and Usability | Clarity and Usability: An important document. Well done! | Thank you for your comment. |
| **Peer Reviewer #1** | General | Quality of the Report: Superior | Thank you for your comment. |
| **Peer Reviewer #2** | General | Quality of the Report: Superior | Thank you for your comment. |
| **Peer Reviewer #3** | General | Quality of the Report: Good | Thank you for your comment. |

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| **TEP #1** | General | Quality of the Report: Good | Thank you for your comment. |
| **TEP #2** | General | Quality of the Report: Good | Thank you for your comment. |
| **TEP #3** | General | Quality of the Report: Superior | Thank you for your comment. |
| **Peer Reviewer #1** | General | General Comments: This topic is highly relevant, given the prevalence of asthma and the potential role of immunotherapy in its treatment. This area is of great interest to the medical community and its patients, and the generation of an evidence-based document will add significantly to the literature and guidance on this important clinical topic. The questions are phrased specifically and are relevant and clinically meaningful. | Thank you for your comment. |
| **Peer Reviewer #2** | General | General Comments: This is an excellent synthesis of the currently available studies/literature on the topic. It is very well written and includes a lot of detailed information.<br>The answers to the key questions are well laid out and answered. This report is clinically meaningful and relevant.<br>The study populations are well defined. The investigators divided the study populations to mirror the age ranges in the EPR-3 "guidelines". | Thank you for your comment. |
| **Peer Reviewer #3** | General | General Comments: The authors have composed a well-written and organized report summarizing the updated literature on the therapeutic benefits of immunotherapy for patients with allergic asthma. This is a well-circumscribed target population, and the rationale for studying these patients is clear. The clinical significance of the work is concisely presented and compelling. The key questions are clearly stated in both the text as well as in the figure, and follow through the rest of the document in a logical manner. Overall, the report is easy to follow and fulfills its objectives. | Thank you for your comment. |

| Commentator & Affiliation | Section | Comment | Response |
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| **TEP #2** | General | Identifying SCIT and SLIT as broad therapeutic approaches without consideration of the differences within each of these (single vs multi-allergen) may allow for incorrect conclusions - not all combinations of SCIT or SLIT are equally effective, nor are all allergens equally effective. This should be stated up front, as the conclusions convey that both approaches work but do not give any insight into the specifics of allergen composition. | We have added following text to Discussion, Applicability section: "Almost all trials utilized a single allergen for immunotherapy, therefore we cannot comment on the comparative effectiveness of different allergen compositions." |
| **TEP #3** | General | General Comments: Report is meaningful. Target population is defined. KQ's are appropriate and well stated. | Thank you for your comment. |
| **TEP #3** | General | Minor concerns: Close grammatical editing is needed. There are a number of grammatical mistakes throughout… some are noted below, but an exhaustive list is not provided in this review. | The final report has been reviewed by a copy editor. |
| **Public comment #1 Michael Blaiss ACAAI - American College of Allergy, Asthma, and Immunology** | General Comments | Key points should include data demonstrated the majority of studies showed improvement in airway hyperresponsiveness to allergen challenge | In the key points we report the most critical outcomes, chosen a priori and outlined in our protocol. AHR was not one of those outcomes and thus is not included in key points. |
| **Public comment #2 Rubin Cohen ACCP-CHEST Guidelines** | General Comments | My only comment is whether a cost analysis should be inserted into the report. The oral regimen is less costly compared to the injectable. A statement may help providers and consumers make a more educated decision | Consideration of cost, or a cost-analysis, was beyond the scope of our review and thus has not been added. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | On behalf of this membership, please accept the following general and explicit comments regarding the Draft Report, "The Role of Immunotherapy in the Treatment of Asthma" Academy leadership would suggest that when the authors are writing generally, and not duplicating specific terms as used in papers, the phrase "systematic allergic reactions" would be preferable to "systematic reactions."1 Academy leadership would observe that there is a dilemma in the use of "systemic reaction", "hypersensitivity reaction", "systemic allergic reaction" and "anaphylaxis", used interchangeably in many papers. Further, anaphylaxis, defined by the NIAID (Sampson et al.), for all practical purposes, involves hypotension and/or respiratory distress. | Per our protocol, "hypersensitivity" was one of our prespecified outcomes. To add clarity, we have now added to our methods section a description of hypersensitivity that reads "Hypersensitivity refers to a mechanism, rather than a clinical description of a reaction" therefore we removed "Hypersensitivity" throughout the Results text when referring to adverse events. We also changed "systemic reactions" to "systemic allergic reactions" throughout all the report. |

| Commentator & Affiliation | Section | Comment | Response |
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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | Academy leadership would also note that in the World Allergy Organization classification, there are five systemic allergic reaction grades, the first three of which do not involve anaphylaxis. Academy leadership would suggest that it may be useful for the authors to address these definitions at the beginning of the paper, i.e., to inform the reader that terms cited from experimental papers are as referenced in these papers, however in other circumstance, the terminology “systematic allergic reaction,” “anaphylaxis,” or “systematic allergic reaction,” could include anaphylaxis. | We added the definition of the WAO grading of systemic reactions to the Methods section. When classifying the different types of reactions, we have tried to fit these into the WAO classification system. However, it is important to note that many articles do not describe the reactions in terms that fit with this classification, and many reactions are not described in detail (e.g., "systemic reaction" without further details); this significantly limits how we can classify these in the report. We added following text to our limitations section in Discussion: "We tried to grade all adverse events using the WAO classification, however, many descriptions of the reactions (or the lack of description) significantly limited our ability to classify the adverse events." |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | Further, Academy leadership would encourage the authors to consider the use of the term “subjects” rather than “patients”, noting these are subjects, not patients, in double-blind controlled studies. In addition, it may be preferable to reference “physicians and other healthcare professionals” rather than “providers” or “prescribers”. The former terms are more descriptive of those who provide such therapy; providers include chiropractors and naturopaths. | Based on the style guidelines and several papers, we prefer the term "patients." See for instance: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1115535/ |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | It would further be recommended that the use of personal pronouns be eliminated in the paper. For example, on page 5, ten personal pronouns are used. To illustrate how personal pronouns can be eliminated, Academy leadership would reference page 7. In the sentence that begins with “We resolved ……. “ this text could be revised to read, “Disagreements were resolved through discussion or adjudication by a third reviewer, as needed.” To continue, the next sentence could better read, “The risk of bias of RCTs was assessed using the Cochrane ….”. Further, the next sentence may be revised to read, “Each risk of bias domain for the RCTs from the prior review was not re-assessed.” | Based on the style guidelines we have used active voice throughout. |

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| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | Academy leadership would note that the term “hypersensitivity reaction,” may be derived from a cited paper, however its meaning may be unclear to the reader. Does it mean a systemic allergic reaction or anaphylaxis? As noted earlier, it may be preferable to consistently use the terminology “systemic allergic reaction” when referring generically to generalized systemic reactions associated with immunotherapy. Alternatively, the authors may use the term “systemic allergic reaction (anaphylaxis)” to be all inclusive. | Per our protocol, "hypersensitivity" was one of our prespecified outcomes. To add clarity, we have now added to our methods section a description of hypersensitivity that reads "Hypersensitivity refers to a mechanism, rather than a clinical description of a reaction, it is well known that the vast majority of systemic (and some local) reactions fall under the umbrella of hypersensitivity reactions to the allergens. Individual reactions will be discussed in their respective RCT and non-RCT categories." therefore we removed "Hypersensitivity" throughout the Results text when referring to adverse events. We also changed "systemic reactions" to "systemic allergic reactions” throughout all the report. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | Further, Academy leadership notes reference to both the term “asthma” and in other circumstances “allergic asthma”. Academy leadership would comment that allergen immunotherapy is used to treat allergic asthma not asthma, in general. Perhaps the term “allergic asthma” may be used throughout the paper more effectively, unless referring to all asthma phenotypes. | We have reviewed and changed to allergic asthma where necessary, otherwise, we kept our term, since all the papers included had asthma appropriately diagnosed as allergic. |
| **Public comment #3 David Peden American Academy of Allergy, Asthma & Immunology** | General Comments | Regarding the word “corticosteroid”, these really are glucocorticosteroids, and therefore, the terminology “glucocorticosteroid” would be more appropriate | We recognize that the inhaled and oral steroids that are used for treating asthma can be referred to as glucocorticosteroids and corticosteroids. We have chosen the latter as it fits better with the current common abbreviation of ICS that is used when discussing treatments. |

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| **Public comment #5<br>Karen Rance<br>ALK Americas** | General Comments | It is not made clear for the reader that SCIT and SLIT formulations show great heterogeneity, nor that most of the SCIT and SLIT drop studies have been conducted outside of the US, including extracts not commercially available in the US. Proper assessment of the quality of the allergen mixture and dosing have not been established in most of the drop studies. Thus, the quality of the data from such studies is unsubstantiated and negative results are not unexpected. It would be scientifically balanced to mention that there is no or very little clinical trial data that document the clinical efficacy and safety of US extracts used for SCIT and SLIT drops. It would be prudent to make a cautionary remark that the data in the analysis cannot be inferred to US clinical practice as there are very little data to support a valid clinical comparison to US allergenic extracts used in SCIT and SLIT drop formulations. Almost all US clinical trial data supporting efficacy of SLIT is based on the FDA approved SLIT tablets and there are no FDA approved SLIT drop formulations. | We have added to the Discussion, Applicability section: "Many of the studies were performed with extracts manufactured outside of the United States and subject to different standardization methods. Therefore, caution does need to be applied when considering the applicability of our results to allergens that have undergone different standardization processes." |
| **Public comment #5<br>Karen Rance<br>ALK Americas** | General Comments | The paper should reference the new 2017 GINA guidelines which recommend SLIT as an add-on therapy for adults with house dust mite sensitivity and asthma who have exacerbations despite inhaled corticosteroid treatment, provided FEV1 is >70% predicted.1 A statement referring to this new addition to GINA should be included | This guideline was released after the start of our project and is thus not included in the Introduction as part of the rationale for the review. We do not mention this guideline in the discussion because the recommendation pertains to adults with asthma and rhinitis, therefore, not applicable to our review.<br>In the introduction, we mention the 2011 Practice Parameters by the Joint Task Force (comprised of members from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council on Allergy, Asthma and Immunology) , the 2007, the Expert Panel Report (EPR-3) from The National Heart, Lung and Blood Institute (NHBLI), the 2010 Cochrane review on SCIT, the 2015 Cochrane review on SLIT, and the 2013 Lin's review on SCIT and SLIT as background and rationale for this review. |

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| **Public comment #4 Yudy Persaud Bronx Lebanon Hospital** | General Comments | "Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful." | Thanks for your comment. We do have details on intervention in the results and details about each reference included are in table 3 in the appendix for each key question. We report interventions as they are reported in the manuscripts, we did not try to convert them to a standardized method (if that was even possible) and as explained in the discussion heterogeneity was a limitation and we say in the future research needs: " Immunotherapy dosing quantity, frequency, and formulation varied substantially and details were often lacking. Standardized methods and reporting of therapy would be helpful." |
| **Public comment #4 Yudy Persaud Bronx Lebanon Hospital** | General Comments | very well written. However would like to see improper ways that immunotherapy is currently being given be addressed. For example some practitioners are allowing SCIT to be given by patients in their home. Also there are companies mentioning "immunotherapy" that are not FDA approved (i.e in a toothpaste)? -should makers of immunotherapy be certified and if so how? (i.e. formal training or is a weekend course acceptable, etc) | We sought to assess home versus clinic setting but found no studies addressing this issue. Assessing practice patterns and marketing practices is beyond the scope of our review. |
| **Public comment #6 Susan Rappaport ALA - American Lung Association** | General Comments | Lastly, the draft report does not consider two negative points related to the use of these drugs—cost and inconvenience—as they may require doctor visits many times over a year. | Cost and measures of convenience were not included as outcomes for our review. |
| **Public comment #7 Rhonda Vosmus Intermed PA** | General Comments | It appears with this extensive review, both options are fairly equal in outcomes, good and not so good. I think it remains that a detailed discussion, shared decision making is key in eliciting a treatment plan. | Thanks for your comment; the purpose of the review is to present evidence available. We hope that the information can be translated into guideline and to be useful for clinicians for discussions with their patients. |

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| **Public comment #7<br>Rhonda Vosmus<br>Intermed PA** | General Comments | There is a huge patient adherence piece that needs consideration when undertaking this treatment plan. I am once again, awed by the level of research and reporting on each of these clinical areas. | Thank you for your comment, The data on compliance/adherence that we were able to find were limited. We have added in the Future Needs section: "For both SCIT and SLIT additional studies are needed to assess compliance/adherence, and the effect compliance may have on management." |