Evidence-based Practice Center Systematic Review Protocol

Project Title: Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma

I. Background and Objectives for the Systematic Review

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program has requested a comparative effectiveness review (CER) of Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma. The topic was selected through the Effective Health Care Program nomination process.

Description of the Condition

Allergic rhinitis is a common clinical problem. Its prevalence in North America is estimated to be as high as 20 to 40 percent of the general population.[1-4] Allergens such as tree, grass, and weed pollens characteristically cause seasonal rhinoconjunctivitis and/or asthma; whereas, cat dander, cockroach, or dust mite allergens may induce symptoms year-round and are associated with perennial rhinitis and/or asthma. The prevalence of asthma in the general population is approximately 8 percent, and approximately 50 to 75 percent of individuals with asthma appear to have an allergic basis to their disease.[5,6]

The medical management of patients with allergic rhinitis and asthma includes allergen avoidance, pharmacotherapy, and immunotherapy.[4-7] Many patients require pharmacotherapy to control symptoms of allergic rhinitis, including "preventive" agents (e.g., topical nasal corticosteroid or cromolyn preparations) and/or antihistamines and decongestants. These agents must be used on a daily basis to provide effective control. This requirement raises critical issues related to long-term compliance, safety (risk vs. benefit), and cost. The long-term use of

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nasal corticosteroids has been shown to be associated with detrimental effects on growth in children[8-10] and may negatively impact bone demineralization in adults.[11] Furthermore, some antihistamines cause sedation and may impair motor skills.[12]

Similarly, the long-term use of inhaled steroids poses the same, if not increased, risk, especially if used together with nasal steroids to control seasonal or perennial respiratory conditions. Furthermore, long-acting bronchodilators have the potential to cause cardiovascular complications, including arrhythmias and sudden death, and leukotriene antagonists have been associated with neuropsychiatric disturbances.[13-15]

Allergen-specific immunotherapy (SIT) is typically recommended for patients whose allergic rhinoconjunctivitis and asthma symptoms cannot be controlled by medication and environmental control, who cannot tolerate their medications, or who do not comply with chronic medication regimens.[16-18]

The U.S. Food and Drug Administration has approved the use of subcutaneous allergen extracts (subcutaneous immunotherapy [SCIT]) for the treatment of seasonal and perennial allergic rhinitis, allergic asthma, and venom sensitivity. Off-label use of the same aqueous materials can also be administered orally (sublingual immunotherapy [SLIT]) and an increasing number of U.S. physicians are employing this alternate immunizing approach in the treatment of allergic respiratory conditions based on European and U.S. studies and subsequent European Medicine's Agency approval of certain oral products.

SCIT has been shown to mute the immediate phase of clinical reactivity (mast cell mediator release), inhibit cellular recruitment (eosinophils and basophils) in the late phase and resolve the underlying inflammatory process that characterizes allergic rhinitis. The mechanisms by which this is accomplished are not well understood but are currently thought to include a reduction of allergen-specific Th2 T-cell responses mediated by increased Th1 or regulatory T-cell responses to the same allergen. Properly performed studies of SLIT are beginning to demonstrate similar mechanistic findings.[19-22]

Overall Rationale and Approach

Immunotherapy (SCIT), as a treatment for allergic diseases, was first introduced by Noon and Freeman in 1911 as a means of treating grass-induced allergic symptomatology "hay fever" (i.e., rhinoconjunctivitis).[23] In the United States, a patient with allergies receives increasing doses of

an allergen-containing extract, comprised of the relevant allergens to which the patient is sensitive, in an attempt to suppress or eliminate allergic symptomatology. With continued administration, it is expected that the treatment regimen will make the patient tolerant to the offending allergen and suppress future untoward responses to the allergen(s) through modulation of the patient's immune system.[4,17-20,22] Controlled clinical trials have demonstrated therapeutic efficacy and have detailed the favorable immunologic changes associated with allergen immunotherapy for the treatment of allergic rhinitis, asthma, and venom sensitivity (the latter will not be addressed in this review).[25]

Conventional SCIT regimens employ increasing doses of the allergen extract, administered once or twice weekly as tolerated, until the patient reaches a predetermined "maintenance" dose (e.g., 6–12 µg Amb a 1 [2000–4000 BAU]/injection). The optimal duration of SCIT with a licensed allergen extract is not well defined; the maintenance dose is typically given once or twice monthly for 3 to 5 years.[26-27] However, this approach is not optimal, as its effects are only partial at best, ineffective in some patients, and saddled with the risk of potentially serious systemic allergic reactions.[28-31]

Through the years, various chemical modifications of allergens (see below) have been attempted to enhance efficacy, improve safety, and foster compliance with SIT. Many of these previous approaches have been unsuccessful, in that the allergenicity (potential to cause an untoward allergic reaction) and immunogenicity (potential to induce a beneficial clinical effect) have either decreased or increased in tandem with no resultant efficacy: safety benefit ratio. However, recent approaches with modified allergens, adjuvants (including immunostimulatory adjuvants), recombinant allergens, T-cell–tolerizing constructs, and improved oral approaches have been demonstrated in various clinical studies to be successful agents for treatment of allergic respiratory disease.[32-34]

Oral immunotherapy (OIT) was first proposed as a method of treatment for allergic disease in the early 1900s. Renewed interest in this form of treatment emerged in the 1940s through 1960s and led to numerous clinical studies; however, these early clinical studies were often poorly designed and improperly controlled. In the 1980s, properly designed clinical trials first demonstrated a dose-dependent therapeutic response with specific and well-characterized aeroallergens. In 1996, a task force on immunotherapy assembled by the World Health Organization cited the emerging clinical data on oral immunotherapy, recognized its potential as a viable alternative to subcutaneous therapy, and encouraged continued clinical investigation to characterize optimal techniques.[17]

In this context, OIT has been administered in various fashions through the years, including:

a. Oral-aqueous immunotherapy (OIT-aqueous swallow), where the allergen is mixed with 1 to 2 ounces of diluent and swallowed.

b. Oral-sublingual immunotherapy (SLIT), where the allergen is placed under the tongue for local absorption (allergen can be administered as an aqueous preparation (SLIT-aqueous) or a dissolvable tablet (SLIT-tablet).

c. Oral-encapsulated immunotherapy (OIT-encapsulated), where the allergen is placed in a liposome, or polymer, or microencapsulated carrier and swallowed. (The encapsulation allows the allergen to be delivered "intact" to the small intestine [jejunum or ileum] where there is pH-dependent release of the allergen to the gut lymphoid tissue [hence, the allergen is not destroyed by gastric juices in the stomach].)

As noted, considerable interest has also evolved in using SLIT (sublingual-aqueous and sublingual-tablet formulations) as an alternate treatment approach to SCIT. The rationale for this route of therapy is based on its perceived improved safety margin (reduced risk of anaphylaxis), its simple and convenient oral-dosing regimen (avoiding the discomfort of injections and the inconvenience of office visits for allergy shots), and possibly a decreased time to achieve its effect. Current clinical trials in the United States are being carried out to address these clinical issues. Over the past decade, sublingual (SLIT) forms of immunotherapy have gained favor in Europe, and sublingual-tablet immunotherapy has been approved by the European regulatory authorities. A recent Cochrane analysis concluded, "SLIT is a safe treatment which significantly reduces symptoms and medication requirements in allergic rhinitis."[35] However, systemic reactions do occur with SLIT, including oral itching, throat irritation, and mouth edema.

Recent European multicenter, double-blind, placebo-controlled clinical trials have been the basis for the approval of grass sublingual-tablet immunotherapy by the European regulatory authorities. The World Allergy Organization has recently issued a position paper on SLIT for respiratory allergies and a consensus statement on this form of treatment.[36] In this context, clinical development programs specifically addressing oral approaches to sublingual immunotherapy for allergic rhinitis and asthma, including sublingual immunotherapy (SLIT) with an aqueous-extract formulation, sublingual-tablet constructs, and microencapsulated preparations are under development by pharmaceutical companies. It is pertinent to our work to examine those constructs that are available in the United States and cite those clinical studies wherein these agents have been compared to SIT.

Immunotherapy for Inhalant Allergies

Cooke and colleagues became strong proponents of SCIT in the - 1920s and 1930s. Subsequently, a group of allergists led by Gay and Winkenwerder performed uncontrolled experiments with very dilute concentrations of allergen extracts in the early 1940s. It remained for Frankland[37] at St. Mary's Hospital in the United Kingdom in 1955 and for Lowell and Franklin[38] at the Massachusetts General Hospital in 1963 to finally carry out controlled studies with SCIT. These studies showed that treatment with native allergens was superior to placebo and ushered in the modern era of SIT studies.

Indeed, numerous carefully controlled clinical trials—in which the allergen dose was incrementally increased—have demonstrated a clear, statistically significant amelioration of the clinical symptoms of allergic rhinoconjunctivitis.[39] For the treatment of asthma, however, the risks and benefits of SIT are less clear. SIT is used widely in the treatment of asthma even though the available evidence supporting its clinical utility, particularly its efficacy relative to current pharmacotherapy, is limited in scope and oftentimes has been shown to be marginal in quality. Nevertheless, a recent Cochrane review shows that there is an effect, suggesting that improved methods should lead to a more marked clinical effect.[41]

Over the subsequent decades, attempts have been made to improve the clinical results of SIT by a variety of techniques. An early effort by Marsh,[42] in which the allergens were modified by partially denaturing them in formalin, led to a product of markedly reduced allergenicity. Unfortunately, the immunogenicity of "allergoids"—as judged by the immunoglobulin G (IgG) antibody response—was also decreased, as was the clinical effectiveness.

Sehon[43] sought to modify and decrease allergenicity by coupling allergens to polyethylene glycol. Again, the result was the same—allergenicity and immunogenicity both decreased. It took markedly more modified allergen to induce the same IgG antiallergic antibody, and the clinical effect paralleled the IgG antibody response. Subsequently, Patterson[44] developed "polymerized" allergens in which gluteraldehyde polymerization was incorporated into the allergen backbone in an attempt to reduce allergenicity and provide a long-lasting therapeutic advantage over classic SCIT.

Although induction of IgG "protective" antibody is a sine qua non of successful immunization with conventional SCIT, Gefter[45] developed synthetic T-cell–tolerizing peptides of cat (Fel d 1) and ragweed (Amb a 1), based on elucidation of the primary structure of these antigens by King.[46] In collaborative studies, Norman (cat) and Creticos[47,48] demonstrated peptide immunization significantly reduced clinical symptoms without an increased IgG antibody response. Their clinical findings were positive, yet the effects were less beneficial than those achieved by SCIT; furthermore, patients experienced late-onset adverse symptoms that mimicked natural allergen exposure. Although this initial peptide

approach was disbanded (shouldn' this be "abandoned"?), new synthetic peptide constructs have now been developed and research is again being undertaken in Europe and North America with cat and certain pollen-related peptides.

Furthermore, this hypothesis of inducing T-cell tolerance to achieve long-term suppression of the allergic diathesis has led to the novel approach developed by Raz and colleagues of allergen vaccination with immunostimulatory DNA.[49] The data from initial clinical trials has been highly promising. For example, a brief 6-week injection regimen (administered only prior to the first ragweed season) demonstrated long-term clinical benefit—with symptom improvement observed over two ragweed seasons—and provided evidence for long-term immune tolerance (as defined by suppression of the allergic antibody [IgE]).[50]

Rationale for a Comparative Effectiveness Review

Although SCIT is used worldwide and oral immunotherapy approaches are in use in many areas of Europe, Latin America, and Asia, oral immunotherapy has not been approved by the U.S. Food and Drug Administration for use in the United States. Based on U.S. manufacturer package inserts, allergen extracts are sold for skin testing and for preparation of immunotherapy solutions for parenteral administration. Thus, use of these allergenic extracts as oral treatment agents is "off-label" in the United States, and third-party payers have generally not yet been willing to pay for SLIT. In addition, there is no standardized information on how to prepare an oral extract with U.S.-licensed allergenic extracts or what doses are appropriate. No sublingual allergen tablets are sold in the United States.

Objectives. Regardless of the significant amount of existent literature, the wide use in Europe and other countries, and the official position papers and guidelines on SCIT and SLIT, several questions remain unanswered about the use of SIT with regard to:

- Optimal dose, dosing frequency of allergen administration, and duration of treatment.
- Use and safety in preschool children.
- Short- and long-term efficacy and effectiveness.
- Potential for preventing the development of asthma in patients with allergic rhinoconjunctivitis.

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- Likelihood to interfere with the natural course of allergic diseases.

A systematic review of the evidence about SCIT and its alternate approaches (including off-label use of oral-aqueous [OIT-aqueous swallow] and oral-sublingual [SLIT-aqueous] immunotherapies) should be informative to clinicians and patients who are considering use of these agents, should be informative to payers for coverage decisions, and should be informative to manufacturers and to regulators. (Note: SLIT-tablet will not be included in this review, since it is not available in the United States.)

These observations on the current state of the art of allergen immunotherapy led to our decision to perform an evidence-based analysis of both SCIT and available forms of oral (oral-aqueous swallow and SLIT-aqueous), subcutaneous, and sublingual immunotherapies for respiratory allergies. We aim to assess the current evidence for the clinical effectiveness and safety of SIT in specific populations with respect to recognized clinical and mechanistic endpoints and, furthermore, to address these parameters in relation to comparators when appropriate studies have been performed.

II. The Key Questions

Summary of Revisions to the Key Questions

Based on the public comments regarding the key questions (KQs) submitted to the Agency for Healthcare Research and Quality, the Evidence-Based Practice Center revised the KQs and protocol by adding to the populations of interest 1) patients with severe asthma and 2) monosensitized individuals.

Key Questions

KQ **1**

What is the evidence for the efficacy and effectiveness of SIT in the treatment of allergic rhinoconjunctivitis and/or asthma?

KQ **2**

What is the evidence for safety of SIT in patients with allergic rhinoconjunctivitis and/or asthma?

KQ **3**

Are the safety and effectiveness of SIT different in distinct subpopulations with allergic rhinoconjunctivitis and/or asthma?

- Children (no age-group distinction)
- Adults (no gender distinction)
- Elderly
- Pregnant women
- Minorities (all races and ethnicities found in the literature)
- Inner-city and rural residents
- Patients with severe asthma
- Monosensitized and polysensitized individuals

PICOTS Framework

Population(s)

We will include studies enrolling patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies. Allergic rhinoconjunctivitis must be confirmed by skin tests or the radioallergosorbent test, and asthma must confirmed by pulmonary lung function tests (forced expiratory volume; metacholine challenge). This includes children, adults, elderly, pregnant women, individuals with severe asthma, monosensitized individuals, minorities, inner-city residents, and rural residents.

Interventions

The intervention will be SIT alone or with usual care. SIT is defined as treatment with sublingual-aqueous, oral-aqueous, and subcutaneous-aqueous preparations, which are the currently available treatments in the United States. No study of SIT will be excluded

because of dosage, timing, or duration of treatment. Only the studies where dosage unit is *not* specified will be excluded.

Other treatments that are not available in the United States will be noted during the review; however, they will not be included in the analyses unless their availability changes before the report is finalized.

- Appendix 1 contains a more comprehensive list of immunotherapy agents, their worldwide availability, and their current status with the U.S. Food and Drug Administration.
- Appendix 2 is a description of allergen unitage.
- Appendix 3 is a tabulation of pertinent airborne allergens (pollens, mold spores, animals, acarids, and insects).

Comparators

We will include studies that compare SIT (SLIT/SCIT) to any of the following:

1. Placebo
2. SIT (SLIT/SCIT; any form available in the United States)
3. Pharmacotherapy (positive control)
4. Environmental control
5. Usual care (e.g., environmental control, pharmacotherapy, etc.)

We will include all the relevant studies where SIT is used alone or in combination with any other treatment and evaluated against the comparators mentioned above or any other treatment. Appendix 4 includes a table of the comparators and their definitions.

Outcomes

1. Outcomes for KQs 1 and 3

KQ 1 evaluates efficacy and effectiveness of SIT, and KQ 3 evaluates the response in the different populations.

a. Evaluable Indices of Treatment Effect

i. Clinical endpoints

a) Symptom control (Improvement in rhinitis, conjunctivitis, or asthma symptoms)

- Rhinitis symptom diary scores
- Asthma symptom diary scores
- Ocular symptom diary scores

b) Medication usage scores
c) Combined symptom + medication diary scores
d) Quality of life

- Rhinoconjunctivitis quality-of-life instrument
- Asthma quality-of-life instrument

e) Effect of SIT on specific allergen challenge (provocation)

- Nasal provocation with allergen
- Bronchial provocation with allergen
- Conjunctival provocation with allergen

ii. Long-term outcomes

a) Evidence for sustained clinical benefit with continued treatment (maintenance control)
b) Evidence for long-term clinical efficacy postdiscontinuation of treatment (disease modification)
c) Effect of SIT on preventing sequelae of disease (sinusitis, otitis, and asthma)
d) Effect of SIT on development of new allergen sensitivities

[See definitions in Appendix 6]

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iii. **Biomarker endpoints** (laboratory measures of induced change)

a) Changes in serum antibody levels (specific IgG, IgG-4, and IgE)
b) Changes in cytokines (blood; secretions)
c) T-cell assay
d) Other laboratory measures

iv. **Convenience**

a) Reduction of injection frequency
b) Reduction of frequency of physician- or nurse-required treatment

v. **Adherence**

2. Outcomes for KQ 2

KQ 2 evaluates safety of SIT; we will include outcomes that assess harms or adverse events. Appendix 5 includes a more detailed list of outcomes than are listed below.

i. **Local reaction** (mouth, throat, and skin; irritation/swelling/pain)

a) Local reaction not requiring treatment
b) Local reaction requiring treatment
c) Local reaction severity and time of onset not specified

ii. Systemic reaction

a) Respiratory: congestion and asthma
b) Gastrointestinal: nausea and pain
c) Other: rash and anaphylaxis

- Systemic reaction not requiring treatment
- Systemic reaction requiring treatment or hospitalization
- Systemic reaction severity and time of onset not specified

iii. Death

3. Outcomes for Cost

The outcomes that we will include to assess economic endpoints are:

i. Overall healthcare utilization, emergency department visits, outpatient visits, and hospitalizations
ii. Missed days of school/work

Timing

Studies with any duration of followup will be included. Timing cannot be an exclusion criterion, since we are dealing with studies for both seasonal and perennial allergies. However, followup duration will be considered in the analyses.

Settings

All study settings will be considered for inclusion.

III. Analytic Framework

Analytic framework for allergen-specific Immunotherapy (SIT) in the treatment of allergic rhinoconjunctivitis and/or asthma

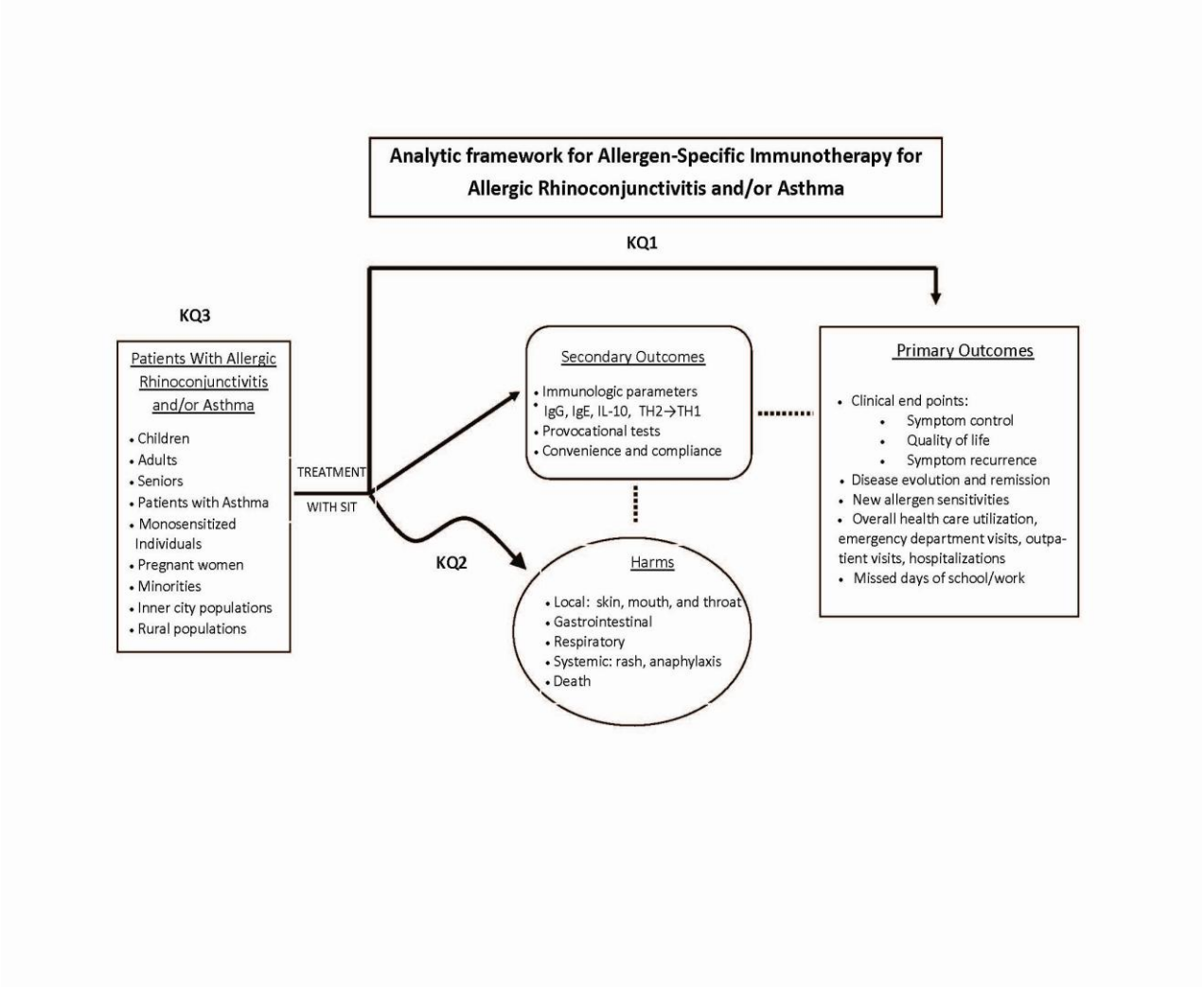

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Figure 1. This figure depicts the key questions (KQs) within the context of the PICOTS described in the previous section. In general, the figure illustrates how allergen-specific immunotherapy, administered to patients with respiratory allergies, may result in intermediate outcomes (e.g., changes in immunologic parameters) and/or long-term outcomes (e.g., improvement of symptoms and quality of life and reduction of health care costs). In addition, adverse events may occur at any point after treatment is received.

Abbreviations: Ig = immunoglobulin; IL = interleukin; TH = helper T lymphocytes.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

For all the KQs, we will include randomized controlled trials (RCTs), quasi-RCTs, and observational studies (to include cohort and case-control studies). Narrative summaries of case reports and case series will also be presented for KQ 3, only when they present serious adverse events. The specific populations, interventions, and outcomes of interest are described in Section II.

B. Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies To Answer the Key Questions

We will search the following databases for primary studies: MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences), and CENTRAL (the Cochrane Central Register of Controlled Trials). We will develop a search strategy for MEDLINE, to be accessed via PubMed, based on an analysis of the MeSH (medical subject heading) terms and text words of key articles identified a priori. This search strategy will be adapted for searches of EMBASE (using EMTREE terms) and CENTRAL. We will search the literature without imposed language, sample size, or date restrictions. We will search reference lists of included studies, relevant review articles, and related systematic reviews to identify any additional studies for inclusion. Conference proceedings or journals will not be hand searched.

The MEDLINE search strategy to be used is:

(allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]) AND ((rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis [mh] OR "allergic conjunctivitis" [tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma[tiab) NOT ("occupational diseases" [mh] OR "trachoma" [mh])) NOT (animals[mh] NOT humans[mh]).

C. Data Abstraction and Management

Potentially relevant citations will be screened by using DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), a Web-based systematic review software. Citations identified by the search strategies will be uploaded to DistillerSR and managed in the following manner: Two reviewers will independently assess titles and abstracts resulting from the literature searches according to the inclusion criteria stated in Section IV-B. The titles and abstracts will be classified as "Include," "Exclude," or "Unsure." Disagreements regarding eligibility are identified by DistillerSR and will be resolved by discussion with each reviewer by providing a rationale based on the review of titles, abstracts, and/or full-text articles. The two reviewers will retrieve the full text for titles and abstracts classified as "Unsure" by both reviewers or classified as "Unsure" by one reviewer and "Include" by a second reviewer and reassess the studies for inclusion. The authors of studies classified as "unsure"' will be contacted for further clarification, as appropriate, after examining the full text according to the guidelines described in Section IV-A. Any disagreements regarding inclusion after full-text review will be resolved through discussion, and unresolved conflicts will be adjudicated during a team meeting of investigators and advisors. Studies labeled as "Exclude" by both review authors will be excluded from the review, and the reasons for exclusion documented. Studies labeled "Include" will be further assessed for methodological quality as described in Section IV-D.

Two reviewers will extract descriptions of the study methods to include the population, intervention(s), comparator(s), and outcomes of interest by using a form designed by the team investigators, advisors, and senior research methodologist. Disagreements will be resolved through discussion. Data will be entered independently by two reviewers into a database designed specifically for this comparative effectiveness review.

D. Assessment of Methodological Quality of Individual Studies

We will use the Cochrane Collaboration's tool for assessing the risk of bias of RCTs and quasi-RCTs or an adaptation appropriate for our body of literature. Two authors will independently assess the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the C*ochrane Handbook for Systematic Reviews of Interventions*[51] and will evaluate the studies for the following criteria: sequence generation

and allocation concealment (selection bias), masking of participants, study investigators, and outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Masking of investigators and participants might not be possible with some of the interventions being examined, but it will be noted when mentioned.

Judgments for each criterion will be reported as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (information is insufficient to assess). Two reviewers will resolve disagreements through discussion. We will contact the authors of the studies for additional information on issues that were unclear from information available in the original reports. In case of failure to communicate with the primary investigators, or if there is no response within 6 weeks, we will assess the methodological quality on the basis of the available information.

We will use the Newcastle-Ottawa Scale[52] to assess the methodological quality of observational studies to include cohort and case-control studies. The Newcastle-Ottawa Scale includes domains to assess the quality of study-group selection (representativeness, case definitions), comparability of cohorts/cases and controls on the basis of design or analysis and ascertainment of exposure(s) or outcome(s). One star is awarded for the four selection questions and three stars for the ascertainment of exposure/outcome questions. Up to two stars are awarded for the comparability domain.

We will apply the World Health Organization criteria to the case reports to judge the likelihood that the intervention was causally related to the observed serious adverse event. (WHO, need citation)

E. Data Synthesis

If there is appreciable variability in the studies with regard to interventions, followup intervals, or assessments of outcomes, we will not combine the results in a meta-analysis and will instead present a narrative summary.

Assessments of Heterogeneity

We will assess the clinical, methodological, and statistical heterogeneity of included studies. We will evaluate clinical and methodological heterogeneity by examining potential variations in treatment, participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes. The I^2 statistic (%), the Chi-square test for heterogeneity, and the degree of overlap in confidence intervals of the included studies will be examined as appropriate to assess statistical heterogeneity.

Assessment of Reporting Biases

A funnel plot might be used to assess reporting biases in conjunction with study characteristics or other factors that may contribute to asymmetry of the plot.

Measures of Treatment Effect

We will calculate summary risk ratios or odds ratios as appropriate for dichotomous outcomes. We will verify normality of continuous outcomes and calculate mean differences; standardized mean differences will be calculated if continuous outcomes are measured by using different scales.

Data Synthesis

If the I^2 statistic suggests considerable heterogeneity (a threshold will be established before undertaking any analyses) or if there are insufficient data (less than three studies), we will not combine the results in a meta-analysis and will instead present a narrative summary. If considerable heterogeneity does not exist based on the I^2 statistic and an inspection of the forest plot, we will combine the results of included trials in a meta-analysis by using fixed- or random-effects methods as appropriate.

Subgroup Analysis

If there are sufficient data, we will conduct subgroup analyses by disease (asthma and rhinoconjunctivitis), method of administration (SLIT and SCIT), type of allergen, and outcomes or by other relevant demographic characteristics as outlined in Populations.

F. Grading the Evidence for Each Key Question

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We will assess the quantity, quality, and consistency of the body of available evidence by addressing all the KQs. We will use an evidence-grading scheme recommended by the GRADE Working Group,[53] adapted by the Agency for Healthcare Research and Quality in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[54]and recently published in the *Journal of Clinical Epidemiology*.[55]

We will consider the strength of the study designs; RCTs will be graded as having the highest level of evidence followed by observational studies as having the lowest. If an outcome is evaluated by at least one RCT and by observational studies, our evidence grade will be based firstly on the RCT and secondly on the quality of the cohort studies. If an outcome is evaluated by one or no RCT, our evidence grade will be based on the single RCT and the best available observational study.

We will assess the quality and consistency of the best available evidence—including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision—as described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[54]and by Owens and colleagues.[55] For each outcome of interest, two reviewers will grade the major outcomes for each KQ and then the entire team will discuss their recommendations and reach consensus.

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VI. Definition of Terms

Definitions and abbreviations are listed in Appendix 6.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description *of the change a*nd the rationale.

VIII. Review of Key Questions

As this is a comparative effectiveness review (CERs), the key questions were posted for public comment and finalized after the comments were reviewed.

IX. Technical Expert Panel (TEP)

We will select a TEP to provide broad expertise and perspectives specific to the topic under development. The TEP will not perform analysis of any kind nor contribute to the writing of the report.

The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived to be healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions,

study designs, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report, and recommend approaches to specific issues as requested by the EPC. The TEP does not perform analyses of any kind nor does it contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewers may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic.

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APPENDIXES

APPENDIX 1:
Allergen-specific immunotherapy

METHOD	APPROACH	FDA APPROVED	AVAILABLE IN THE U.S.	CURRENT STATUS in the U.S.	OTHER COMMENTS
ORAL IT Oral Immunotherapy	**Oral Aqueous [OIT]** (Swallowed in 2 ounces of water or juice)	NO	**YES**	Clinical trials	Only off-label use
	Sublingual aqueous [SLIT] (held under tongue x 2 minutes then swallowed)	NO	**YES**	Clinical trials	Only off-label use
	Sublingual tablet (dissolvable tablet; held under tongue) Grazax Oralair	NO	NO	Clinical trials	Available and approved in Europe
	Liposomes/Polymers (microencapsulated/enteric/liposomal/polymer coat)	NO	NO	Pending clinical trials	--
SCIT Subcutaneous Immunotherapy	Aqueous	**YES**	**YES**		Approved and available in the US for allergic rhinoconjunctivitis and asthma in adults and children
	Conventional Adjuvants	Alum**: YES**	Alum: **YES**		--

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	(Alum,CaCl,etc)	Others: NO	Others: NO		
	Immunostimulatory Adjuvants (CpG, MPL)	NO	NO		Experimental
	Peptide constructs	NO	NO		Experimental
	Recombinant allergens	NO	NO		Experimental
	Polymerized allergens	NO	NO		Approved in South America
	Allergoids	NO	NO		Approved in Europe
OTHER	Epicutaneous	NO	NO	No U.S. studies	Recent European reports.
	Intranasal	NO	NO		Studied in the past
	Intrabronchial	NO	NO		Studied in the past
	Lymph node injection of allergens	NO	NO		Recent European reports.
OLD TECHNOLOGIES	Autovaccines Autogenous vaccines (bacterial)	NO		NO	
	Repository therapy Emulsified allergens	NO		NO	

Immunotherapy, as practiced by allergists in the United States, is based principally on the use of aqueous extracts (of allergens). In fact, the only other construct that has FDA approval is an alum-based product. However, in Europe, various modified allergens are approved, and in use, including allergoids (formaldehyde-linked extracts), polymerized constructs (typically gluteraldehyde-linked polymers), and tyrosine-absorbed products (allowing for slow-release of the allergen). Furthermore, various combinations of these entities are in use in Europe. [See "Background" section of AHRQ document]. Additionally, adjuvants afford the opportunity to "energize" the immunotherapeutic vaccine by incorporating immunostimulatory DNA into the allergen construct. Examples of adjuvants include CpG [immunostimulatorysequences based on a cytosine phosphorylated to guanosine (CpG) backbone in which the CpG is covalently linked to the allergen moiety (eg: ragweed Amb a 1)] and MPL [Monophosphoryl Lipid A)] which is mixed with the allergen. [Of note, CpG is derived from mycobacterium bovis, whereas, MPL is derived from staphylococcus].

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APPENDIX 2:

ALLERGEN UNITAGE SPECIFICATIONS, CHARACTERIZATION, AND STANDARDIZATION

UNITAGE SPECIFICATIONS

BIOEQUIVALENT ALLERGY UNITS/ML (BAU/ML)- biological potency unit assigned to standardized grass pollen and cat allergenic extracts, following in-vitro comparison of the test extract to a FDA CBER reference standard. The FDA CBER reference standard is assigned a specific BAU unitage based on quantitative skin testing.

ALLERGY UNITS/ML (AU/ML) - biological potency unit assigned to standardized mite and short ragweed pollen allergenic extracts, following in-vitro comparison of the test extract to a FDA CBER reference standard. The FDA CBER reference mite standard is assigned a specific AU unitage based on quantitative skin testing. For the short ragweed pollen allergen extract FDA CBER reference mite standard is assigned a specific AU unitage based on specific ragweed allergen content.

MAJOR PROTEIN UNITS (mcg Ag/ML) – micrograms of the major protein moiety(s) of the specific allergen (e.g. ragweed, Amb a 1; cat, Fel d 1)

PROTEIN NITROGEN UNIT (PNU) - potency unit based on the micro-Kjeldahl measurement of protein nitrogen in an acid precipitated extract. Compared with other protein determination methods, 1 mg of protein nitrogen typically equals 100,000 PNU.

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WEIGHT TO VOLUME (W/V) - potency unit expressed as a ratio of the weight of allergen source material extracted to the volume of diluting fluid, and adjusted based on subsequent dilutions.

HISTAMINE EQUIVALENT PRICK (HEP) – histamine equivalent prick unitage for standardization of an allergen.

BIOLOGIC UNITS/ML (BU/ML) – biological unitage assigned to define allergen potency.

STANDARDISED QUALITY-**UNIT** (SQ-U) - biological potency unit assigned to certain allergen extracts by a manufacturer.

OTHER – we will include other allergen characterization unitage were noted in a paper.

CHARACTERIZATION AND STANDARDIZATION

Many (some) of the allergens currently commercially available for use have been characterized by manufacturers or researchers based on major (and minor) proteins, but many others (most trees, molds, and pollens) have not. The FDA has characterized and standardized certain of the allergens that are currently commercially available (see below). The FDA feels that "biological" potency is a more robust and accurate methodology for assaying allergens as opposed to major protein, alone (ie: various other proteins in an allergen's make-up may be important and would be overlooked by only assaying and defining a product based on 1 or 2 proteins). Hence, the FDA and the WHO are not in agreement on standardization, and the U.S. and European manufacturers "march to a different drum" (often their own internal standardization methods (SQ units/IR units/etc)].

FDA STANDARDIZED ALLERGENS:

a) Ragweed: FDA actually standardized this allergen based on Amb a 1 content prior to the development of BAU/AU (and because 95% of RW's allergenicity is recognized as being due to Amb a 1, they never felt the need to rename it based on BAU) [a RW extract containing 350 +/- 20% mcg Amb a 1 would be considered = to a 100,000 AU product];

Background Information: "FDA would like to add the following unit of measure to UCUM: Amb a 1 Units/ML – an arbitrary unit for the measurement of Amb a 1, a 38 kD glycoprotein that is the major allergen in short ragweed pollen allergen extracts. The amount of Amb a 1 units are determined by an in-vitro comparison of a test short ragweed extract to a FDA CBER Amb a 1 reference standard.

Antigen E and Amb a 1 are synonymous. Antigen E is the old term that was in the regulations for allergenics back in the 80s. The more up-to-date scientific name is Amb a 1. [However, you will still have manufacturers using the old term of Antigen E since that is in their license].

In the old regulations (which have since been removed), the Radial Immuno Diffusion (RID) method for determining Antigen E potency was specified. The number of units/ml is simply that which is obtained by comparison of a test sample (lot for release) against the US reference standard that has a labeled content of Antigen E (also a US reference preparation of anti-antigen E serum is used in the test). The requirement is for the assayed value of the US reference for antigen E to be within +/- 25% of the labeled value.

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The general working theory is that a Unit/mL of Antigen E(Amb a 1) is equivalent to a microgram of AntigenE(Amb a 1)/mL but we are still looking for solid references discussing this fact - this was not an FDA mandated unit expression due to the incorporation of the old methods specified under the regulation into the firm's BLAs under 52 FR 37605. FDA has not since initiated the legal process required under the 680s for a unit change (see below discussion on BAU/mL). The benefit of a unit change for allergenics always has to be balanced against the risk to patients on incorrect dosing that may occur despite all best education efforts when such a change is made".

1.Amb a 1 is the up-to-date term for the short ragweed pollen allergen that was originally described as Antigen E. They are synonyms. Although Antigen E is no longer used in the scientific literature, its meaning is unambiguous. The manufacturers are still licensed to use Antigen E as the designation.

2.Amb a 1 U = AgE U

3.The relationship between AgE U and BAU (350 AgE U/mL = 100,000 BAU/mL) was based on studies done decades ago, reportedly on 15 study subjects. CBER considered mandating a conversion to BAU/mL in the labeling of short ragweed pollen products, based on AgE content, but this was never implemented.

4.CBER provides two US standard reagents to manufacturers for their determination of Amb a 1 content, a reference standard and a reference serum. The assay used is a radial immunodiffusion assay (RID).

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5.Solid references discussing the relationship between Antigen E U/mL/Amb a 1 U/mL and micrograms of Antigen E U/mL/Amb a 1/mL are being researched]".

b) Grasses: Bermuda grass (10,000 BAU/ml) and eight related Northern Pasture grasses [Timothy, Kentucky bluegrass, perennial rye grass, orchard grass, meadow fescue, red top, and sweet vernal] (expressed as 100,000 BAU/ml); these were initially standardized by quantitative skin testing in highly allergic subjects, and subsequently standardized to the standard extract by in vitro methods];

c) House Dust Mites (Dermatophagoides pteronyssinus and farina): expressed as either 10,000 or 5,000 BAU/mL [initially standardized by quantitative skin testing in highly allergic subjects (identified by hx), and subsequently standardized to the standard extract by in vitro methods];

d) Cat hair or pelt: The potency of Standardized Cat Hair Extract is based on the amount of Fel d 1 allergen in the extract. Extract containing 5-9.9 units per mL is assigned a potency of 5,000 Bioequivalent Allergy Units (BAU/mL). Extract containing 10-19.9 Fel d1 units is assigned a potency of 10,000 BAU/mL. [BAU/mL values are based on quantitative skin testing].

Background Information: "The primary allergen of Standardized Cat Hair Extract is Fel d1. Standardized Cat Pelt Extract contains Fel d1, as well as non-Fel d1 allergens. The latter are believed to be components of cat serum, such as albumin. Pelt extracts have a higher protein content than hair extracts, and the isoelectric focusing (IEF) pattern of the pelt extract reveals protein bands that are not present in cat hair extracts. The IEF pattern of cat hair extracts shows primarily Fel d1 allergen without serum components. The importance of Fel d1 as a means of standardizing the potency of cat extract is based on the following observations:

The intensity of skin reactions to cat extract correlates with the Fel d1 content of the extract in most cat sensitive patients1; the absorption of cat extract with monospecific antisera to Fel d1 causes a reduction in the allergenic activity of cat extract1; the precipitin arc of Fel d1 in cat extract binds most of the IgE antibody in sera obtained from cat-allergic individuals"].

WHO standardized extracts also include dog (based on Can 1), alternaria (based on Alt 1), and various grasses (based on Phl p 5; Lol p 1; etc), birch (based on Bet v 5).

APPENDIX 3:

AIRBORNE ALLERGENS

I) TREES

Family	Genus/Species	Common Name
Aceraceae	*Acer negundo*	Box elder
	Acer saccharum	Sugar Maple
Betulacae	*Alnus incana*	American hazelnut
	Corylus Americana	Red birch
	Betula nigra	White birch
Casuarinaceae	*Casurina equisetifolia*	Australian pine
Cupressaceae	*Cupressus arizonica*	Arizona cypress
	Juniperus ashei	Mountain cedar
	Juniperus virginana	Red cedar
	Taxodium distichum	Bald-cypress
Fabaceae	*Acacia spp*	Acacia
	Prosopis grandulosa	Mesquite
Fagaceae	*Fagus grandifolia*	American beech
	Quercus velutina	Black oak
	Quercus rubra	Red oak
	Quercus alba	White oak
	Quercus agrifolia	California live oak
Hamamelidaceae	*Liquidambar styraciflua*	Sweet gum
Juglandaceae	*Carya alba*	White hickory
	Carya illinoensis	Pecan
	Juglans nigra	Black walnut
	Juglans regia	English walnut
Moraceae	*Broussonetia papyrifera*	Paper mulberry
	Morus rubra	Red mulberry

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Myricaceae	*Myrica cerifera*	Bayberry/wax myrtle
Oleaceae	*Olea europaea*	Olive
	Fraxinus pennsylvanica	Red/green ash
	Ligustrum vulgare	Privet
Platanaceae	*Platanus occidentalis*	American sycamore
	P. racemosa	California sycamore
	Platanus x acerifolia	London plane
Salicaceae	*Populus monilifera*	Western connonwood
	Populus deltoids	Eastern cottonwood
	Populus alba	White popular
	Salix nigra	Black willow
Ulmaceae	*Ulmus americana*	American elm
	Celtis occidentalis	Hackberry

Middleton's Allergy: Principles and Practice, 6th edition 2003. Volume 2 Chapter 33 pgs 533-534

II) GRASSES

Sub Family	Genus/Species	Common Name
Chloridoids	*Cynodon dactylon*	Bermuda grass
Panicoids	*Paspalum notatum*	Bahia grass
	Sorghum halepense	Johnson grass
Pooids	*Dactylis glomerata*	Orchard grass
	Festuca pratensis (elatior)	Meadow fescue
	Lolium perenne	Perennial ryegrass
	Poa pratensis	Kentucky bluegrass
	Agrostis gigantea (alba)	Redtop, bent grass
	Anthoxanthum odoratum	Sweet vernal grass
	Phleum pratense	Timothy grass

Middleton's Allergy: Principles and Practice, 6th edition 2003. Volume 2 Chapter 33 pgs 533-534

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III) WEEDS

Family	Genus/Species	Common Name
Amaranthaceae (inc. Chenopodideae)	*Allenrolfea occidentalis*	Iodine bush
	Amaranthus retroflexus	Rough pigweed
	Amaranthus spinosus	Spiny pigweed
	Amaranthus hybridus	Careless weed
	Atriplex wrightii	Annual saltbush
	Atriplex polycarpa	Allscale
	Atriplex lentiformus	Lenscale
	Chenopodium album	Lamb's quarter
	Chenopodum botrys	Jerusalem oak
	Kochia scoparia	Burning bush
	Salsola kali	Russian thistle
Asteraceae	*Ambrosia artemisiifolia*	Short ragweed
	Ambrosia trifida	Giant ragweed
	Ambrosia psilostachya	Western ragweed
	Artemisia tridentata	Sagebrush
	Artemisia vulgaris	Mugwort
	Baccharis spp	Groundsel-tree
	Eupatorium capillifolim	Dog fennel
	Iva xanthifolia	Burwood marsh elder
	Xanthium strumarium	Cocklebur
Plantaginaceae	*Plantago lanceolata*	English plantain
Polygonaceae	*Rumex acetosella*	Red sorrel
	Rumex crispus	Curly dock
Urticaceae	*Urtica dioica*	Nettle
	Parietaria spp	Pellitory

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IV) SOURCES OF INDOOR ALLERGENS:

A) Animals	Mammals Domestic animals (pets)	a) Cat b) Dog c) rabbits d) ferrets e) Horse f) Cow
	Rodents (Pests)	a) mice b) rats (Rattus norvegicus) c) gerbils d) guinea pigs d) hamsters
B) Acarids (Arachnids):	House dust mites	a) Dermatophagoides farina b) Dermatophagoides pteronyssinus c) Bromia tropicalis d) Euroglyphus maynei e) Storage mites
	Other Acarids:	a) spiders b) silverfish (centipedes)
C) Insects:	Cockroaches	a) Blattella germanica (German) b) Periplaneta Americana (American) c) Blatta orientalis (Oriental)
	Other Insects	a) Moths

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b) Fleas
c) Crickets
d) Flies
e) Beetles

V) FUNGI

A. Inside home [grow in damp areas/rotting wood]

a) Penicillium b) Aspergillus
c) Cladosporium
d) Other species

B. Outside home [enter home w/ incoming air]

a) Alternaria
b) Cladosporium
c) Helminthosporium
d) Epicoccum
e) Botrytis
f) Fusarium
g) Phoma
h) Stemphylium
i) Rhizopus
j) Geotrichum
k) Rusts/Smuts
l) Basidiospores
m) Candida
n) Trichophyton

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o) Other

VI) ALLERGENS NOT INCLUDED IN THIS REVIEW:

a) Foods
b) Medicines
c) Latex
d) Occupational
e) Chemicals
f) Miscellaneous

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APPENDIX 4:

COMPARATORS

Comparator	SCIT	Oral AQ /SLIT-AQ
NON-SIT	YES	YES
SCIT	YES*	YES
SLIT-AQ/ Oral-AQ	YES	YES*
SLIT-Tablet	NO	NO
Other	NO	NO

Table of comparators and definitions

Treatments (**) to be included in the review;

Non-SIT**:

a) placebo; pharmacotherapy; usual care; environmental control; homeopathy

SCIT**:

a) U.S. FDA-approved aqueous extracts for SCIT

b) U.S. FDA-approved alum extract (and the comparable non-pyridine European alum products)

Oral IT:

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a) Oral-swallow IT**: an aqueous allergen extract (which is swallowed) - available in U.S. as off-label products from U.S. manufacturers (and the comparable aqueous extracts from European manufacturers) [off-label in U.S.; approved in EU]

b) SLIT-AQ**: aqueous sublingual extracts - available in U.S. as off-label products from U.S. manufacturers (and the comparable aqueous extracts from European manufacturers) [off-label in U.S.; approved in EU]

Treatments to be excluded (§§) from the review:

c) SLIT-Tablet[§§]: sublingual dissolvable tablet products [not available in U.S.; approved in Europe (eg: Grassex; Oralair)]

Modified Allergens[§§]: tyrosine-absorbed extracts; allergoids; polymerized allergens [not available in U.S.; approved in Europe]

Adjuvants[§§]: CpG-oligonucleotides; MPL; alum-precipitated extracts; pyridine-extracted alum extracts [not available in U.S. except in clinical trials; some approved in Europe]

Peptides[§§]: treatment with specific allergen epitope sequences [not available in U.S. or Europe except in cx trials]

Recombinant Allergens[§§]: alteration of the allergen molecule by substitution of an amino acid [not available in U.S. or Europe except in cx trials]

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Combination Products[§§]: European products in which several of the above are coupled (ex: Timothy Quattro: aqueous Timothy grass extract prepared as an allergoid modification + Tyrosine absorption + incorporation of an MPL adjuvant onto the molecule)

Other[§§]: lymphatic injection of allergen; local nasal IT; bronchial inhaled IT; epicutaneous IT; etc [not available in U.S. or Europe except in clinical trials]

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APPENDIX 5:

SPECIFIC OUTCOMES FOR RHINOCONJUNCTIVITIS OR ASTHMA STUDIES

A) Rhinitis Studies:

Typically, one of these clinical endpoints is defined as the "primary" endpoint and then the others fall to "secondary" endpoints.

Primary Outcomes:

a) Symptom diary score [eg: TNSS (Total Nasal Symptom Score); TSS (Total Symptom Score)]

b) Medication score

c) Combined symptom-medication scores

Additional Secondary Endpoints:

a) Individual symptoms (sneezing/nasal congestion/rhinorrhea/itchy nose/ocular symptoms/etc)

b) QOL

c) symptom-free days

d) Days with no use of rescue medicine (eg: antihistamine; decongestant)

e) Visual analog score

f) Asthma symptoms (asthma may develop in a pt for the first time during the study)

g) Adverse events

h) Safety blood indices

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Biomarkers:

Various biomarkers may be measured, but only "change in skin test reactivity" (in-vivo) and "change in antibody" (in-vitro) are accepted indicators of a therapeutic response that correlates with effect; various studies have shown "associations" between certain cytokines or mediators and clinical change (but these are observations and not validated criteria -- not accepted as surrogate markers by a regulatory agency or society

a) Antibody measurements (IgG/IgG4/IgE)

b) Certain cytokines (IL-10/IL-4/IL-5/IL-13/IL-17/TNFa/TGFb/myriad of others)

c) Mediators (histamine/PGs/LTs); albumin; mucus markers

d) Nasal eosinophils (eos markers)

e) Others

<u>B) Asthma Studies:</u>

Essentially the same methods for assessing clinical response

Primary Outcomes:

a) Symptom diary score [eg: TASS (Total Asthma Symptom Score)]

b) Asthma medication score

c) Combined asthma symptom-medication scores

Additional Secondary Endpoints:

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a) Individual symptoms (wheezing/chest tightness/shortness of breath/cough)

b) QOL

c) Symptom-free days

d) Days with no use of rescue medicine (eg: albuterol)

e) Visual analog score

f) Asthma exacerbations

g) PEFR (peak expiratory flow readings; done at home)

h) Pulmonary function tests (FEV1/FVC/ratio)

i) Adverse events

j) Safety blood (to assess effect of disease or study drug)

Biomarkers:

a) Antibody measurements (IgG/IgG4/IgE)

b) Certain cytokines (IL-10/IL-4/IL-5/IL-13/IL-17/TNFa/TGFb/myriad of others)

c) Sputum eosinophils (eos markers)

d) Exhaled nitric oxide

e) Others

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APPENDIX 6:

DEFINITIONS

1) Conditions:

a) Allergic rhinitis/conjunctivitis (SAR vs. PAR vs. NAR):

i) SAR (Seasonal allergic rhinitis/conjunctivitis) is an allergic condition that occurs on a seasonal basis (e.g.: spring; summer; fall) characterized by nasal and ocular symptomatology (itchy and watery eyes, itchy and runny nose, nasal congestion, sneezing, post nasal drip and itchy throat). It is triggered by exposure to seasonal pollens [trees (spring-early summer)/grasses (late spring-summer)/weeds (classically late summer-fall; although select weeds pollinate in spring-summer) and mold spores (when leaves fall in autumn). Symptoms may be episodic or persistent (lasting through the course of the season).

ii) PAR (Perennial allergic rhinitis/conjunctivitis) is an allergic condition that typically occurs on a chronic basis throughout the year as a result of exposure to perennial aeroallergens (dust mites/insects/indoor mold/animals). The symptoms may be episodic in nature but are more apt to be persistent because of chronic exposure to the allergen load.

iii) NAR (Non-allergic rhinitis/conjunctivitis: is triggered by exposure to pollutants and irritants (smog/odors/perfumes/diesel exhaust fumes/cigarette smoke/etc), weather factors (changes in temperature, humidity, barometric pressure), and self-limited viral illnesses.

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b) Asthma (Allergic vs. non-allergic asthma)

Asthma is a condition characterized by chest tightness, wheezing, shortness of breath, and/or cough. It can be allergic or non-allergic in nature. It can be intermittent or persistent in pattern. Many patients have an allergic basis to their asthma (allergic inflammation is the subsoil leading to chronic inflammation in/of the airways with the result that both allergic and non-allergic factors perpetuate the problem leading to chronic inflammation and chronic symptoms.

Allergic rhinitis may be a critical precursor condition, and in fact 40-60% of patients with allergic rhinitis go on to develop asthma (conversely, ~60-80% of asthmatics have rhinitis-related problems). Not all patients with asthma are allergic. In non-allergic asthmatics, pollutants, irritants, weather changes, exercise, and infection are pertinent triggers of symptomatology.

i) Allergic asthma: Allergic (extrinsic) asthma is characterized by symptoms that are triggered by an allergic reaction. Allergic asthma is airway obstruction and inflammation that is partially reversible with medication, triggered by inhaled allergens such as dust mite allergen, pet dander, pollen, mold, etc. resulting in asthma symptoms. (Asthma and Allergy Foundation of America, 7/8/10; http://www.aafa.org/display.cfm?id=9&sub=16)

ii) Non-allergic asthma: Non-Allergic (intrinsic) asthma is triggered by factors not related to allergies. Like allergic asthma, non-allergic asthma is characterized by airway obstruction and inflammation that is at least partially reversible with medication, however symptoms in this type of asthma are NOT associated with an allergic reaction. Non-allergic asthma is triggered by other factors such as anxiety, stress, exercise, cold air, dry air, hyperventilation, smoke, viruses or other irritants. In non-allergic asthma, the immune system is not involved in the reaction. (Asthma and Allergy Foundation of America

2) Immunotherapy:

Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection.

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a) Oral IT: oral administration of allergen immunotherapy in which the allergenic material is given in a variety of treatment forms: a) as an aqueous preparation which is swallowed in 1-2 ounces of liquid; b) as an aqueous preparation which is held under the tongue for a pre-determined time and then swallowed or spit out of the mouth; c) Sublingual - SLIT: the administration of an allergen extract as a dissolvable sublingual tablet or an oral aqueous preparation; d) as a micro-encapsuled/liposomal/ enteric-coated/polymer type delivery system wherein the allergenic extract reaches the lymphoid tissue of the small intestine (GALT-associated lymphoid tissue) and is pH-dependent released.

b) SCIT: the administration of an allergen extract by means of a subcutaneous injection.

3) Immunotherapy Outcome Terms:

Disease remission: capability of SIT to result in remission of the disease entity itself; this may be manifest as an effect of continued treatment or may be observed even once SIT is discontinued.
Disease modification: capability of SIT to modify the clinical course and natural history of the disease and attenuate disease symptomatology and underlying pathophysiology.
Modulation of immune system: capability of SIT to modify the immunologic pathways that are responsible for, or play a role in, the disease process.
Immune tolerance: capability of SIT to induce tolerance with suppression of the untoward clinical and immunologic response.
Maintenance control: capability of SIT to provide sustained clinical benefit with continued use.

4) Mechanistic Terms:

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a) Immunoglobulins (Ig): Multi-subunit proteins which function in IMMUNITY. They are produced by B lymphocytes from the Immunoglobulins genes. They are comprised of two heavy chains (Immunoglobulins heavy chains) and two light chains (Immunoglobulins light chains) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms includes monomeric or polymeric forms, and transmembrane forms (B-Cell antigen receptors) or secreted forms (antibodies). They are divided by the amino acid sequence of their heavy chains into five classes; Immunoglobulin A (IgA), Immunoglobulin D (IgD), Immunoglobulins E (IgE), Immunoglobulin G (IgG), Immunoglobulin M (IgM), and various subclasses.

i) IgG: The major immunoglobulin isotype class in normal human serum. There are several isotype subclasses of IgG, for example, IgG1, IgG4, IgG2A, IgG2B.

ii) IgE: An immunoglobulin associated with MAST CELLS. Overexpression has been associated with allergic hypersensitivity (immediate hypersensitivity).

b) T-Lymphocytes: Lymphocytes responsible for cell-mediated immunity. Two types have been identified - cytotoxic (cytotoxic T-cells) and helper T-lymphocytes (helper/inducer Tcells). They are formed when lymphocytes circulate through the thymus gland and differentiate to thymocytes. When exposed to an antigen, they divide rapidly and produce large numbers of new T cells sensitized to that antigen.

ii) Th-2 T cells: Stimulates the humoral immune system. Produces cytokines IL-4, IL-5, IL-6, IL-10, IL-13.

iii) Th-1 T cells: Stimulates the cellular immune system; stimulates macrophages and CD8 T-cells. Produce cytokines IFN-gamma, TNF-beta.

c) Cytokines (IL4/IL5/IL10/etc): Non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner. (MeSH)

i) IL-4: A soluble factor produced by activated T-LYMPHOCYTES that induces the expression of MHC CLASS II GENES and FC RECEPTORS on B-LYMPHOCYTES and causes their proliferation and differentiation. It also acts on T-lymphocytes, MAST CELLS, and several other hematopoietic lineage cells. (MeSH)

ii) IL-5: A cytokine that promotes differentiation and activation of EOSINOPHILS. It also triggers activated B-LYMPHOCYTES to differentiate into IMMUNOGLOBULIN-secreting cells. (MeSH)

iii) IL-10: A cytokine produced by a variety of cell types, including T-LYMPHOCYTES; MONOCYTES; DENDRITIC CELLS; and EPITHELIAL CELLS that exerts a variety of effects on immunoregulation and INFLAMMATION. Interleukin-10 combines with itself to form a homodimeric molecule that is the biologically active form of the protein. (MeSH)

4) Objective Tests:

a) Spirometry (FEV1;FVC;FEV1/FVC ratio)

b) PEFR [peak expiratory flow rate]: as opposed to formal spirometry (which is performed in a physician's office), the patient can use a home peak flow meter (hand-held device) to check his/her peak flow readings on a regular basis. These measurements are simple and easy to do and provide the patient with immediate feedback with which to monitor his asthma and make medication adjustments on a daily basis.

c) PNIF [peak nasal inspiratory flow]: this is principally a research tool that allows measurement of nasal inspiratory flow (and hence nasal patency); in contrast, nasal congestion, as a result of nasal edema and vascular engorgement, would result in impaired nasal flow.

d) Nasal provocation: research tool in which allergen is insufflated into the nose. The challenge methodology allows characterization of both the clinical (symptoms) and objective nasal response to allergen exposure (nasal scrapings/nasal biopsy/lavage for inflammatory mediators/etc).

e) Bronchial provocation: research tool in which allergen is inhaled into the airways in a controlled fashion in order to reproduce allergen-induced asthma symptoms and characterize the patient's allergic response and response to treatment. Again, both subjective and objective clinical parameters can be measured.

f) Conjunctival provocation: research tool in which allergen is placed into the eye (s).

g) Methacholine challenge: research tool in which a chemical irritant
substance is inhaled into the airways in a controlled fashion in order to induce asthma symptoms. It can be used to diagnose asthma, characterize the severity of asthma, and/or assess the patient's response to treatment.

h) Allergen provocation: term to denote allergen challenge to the skin, nose, conjunctiva, and/or lungs.

5) Medications:

a) Corticosteroids

i. Nasal corticosteroid (NCS): Beclomethasone nasal (Beconase), Fluticasone propionate nasal (Flonase), Triamcinolone nasal (Nasacort), Flunisolide nasal (Nasarel), Mometasone nasal (Nasonex), Ciclesonide nasal (Omnaris), Budesonide nasal (Rhinocort), Fluticasone furoate nasal (Veramyst)

ii. Inhaled corticosteroid (ICS): Beclomethasone dipropionate (QVAR, Vanceril, Beclovent)), budesonide (Pulmicort), Flunisolide (Aerobid), Fluticasone propionate (Flovent), Triamcinolone acetonide (Azmacort)

b) Leukotriene antagonist (LTRa): A class of drugs designed to prevent leukotriene synthesis or activity by blocking binding at the receptor level. (MeSH)

i) Montelukast (Singulair), Zafirlukast (Accolate), Zileuton (Zyflo)

c) Antihistamine (Histamine H1 antagonists): Drugs that selectively bind to but do not activate histamine H1 receptors, thereby blocking the actions of endogenous histamine. Included here are the classical antihistaminics that antagonize or prevent the action of histamine mainly in immediate hypersensitivity. They act in the bronchi, capillaries, and some other smooth muscles, and are used to prevent or allay motion sickness, seasonal rhinitis, and allergic dermatitis and to induce somnolence. The effects of blocking central nervous system H1 receptors are not as well understood.

i) Brompheniramine (Dimetapp), chlorpheniramine (Chlor-Trimeton), dimenhydrinate (Dramamine), diphenhydramine (Benadryl), doxylamine (Vicks NyQuil), loratadine (Alavert, Claritin), cetirizine (Zyrtec)

d) Decongestant (Nasal decongestants): Drugs designed to treat inflammation of the nasal passages, generally the result of an infection (more often than not the common cold) or an allergy related condition, e.g., hay fever. The inflammation involves swelling of the mucous membrane

that lines the nasal passages and results in inordinate mucus production. The primary class of nasal decongestants is vasoconstrictor agents. (From PharmAssist, The Family Guide to Health and Medicine, 1993). (MeSH)

i) Pseudoephedrine (Contac, Sudafed), phenylephrine (Sudafed)

e) Cromolyn (Cromolyn sodium): A chromone complex that acts by inhibiting the release of chemical mediators from sensitized mast cells. It is used in the prophylactic treatment of both allergic and exercise-induced asthma, but does not affect an established asthmatic attack. (MeSH)

f) Bronchodilators

i. Short-acting bronchodilator: albuterol (Proventil, Ventolin, Accuneb), Alupent (Metaproterenol), Levalbuterol (Xopenex)

ii. Long-acting bronchodilator (LABA): Salmeterol (Serevent), formoterol (Foradil, Perforomist)

g) Controller drug: Controller medications work over a period of time to reduce airway inflammation and help prevent asthma symptoms from occurring. They should be taken daily, work over time rather than immediately, reduce or prevent inflammation and scarring of airways. (Include inhaled corticosteroids, cromolyn, leukotriene antagonists, long-acting bronchodilators.)
Combination controller (ICS + LABA): fluticasone propionate + salmeterol xinafoate (Advair), budesonide + formoterol (Symbicort)

h) Rescue/relief medication: Rescue/reliever medications are **fast-acting** medications used to relieve asthma symptoms when they occur. These types of medicines are often inhaled directly into the lungs, where they open up the airways and relieve symptoms such as wheezing, coughing, and shortness of breath. But as effective as they are, rescue medications don't have a long-term effect. (Include albuterol, levalbuterol)

i) Placebo: Any dummy medication or treatment. Although placebos originally were medicinal preparations having no specific pharmacological activity against a targeted condition, the concept has been extended to include treatments or procedures, especially those administered to control groups in clinical trials in order to provide baseline measurements for the experimental protocol.

6. Efficacy measures

a) Symptom diary scores: For example: In the diaries participants recorded morning and evening peak expiratory flow as the best of three attempts; perceived asthma severity on a visual analogue scale with high scores indicating worse asthma; and perceived mood on a bipolar scale with high scores indicating better mood.

b) Medication diary scores: For example: In the diaries participants recorded morning and evening peak expiratory flow as the best of three attempts; and medications taken each time.

c) Quality of life (QOL): Asthma Quality of Life Questionnaire: There are 32 questions in the AQLQ and they are in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). The activity domain contains 5 'patient-specific' questions. This allows patients to select 5 activities in which they are most limited and these activities will be assessed at each follow-up. Patients are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all - 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. (Includes strenuous activities (such as hurrying, exercising, running up stairs, sports), moderate activities (such as walking, housework, gardening, shopping, climbing stairs), social activities (such as talking, playing with pets/children, visiting friends/relatives), work-related activities, and sleeping.

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d) Safety terms [adverse events (AE); serious AE (SAE); anaphylaxis]

i) Adverse events (AE): An injury caused by medical management–rather than by the underlying disease–which prolongs hospitalization, produces a disability at the time of discharge, or both. Etiology: Drug effects, wound infections, technical complications, negligence, diagnostic mishaps, therapeutic mishaps, and events occurring in the emergency room. (McGraw Hill Concise Dictionary of Modern Medicine, 2002)

aa) An adverse event is any undesirable experience associated with the use of a medical product in a patient. (Food and Drug Administration, 2009: http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm)

ii) Serious adverse events (SAE): The event is serious and should be reported when the patient outcome is: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or requires intervention to prevent permanent impairment or damage. (Food and Drug Administration, 2009)

iii) Anaphylaxis: An acute hypersensitivity reaction due to exposure to a previously encountered ANTIGEN. The reaction may include rapidly progressing URTICARIA, respiratory distress, vascular collapse, systemic SHOCK, and death. (MeSH)

7) Other Terms

a) Efficacy: measure under ideal conditions; e.g.: demonstrated in clinical trial

b) Effectiveness: measure under field conditions; e.g.: demonstrated in practice

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