*Workshop summary*

# Mind the gaps: Clinical trial concepts to address unanswered questions in aeroallergen immunotherapy—An NIAID/AHRQ Workshop

**Lisa M. Wheatley, MD, MPH,[a] Robert Wood, MD,[b] Kari Nadeau, MD, PhD,[c] Andrew Liu, MD,[d] Edward Zoratti, MD,[e] Leonard Bacharier, MD,[f] Erica Brittain, PhD,[g] Moises Calderon, MD,[h] Thomas Casale, MD,[i] Bradley Chipps, MD,[j] Linda Cox, MD,[k] Peter S. Creticos, MD,[l] Manisha Desai, PhD,[m] Sten Dreborg, MD, PhD,[n] Stephen Durham, MD, FRCP,[h] Peter J. Gergen, MD, MPH,[a] Rebecca Gruchalla, MD, PhD,[o] Harold Nelson, MD,[p] Robyn E. O'Hehir, PhD, FRACP, FAHMS,[q] Marshall Plaut, MD,[a] Julie M. Schwaninger, MS,[a] Stephen Tilles, MD,[r] Brian Vickery, MD,[s] Kim M. Wittenberg, MA,[t] and Alkis Togias, MD[a]**

*Rockville and Baltimore, Md, Stanford and Sacramento, Calif, Aurora and Denver, Colo, Detroit, Mich, St Louis, Mo, London, United Kingdom, Tampa and Fort Lauderdale, Fla, Uppsala, Sweden, Dallas, Tex, Melbourne, Australia, Seattle, Wash, and Chapel Hill, NC*

**The Agency for Healthcare Research and Quality and the National Institute of Allergy and Infectious Diseases organized a workshop to develop trial concepts that could improve the use and effectiveness of aeroallergen immunotherapy (AAIT). Expert groups were formed to accomplish the following tasks: (1) propose a study design to compare the effectiveness and safety of subcutaneous versus sublingual AAIT; (2) propose a study design to compare the effectiveness and safety of AAIT by using 1 or a few allergens versus all or most allergens to which a patient is sensitized; (3) propose a study design to determine whether AAIT can alter the progression of childhood allergic airways disease; and (4) propose a study design to determine the optimal dose and duration of AAIT to achieve maximal effectiveness with acceptable safety. Study designs were presented by the workgroups, extensively discussed at the workshop, and revised for this report. The proposed trials would be of long duration and require large highly characterized patient populations. Scientific caveats and feasibility matters are discussed. These concepts are intended to help the development of clinical trials that can address some of the major questions related to the practice of AAIT for the management and prevention of allergic airways disease. (J Allergy Clin Immunol 2019;143:1711-26.)**

***Key words:*** *Aeroallergen, immunotherapy, asthma, allergic rhinitis, rhinoconjunctivitis, multi-allergen, prevention*

Aeroallergen immunotherapy (AAIT) has been used for more than 100 years, and its efficacy in allergic rhinitis and asthma has been well established. Until the last decade, AAIT in the United States was delivered only through subcutaneous injections, but

From [a]the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville; [b]Johns Hopkins University, Baltimore; [c]Stanford University; [d]Children's Hospital Colorado and University of Colorado School of Medicine, Aurora; [e]Henry Ford Hospital, Detroit; [f]Washington University School of Medicine, St Louis; [g]the Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville; [h]Imperial College London; [i]the University of South Florida, Tampa; [j]Capital Allergy and Respiratory Disease Center, Sacramento; [k]Nova Southeastern University, Fort Lauderdale; [l]Johns Hopkins University School of Medicine, Baltimore; [m]the Quantitative Sciences Unit, Stanford University; [n]Uppsala University; [o]the University of Texas, Southwestern Medical Center, Dallas; [p]National Jewish Health, Denver; [q]the Alfred Hospital and Monash University Medical School, Melbourne; [r]the University of Washington, Seattle; [s]North Carolina Children's Hospital, University of North Carolina at Chapel Hill, Chapel Hill; and [t]the Center for Evidence and Practice Improvement, Agency for Healthcare Research and Quality, Rockville.

The workshop was supported by funds from the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases (NIAID). The associated AHRQ product was funded under contract no. HHSA 290-2007-10061-I (Task Order 2) from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services (HHS). The authors of this manuscript are responsible for its content. Statements in the manuscript do not necessarily represent the official views of or imply endorsement by AHRQ, NIAID, or HHS.

Disclosure of potential conflict of interest: R. Wood receives grants from the NIH/NIAID, DBV, Astellas, Sanofi, and HAL Allergy and receives royalties from UpToDate. A. Liu receives personal fees from Merck Sharpe & Dohme, and from Phadia Thermo Fisher. E. Zoratti receives grants from the NIH/NIAID. M. Calderon receives consultancy fees from ALK-Abelló, Merck, Allergopharma, and Hal Allergy and lecture fees from ALK-Abelló, Merck, Allergopharma, Hal Allergy, and STGG. T. Casale receives grant support and consultant fees from Stallergenes. B. Chipps receives speakers' honoraria from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Novartis, Regeneron, Sanofi, and Teva. P. S. Creticos receives grants and personal fees from Stallergenes-Greer, Circassia, and Merck and personal fees from ASIT, Allergy Therapeutics, and UpToDate. S. Durham reports grants from ALK-Abelló, the Food Standards Agency (United Kingdom), the Medical Research Council (United Kingdom), GlaxoSmithKline, and the National Institutes of Health (NIH) and personal fees from Anergis, Biomay, Allergy Therapeutics, Med Update, and Tori Pharmaceuticals. R. Gruchalla reports grants from NIH/National Institute of Allergy and Infectious Diseases Biologics Evaluation and Research and personal fees from Consulting Massachusetts Medical Society. S. Tilles receives grants and personal fees from DBV Technologies, Genentech, and the Immune Tolerance Network; receives grants from Aimmune, Astellas, Stanford University, Amgen, Circassia, Gilead, GlaxoSmithKline, Merck, Novartis, Pulmagen, Teva, Mylan, AstraZeneca, and FARE; and receives personal fees from Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 25, 2018; revised January 8, 2019; accepted for publication January 22, 2019.

Available online February 5, 2019.

Corresponding author: Lisa M. Wheatley, MD, MPH, Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane MSC9827, Bethesda, MD 20892. E-mail: lisa.wheatley@nih.gov.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749

Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

https://doi.org/10.1016/j.jaci.2019.01.032

*Abbreviations used*
AAIT: Aeroallergen immunotherapy
AHRQ: Agency for Health Care Research and Quality
HDM: House dust mite
PAT: Preventive Allergy Treatment
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TCRS: Total Combined Rhinitis Score

sublingual administration is now an established form as well. Immunotherapy with a variety of aeroallergens is effective in those with both seasonal and perennial allergic rhinitis, as well as in patients with asthma associated with sensitization to perennial allergens.[1] A distinctive feature of AAIT is its ability to induce allergen-specific clinical tolerance that persists after discontinuation of treatment.[2,3] Additionally, AAIT used in childhood can alter the natural history of allergic airway disease and prevent asthma development.[4,5] These attributes appear to be unique for AAIT compared with other available treatment modalities and constitute significant advantages of this form of treatment for allergic diseases.

Despite these advantageous characteristics, AAIT has several limitations, including a requirement for prolonged treatment, the risk of systemic allergic reactions sometimes progressing to severe anaphylaxis, and a clinical response effect size that has not, under the best circumstances, surpassed 50%.[6-8] Thus AAIT is a therapeutic field in which significant opportunities for improvements in both efficacy and patient acceptability exist. Such improvements can derive from the development of new forms of immunotherapy but also from optimizing the dosing and treatment duration of available forms and identifying patients who are most likely to benefit from subcutaneous versus sublingual treatment.

Some of these research objectives were raised by the authors of a comparative effectiveness review that the US Agency for Health Care Research and Quality (AHRQ) commissioned and published in 2013.[1] In this systematic literature review of the effectiveness of subcutaneous and sublingual (with liquid extracts) AAIT in patients with allergic rhinoconjunctivitis and asthma, the investigators who conducted the work identified important knowledge gaps and the need for future research to improve the use of this form of treatment. Consequently, the AHRQ collaborated with the National Institute of Allergy and Infectious Diseases in organizing a workshop entitled "Improving the treatment for allergic rhinoconjunctivitis and asthma through allergen immunotherapy" that took place in June 2015. The workshop, which involved clinical investigators, clinicians, and other health care professionals, was structured around 5 workgroups, each given the task to address the following areas: (1) subcutaneous immunotherapy (SCIT) versus sublingual immunotherapy (SLIT), (2) monoallergen versus multiallergen immunotherapy, (3) whether immunotherapy alters the progression of childhood asthma/allergy, (4) dosing strategies and duration of immunotherapy treatment, and (5) immunotherapy utilization. The goal was not to review these topics but to propose concepts for clinical trial protocols that could adequately address some of the identified gaps.

All workgroups presented their study proposals at the workshop, received constructive input from workshop participants, and revised their proposals accordingly. This report summarizes the clinical trial concepts proposed by each of the first 4 workgroups (Table I). Some workgroups proposed more than 1 trial concept, and 3 additional proposals (Figs E1-E3 and Tables E1-E3) are included in this article's Online Repository at www.jacionline.org. It is hoped that all these concepts will offer a backbone for studies that can be conducted in the near future with investigator-initiated proposals or by funding announcements that could be supported by governmental and nongovernmental organizations.

## GENERAL FEASIBILITY, SAFETY, AND DESIGN CONSIDERATIONS FOR THE PROPOSED CLINICAL TRIAL CONCEPTS

Although the proposed concepts include some details, particularly with regard to sample size calculations, they should be considered frameworks for the design of specific trials to address the questions presented to each workgroup. For each proposed trial concept, it is important to consider a number of feasibility, safety, and design aspects in the development of a full trial protocol.

For example, some trial concepts involve large numbers of participants. These are necessary based on the complexity of the proposed designs. Although funding agencies in many areas of the world are capable and willing to support large trials, simplified versions of some of these designs with narrower objectives or objectives that can be addressed in stepwise fashion might need to be considered.

Because the proposed trial concepts were designed to primarily address the needs of practitioners in the United States, use of currently available allergen extracts requires several considerations. Clinical effectiveness for most of these extracts has not been established, and this constitutes a concern in view of the length, potential effort, and cost of the proposed trial concepts. To address this concern, one approach would be to add allergen provocations (challenges) early in the trials to confirm, through interim analyses, the biologic activity of the extract or extracts in question. Alternatively, small pilot trials can be conducted to assess the same question before initiation of a large trial in which several such extracts will be used.

Another concern is that several extracts are not standardized and therefore their potency can vary significantly between batches, raising safety and efficacy problems. Such matters will need to be addressed in advance by setting up specific standards for allergens to be used in these trials and by generating agreements with the producers of the allergen extracts that will ensure batch consistency over time.

Another topic for consideration is the follow-up period after AAIT discontinuation. The proposed trial concepts were designed with the currently recommended minimum of 3 years of treatment so that participants can receive the potential benefit of the prolonged duration of effect that, as noted above, is one of the major benefits of effective AAIT. A long period of follow-up is generally not included; however, should a positive outcome occur at the time referenced in the design, an extension of the study might need to be considered.

Some of the trial concepts propose inclusion of children or are uniquely conducted with very young children. Although workshop participants agreed that the benefit to children of a therapy that could potentially lead to asthma prevention outweighs the risk of AAIT, including SCIT, special considerations are needed to ensure that all pediatric participants benefit from study

**TABLE I.** Participants in workgroups 1 to 4

| Workgroup 1: SCIT vs SLIT | Workgroup 2: Monoallergen (or oligoallergen) vs polyallergen immunotherapy |
|---|---|
| *Chair*: Robert Wood, MD, Johns Hopkins University<br>*Members*:<br>● Linda Cox, MD, Nova Southeastern University<br>● Stephen Durham, MD, FRCP, Imperial College London<br>● Robyn O'Hehir, PhD, FRACP, FAHMS, Alfred Hospital and Monash University Medical School<br>● Marshall Plaut, MD, NIH/NIAID<br>● Stephen Tilles, MD, University of Washington | *Chair*: Kari Nadeau, MD, PhD, Stanford University<br>*Members*:<br>● Leonard Bacharier, MD, Washington University School of Medicine<br>● Thomas Casale, MD, University of South Florida<br>● Peter Creticos, MD, Johns Hopkins Medicine and Creticos Research Group<br>● Manisha Desai, PhD, Stanford University<br>● Lisa Wheatley, MD, MPH, NIH/NIAID |
| **Workgroup 3: Can allergen immunotherapy alter the progression of childhood asthma/allergy?** | **Workgroup 4: Dosing strategies and duration of allergen immunotherapy** |
| *Chair*: Andrew Liu, MD, Children's Hospital Colorado and University of Colorado School of Medicine<br>*Members*:<br>● Bradley Chipps, MD, Capital Allergy & Respiratory Disease Center<br>● Sten Dreborg, MD, PhD, Uppsala University<br>● Peter Gergen, MD, NIH/NIAID<br>● Brian Vickery, MD, University of North Carolina at Chapel Hill | *Chair*: Edward Zoratti, MD, Henry Ford Hospital<br>*Members*:<br>● Moises Calderon, MD, Imperial College London<br>● Rebecca Gruchalla, MD, PhD, University of Texas, Southwestern<br>● Harold Nelson, MD, National Jewish Health<br>● Alkis Togias, MD, NIH/NIAID |

*NIH/NIAID*, National Institutes of Health/National Institute of Allergy and Infectious Diseases.

participation, and enhanced safety precautions are required. For example, it might be important for the clinical units that will conduct the trials to assume full care of the respiratory illnesses being studied and that free medications are provided to participants so that even children treated with placebo benefit from study participation. In addition, special care should be provided and psychological measures might need to be implemented for children who will receive SCIT or placebo for SCIT to avert the development of needle phobia. Finally, clinical teams will need to receive special training to recognize signs of systemic reactions and treat anaphylaxis in young children. The experience that allergists have acquired in the past decade with oral food challenges and oral immunotherapy for food allergy in very young children should be used to guide safety considerations for AAIT.

In calculating sample sizes, the dropout rate of 15% was chosen for all but the longest trial concept, with the intention of maintaining statistical rigor by avoiding the potential bias introduced by dropout while recognizing the major effort on the part of the clinical staff that is required to retain 85% of participants over a multiyear study. Although difficult, other AAIT studies have been able to meet this standard.[9] However, if 20% is viewed as more realistic, then the planned sample sizes would need to be inflated by 6%. Higher dropout rates have added costs in terms of recruitment, and therefore the clinical effort might balance between retention and recruitment.

## CLINICAL TRIAL CONCEPTS

### Workgroup 1: SCIT vs SLIT

**Charge.** Workgroup 1 was charged with proposing a study design to compare the effectiveness and safety of subcutaneous versus sublingual AAIT.

**Background and recommendations.** Although SCIT has been a standard of care for decades, SLIT is a relatively new treatment option. With the emergence of SLIT, it is essential that clinicians are sufficiently informed regarding the relative benefits and risks of both SLIT and SCIT so that optimal treatment decisions are possible. Unfortunately, although there are numerous studies examining the efficacy of both SLIT and SCIT, including several meta-analyses,[10-17] there have been relatively few studies directly comparing the 2 treatments. For example, with regard to house dust mite (HDM) allergy, an extensive search could locate only 6 such studies, all of which were small and/or open label.[18-23]

The proposed trial concept would study HDM immunotherapy because of this allergen's overall importance on a worldwide basis, as well as its greater relevance to both rhinitis and asthma compared with pollen allergens. Furthermore, we believe that HDM is the ideal candidate for study given that there is a large body of data supporting the efficacy of mite SCIT and an emerging body of data on the efficacy of mite SLIT.[8] Although the primary end point of the proposed trial focuses on allergic rhinitis, it is suggested that secondary data should also be gathered on lower airway responses. These data, in addition to the rhinitis outcomes, will help guide future studies on HDM immunotherapy for asthma with regard to dosing, safety, and overall efficacy.

A variety of potential end points for this trial were considered, and a chamber challenge was believed to provide the best model of response because it most closely mimics natural exposure and would potentially provide information on both upper and lower airway responses to allergen exposure. In addition, a chamber challenge has the advantage of being able to control and measure exposure, providing an equal and adequate provocative dose for all participants.[24] The specifics of the chamber challenge for HDM are described in the recent publication on HDM SLIT by Nolte et al,[25] in which the HDM chamber was successfully used in a multicenter trial. Although confidence is high that chamber challenge is a valid measure of response, how its outcomes relate to those during natural exposure is less clear, and therefore

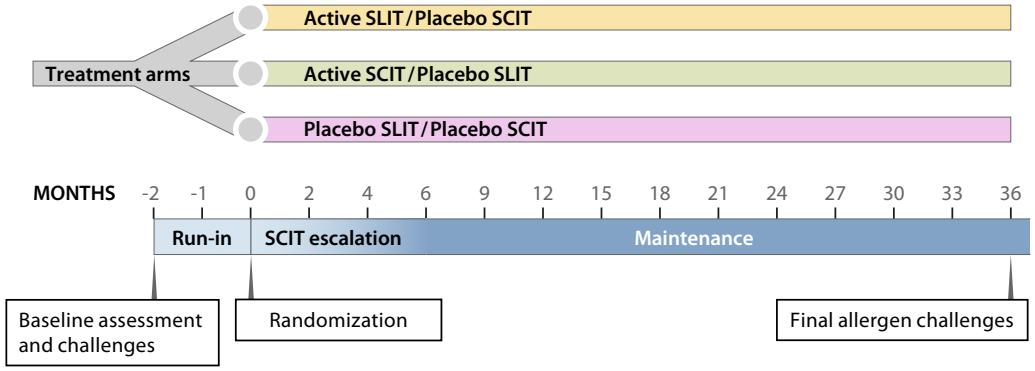


**FIG 1.** Workgroup 1: SCIT versus SLIT trial concept. A study schematic for a randomized, double-blind, double-dummy, placebo-controlled trial comparing HDM SLIT and SCIT with placebo SLIT and SCIT in an environmental chamber challenge is shown.

clinical data will need to be gathered to assess the relationship between the response in the chamber and the effect of treatment on the clinical presentation of airway disease.

**Proposed clinical trial concept.** A comparative trial of HDM SLIT versus SCIT.

**Study objectives.** The primary objective of this study would be to determine whether allergic reactivity to HDM, as assessed based on nasal responses in a chamber challenge, can be equally reduced with HDM SLIT or SCIT. Major secondary objectives include comparisons of the effects of both treatments on lower airway responses to allergen exposure, measures of clinical efficacy outside of the challenge, assessments of safety, and *in vivo* and *in vitro* biomarkers.

**Study design.** For the study design, see Fig 1 and Table II.

**Discussion.** The goal of this study would be to provide clinically meaningful data regarding the relative efficacy of SLIT versus SCIT. Sample size was calculated for a noninferiority study to provide 80% power in determining whether the effects of SCIT and SLIT are within the minimally important clinical difference of 0.5 in Total Nasal Symptom Score.[26] The calculation assumed use of a baseline adjusted linear model with an SD of 2.5 and accounted for 15% loss to follow-up. (Note: All sample size calculations in this article use a 2-sided $\alpha$ value of .05.) A small placebo group ensures that failure to see a difference between SCIT and SLIT is not due to both treatments being ineffective, with 90% power to detect a treatment benefit of 1.42 between each of the active arms and placebo. The sample size was based on a trial in patients with seasonal allergic rhinitis.[27] Given the sensitivity of power to the true SD, it would be prudent to consider a sample size re-estimation based on an interim estimate of variance.

The proposed study has many strengths. First, although the study is large, recruitment should be possible given the high prevalence of HDM allergy. Second, the focus on HDM is justified by its worldwide importance, especially as a perennial allergen that is linked to both allergic rhinitis and asthma. Third, the necessary immunotherapy products are available for HDM, with a standardized extract for SCIT and an approved SLIT product.[8,28]

The most important potential limitation relates to reliance on the chamber challenge for the primary outcome. Although this is a valid measure of response, we do not have the evidence to argue that it can substitute for clinical efficacy, even for the primary end point of allergic rhinitis. Because this study will collect both chamber and clinical data, it is also meant to provide data to determine the role of chamber challenge as a surrogate for the clinical efficacy of such interventions. Importantly, because multiple study sites might be needed for this trial, standardization and between-site agreement of challenge outcomes need to be demonstrated.[24] Because of the number of participants needed for adequate statistical power, the cost of this study could be very high. Therefore consideration could be given to 24 rather than 36 months of AAIT, which would decrease costs and is supported by prior studies[8,9]; however, multiple sources of funding might still be required. Interim analyses can also be introduced to assess futility.

Children were not included in this study because HDM SLIT is not approved for use in those less than 12 years of age, and there are no studies that have evaluated the safety of environmental chambers in children.

The inclusion criteria needed to strengthen confidence that the participants will be clinically allergic while recruitment will be feasible are important aspects of this trial. Both lower and higher skin test and specific IgE cutoffs were considered, as were different combinations of skin test and IgE sensitivity. In the end, the entry criteria chosen should identify sufficiently allergic patients and be feasible from a recruitment standpoint; a positive baseline challenge result is an essential entry criterion.

The ability to assess asthma in the chamber, as well as in the field, should be considered a major strength of this protocol, especially given the importance of HDM in asthmatic patients. Although not powered to specifically address asthma outcomes, stratification to include a sufficient number of participants with asthma should be considered. However, there are concerns about risks to such participants in a chamber challenge if allergen is present in a form that can be delivered to the lower airways. Published studies have included only participants with either no requirement for controller medications or, in one case, asthma that was well controlled by low-dose inhaled corticosteroids.[29] In the latter study most participants with asthma had symptoms in the pretreatment challenge. Inclusion of patients with moderate well-controlled asthma will require close monitoring for asthma symptoms and changes in pulmonary function during the EEC exposure. If more than 1 EEC is to be used in such a trial, another important consideration is that a pilot study will need to be done to ensure between-chamber agreement.

**TABLE II.** Workgroup 1: SCIT versus SLIT trial concept—Synopsis of key elements of the recommended trial concept

| | |
|---|---|
| Study type/description | Randomized, double-blind, double-dummy, placebo-controlled trial comparing HDM SLIT and SCIT with placebo SLIT and SCIT in an ECC |
| Overall study objective | Comparative effectiveness and safety of SLIT vs SCIT |
| Primary study objectives | To determine whether allergic reactivity to HDM, as assessed based on nasal responses in an ECC, can be reduced to an equivalent degree by treatment with HDM SLIT and SCIT |
| Secondary and/or exploratory Study objectives | *To compare SLIT vs SCIT for*:<br>● Effects on lower airway responses<br>● Measures of rhinitis clinical efficacy outside of the challenge chamber<br>● Safety assessments<br>● Effects on immunologic outcomes (antibody, T-cell, and basophil activation responses to treatment)<br>● Effects on biomarkers of allergic inflammation |
| Study population age | 18-55 y |
| Key inclusion/exclusion criteria | *Key inclusion criteria*:<br>● Perennial allergic rhinitis, (preferably without seasonal exacerbations), with or without a history of mild asthma and with positive SPT responses and/or sIgE levels to either *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*<br>● Must have a minimum TNSS within the first 2 hours of a screening HDM chamber challenge<br>● Initial and final challenge must be performed outside of a seasonal allergy period (if applicable)<br>*Key exclusion criteria*:<br>● Chronic rhinosinusitis with or without polyps<br>● $FEV_1$ <70% of predicted value or unstable, uncontrolled, or severe asthma<br>● Other chronic respiratory diseases<br>● History of anaphylaxis or receiving medications that might interfere with treatment of anaphylaxis<br>● Any allergen immunotherapy within the last 5 years or any antiallergic biologic therapy within 1 year<br>● Sensitized to and in regular contact with an animal or sensitized to pests and living in an infested home |
| Sample size | Four hundred sixty-five participants for each active group and 45 placebo-treated participants |
| Interventions and comparators | ● HDM SLIT tablet administered daily plus placebo injection every 4 weeks OR<br>● HDM SCIT using a standardized extract with a maintenance dose of 1500 BAU every 4 weeks plus placebo tablet daily OR<br>● Placebo tablet daily and placebo injections every 4 weeks at maintenance |
| Primary outcome | Average TNSS at week 104 in the ECC (adjusted for baseline value) |
| Secondary and/or exploratory outcomes | *Outcomes during ECC*:<br>● Asthma symptom score<br>● Ocular symptom score<br>● PNIF<br>● PEF or spirometry<br>● Biomarkers of allergic inflammation (eg, peripheral blood and airway eosinophilia, type 2 cytokines or other inflammatory molecules)<br>*Clinical outcomes outside challenge*:<br>● Safety outcomes<br>● Asthma control as assessed by using the ACQ/ACT and exacerbations<br>● RQLQ<br>● TCRS (the sum of the rhinoconjunctivitis daily symptom score and daily medication score)<br>● Immunologic outcomes assessing antibody, T-cell, and basophil activation at baseline and in response to treatment |
| Duration (per participant) | Thirty-six months from start of therapy |

*ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *ECC*, environmental chamber challenge; *PEF*, peak expiratory flow; *PNIF*, peak nasal inspiratory flow; *RQLQ*, Rhinitis Quality of Life Questionnaire; *sIgE*, specific IgE; *SPT*, skin prick test; *TNSS*, Total Nasal Symptom Score.

## Workgroup 2: Monoallergen or oligoallergen versus polyallergen immunotherapy

**Charge.** Workgroup 2 was charged with proposing a study design to compare the effectiveness and safety of immunotherapy using 1 or only a few (2 or 3) allergens (monoallergen and oligoallergen immunotherapy, respectively) versus immunotherapy with all or most of the allergens to which a patient is sensitized (polyallergen immunotherapy). (Note: This question currently applies to SCIT only.)

**Background and recommendations.** Most patients with allergic rhinitis or asthma are sensitized to more than 1 allergen. The multiplicity of allergens results in increased frequency and prolongation of symptoms and more comorbidities (eg, patients with rhinitis and asthma are sensitized to more allergens compared with those with rhinitis alone).[30] Additionally, polyallergic patients might represent a phenotype with more severe clinical symptoms and greater medication requirements.[31] Because of this, there is widespread clinical use of polyallergen immunotherapy, although there are very limited data on the efficacy of polyallergen immunotherapy.

Many studies have reported long-term benefits of SCIT and SLIT using single allergens,[4,6,7,32-55] whereas the number of randomized, controlled clinical studies on polyallergen immunotherapy is extremely limited, and the results are variable, with some studies showing that the therapy is beneficial and others indicating no benefit.[56-66] One school of thought advocates that

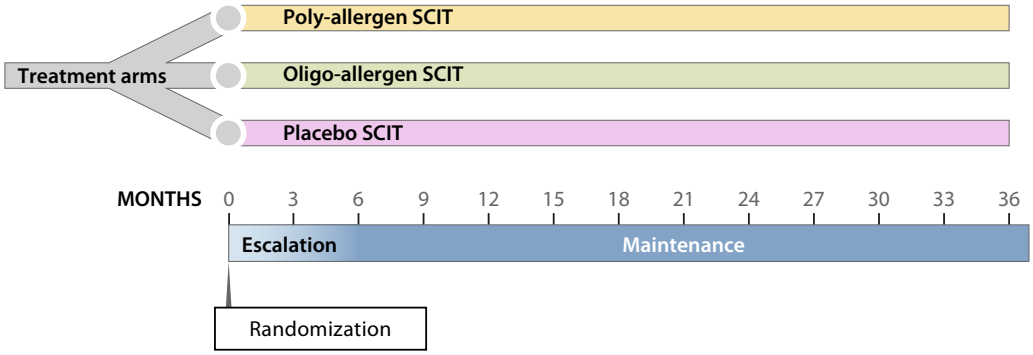


**FIG 2.** Workgroup 2: Oligoallergen versus polyallergen immunotherapy trial concept. A study schematic for a multisite, randomized, double-blind, placebo-controlled field study of polyallergen (Timothy grass and up to 7 other allergens) versus oligoallergen (Timothy grass, oak, and another specified tree allergen) SCIT in subjects with multisensitization to spring tree and grass allergens is shown.

immunotherapy should be limited to 1 or very few allergens that are considered clinically most important for the individual patient. However, monoallergen or oligoallergen versus polyallergen immunotherapy strategies have never been compared in a head-to-head approach.

The assigned task was to compare the therapeutic efficacy of polyallergen immunotherapy, as currently practiced by a majority of allergists in the United States, to immunotherapy with a single allergen or a limited number of allergens.[67]

Planning such a study requires assiduous attention to several critical factors, such as confounding allergen exposures, lack of standardization (or quality characterization) of many of the relevant allergens to be studied, and limited information on appropriate dosing. A clinical trial design that attempts to address sensitivities throughout the year would be difficult in terms of a "window" for assessment of symptom improvement and in terms of complexities related to allergen exposure (uncertainties about the period and extent of allergen exposure and overlapping allergen exposures). Therefore a trial that centers on seasonal pollen exposure was chosen. However, even in this more limited scenario, issues of allergen selection and dosing, overlapping pollen seasons, pollen variation in relationship to climatic conditions, and effects of confounding allergens are still confronted.

A spring seasonal clinical trial was designed in which an oligoallergen would be compared with a polyallergen mix and placebo. The choice of an oligoallergen mix is favored over monoallergen therapy because therapy with a single allergen comparator has the obvious disadvantage of providing coverage over only part of the assessment period. Varying the number of allergens to be included in the mix but in all cases having most of the season represented maximizes the ability to collect symptom-medication diary data during the entire period under observation and optimizes the study's power. It is possible to identify a period of pollination in the spring during which Timothy grass and certain tree allergens would dominate. This would allow selection of patients with Timothy grass allergy who are also required to be sensitive to a subset of predefined trees in the oligoallergen mix.

The proposed study design is a field study that reflects current practices and could be performed at many sites in the United States. The allergens will be selected based on region; therefore treatment mixes will vary, except for the identity set (Timothy grass plus oak and another specified tree), which comprises the oligoallergen mix and will be part of the polyallergen mix. In addition to the identity set, the polyallergen mix will include 3 to 5 additional spring seasonal allergens but should avoid multiple cross-reactive allergens (eg, northern grasses) in favor of different families of trees and grasses.

An algorithm based on prevalence (pollen counts for the given region) and relevance (history and skin test reactivity cutoff) will be needed to select allergens for individual participant mixes. A very important question that this study could answer will be whether the addition of nonstandardized and often poorly characterized tree allergens can provide meaningful clinical benefit in the treatment of allergic rhinitis with allergen immunotherapy.

The trial proposed below represents the workgroup's first priority trial, but 2 additional trial proposals (Figs E1 and E2, Tables E1 and E2) can be found in this article's Online Repository at www.jacionline.org.

**Proposed clinical trial concept.** Multisite, randomized, double-blind, placebo-controlled field study of polyallergen versus oligoallergen SCIT in patients with multisensitization to spring tree and grass allergens.

**Study objectives.** The primary objective of this study is to determine the efficacy and safety of polyallergen SCIT (Timothy grass and 7 other allergens) versus oligoallergen SCIT (Timothy grass, oak, and another specified tree allergen). The hypothesis is that study participants given polyallergen immunotherapy will experience improved outcomes compared with those given oligoallergen immunotherapy (as tested by clinically based outcomes) without a significant increase in systemic reactions to the allergen injections.

**Study design.** For the study design, see Fig 2 and Table III.

**Discussion.** The proposed trial is just one of a panoply of potential studies addressing different aspects of polyallergen versus oligoallergen or monoallergen immunotherapy. As such, it cannot be the single study that proves or disproves the value of polyallergen immunotherapy. Although challenge studies were considered, strength is added to this trial by the field study design in which the primary efficacy end point is the recommended total combined medication and symptom score for allergic rhinitis.[68] Other strengths include the ability to include sites across a broad geographic range, a relatively compact season for assessment of effect, no concerns over allergen degradation caused by mixes containing proteases, similarity to current practices, and the

**TABLE III.** Workgroup 2: Oligoallergen versus polyallergen immunotherapy trial concept—Synopsis of key elements of the recommended trial concept

| | |
|---|---|
| Study type/description | Multisite, randomized, double-blind, placebo-controlled field study of polyallergen vs oligoallergen SCIT in subjects with multisensitization to spring tree and grass allergens |
| Overall study objective | Comparative effectiveness and safety of polyallergen vs oligoallergen SCIT |
| Primary study objectives | To compare the efficacy of polyallergen SCIT (Timothy grass and up to 7 other allergens) vs oligoallergen SCIT (Timothy grass, oak, and another specified tree allergen) on seasonal symptoms and medication requirements for allergic rhinitis |
| Secondary and/or exploratory study objectives | *To compare polyallergen SCIT vs oligoallergen SCIT vs placebo for*:<br>● Safety assessments<br>● Other rhinoconjunctivitis outcome measures<br>● Seasonal asthma outcomes<br>● Effects on immunologic outcomes (antibody, T-cell, and basophil activation responses to treatment)<br>● Effects on biomarkers of allergic inflammation |
| Study population age | 8-55 y |
| Key inclusion/exclusion criteria | *Key inclusion criteria*:<br>● Spring seasonal rhinitis<br>● Sensitized based on SPT responses and/or sIgE levels to at least 6 tree and grass allergens, including Timothy grass and oak<br>*Key exclusion criteria*:<br>● Chronic rhinosinusitis with or without polyps<br>● $FEV_1$ <70% of predicted value or severe or uncontrolled asthma<br>● Other chronic respiratory diseases<br>● History of anaphylaxis or receiving medications that might interfere with treatment of anaphylaxis<br>● Allergen immunotherapy within 5 years or any antiallergic biologic therapy within the past year<br>● Sensitized to and in regular contact with an animal or sensitized to pests and living in an infested home<br>● Preferably asymptomatic or with low levels of perennial rhinitis symptoms |
| Sample size | Five hundred participants per arm |
| Interventions and comparators | Each participant will be randomized to receive 3 years of SCIT (dose escalation and maintenance) with 2 injections as *follows*:<br>● Oligoallergen SCIT: 1 injection containing the identity set* and 1 placebo injection OR<br>● Polyallergen SCIT: 1 injection containing the identity set* and 1 injection containing up to 5 additional spring allergen extracts OR<br>● Placebo: 2 placebo injections |
| Primary outcome | TCRSs averaged over the spring season relative to baseline |
| Secondary and/or exploratory outcomes | ● Safety outcomes<br>● Average rhinoconjunctivitis daily symptom score<br>● Average rhinoconjunctivitis daily medication score<br>● Average weekly RQLQ score<br>● Asthma control as assessed by using the ACQ/ACT and exacerbations during spring<br>● Immunologic outcomes assessing antibody, T-cell, and basophil activation responses to treatment<br>● Component-resolved diagnostics of pretreatment IgE<br>● Biomarkers of allergic inflammation (eg, peripheral blood and airway eosinophilia, type 2 cytokines, or other inflammatory molecules) |
| Duration (per participant) | 3 y |

*ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *RQLQ*, Rhinitis Quality of Life Questionnaire; *sIgE*, specific IgE; *SPT*, Skin prick test.
*Identity Set: Timothy grass plus oak and another specified tree.

anticipated ability to deliver adequate allergen doses.[69] However, it should be noted that none of the tree mixes are standardized and the major allergens have only been characterized for birch and mountain cedar.[70,71] The work by Turkeltaub[70] demonstrates that even the most potent tree allergen extracts are less than 10,000 BAU/mL, which is much lower than grasses (Timothy grass is 100,000 BAU/mL). This presents a limiting factor in determining optimally effective doses. The chosen duration of 3 years of immunotherapy not only aligns with current practice guidelines and potential for sustained benefit but might also help mitigate potential issues with allergen concentration by increasing the cumulative dose. However, given the large number of participants required, pilot studies to address the effectiveness of the tree extracts by using a challenge outcome would be prudent. This protocol does not evaluate a specific polyallergen therapy but rather the concept of polyallergen therapy as currently practiced. There will most likely be inadequate power to enable subgroup analyses to evaluate the benefit of the various components of the polyallergen mix.

SCIT was chosen instead of SLIT for the range of allergens available. Although 8 is the average number of allergens in individual patient SCIT prescriptions in the United States,[67] these prescriptions would frequently include perennial and autumnal allergens that are not part of this trial. Therefore a minimum of 6 spring allergens was chosen to balance the feasibility of recruitment with the feasibility of assessment. Because this study can be conducted over a wide geographic and age range, consistent with current practice, recruiting 500 subjects per arm with spring seasonal allergies should be feasible. Based on prior immunotherapy trials, there is 80% statistical power using a longitudinal

mixed-effects model to detect a 0.6-point difference in change of the Total Combined Rhinitis Score (TCRS) from baseline between the 2 active study arms, assuming an SD of change in TCRS from baseline of 3.1 (based on an SD of TCRS of 4.0 and a within-subject correlation of 0.7) and accounting for 15% loss to follow-up.[72]

This trial design notably does not address perennial allergens, such as HDM or cockroach, which have the strongest association with asthma. Also, the proposed trial does not address the potentially important role that ragweed, an autumnal seasonal allergen, plays in initiating the inflammatory cascade that evolves through the course of early fall through winter with implications for increased susceptibility to viral and bacterial infection. To help address some of these gaps, additional trials (Figs E1 and E2, Tables E1 and E2) are outlined in this article's Online Repository at www.jacionline.org.

## Workgroup 3: Can allergen immunotherapy alter the progression of childhood asthma/allergy?

**Charge.** Workgroup 3 was charged with proposing a study designed to determine whether allergen immunotherapy can alter the progression of childhood asthma or allergic airway disease.

**Background and recommendations.** Despite national and global investments leading to significant improvements in asthma management and control, there continues to be no established intervention to either prevent asthma from occurring or to reduce its persistence or severity in a lasting way. If AAIT can reduce the inflammatory response to allergens that are asthma initiators and additionally prevent the progression of allergen sensitization to other aeroallergens,[73] it could become the first therapeutic intervention to invoke lasting posttreatment severity reduction and prevent asthma.[4,74,75]

Allergen exposure in early life has the potential to prevent development of allergic disease. This was recently and best demonstrated with peanut allergen oral exposure in early life, preventing development of peanut allergy in the Learning Early about Peanut Allergy study.[76,77] Natural history studies suggest that this concept might also be relevant to aeroallergens. For example, exposure to dogs and cats in early life is associated with less allergen sensitization to cat, dog, and other aeroallergens, as well as less asthma.[78-80] In US inner-cities cockroach, mouse, and cat allergen exposures are similarly associated with less recurrent wheeze at age 3 years[81] and less asthma at age 7 years.[82] It is unclear whether the protective effect of these animal/insect allergen exposures is due to the allergens themselves and/or exposure to microbes or microbial products that are associated with these animals and insects.

For AAIT to prevent persistent asthma, modify disease severity, or both, it might be necessary to begin in asthma's formative preschool years. For most patients, asthma begins in the preschool years, at a time when up to 40% of young children[83,84] experience recurrent coughing and wheezing episodes that are primarily provoked by common respiratory tract viruses.[85,86] Although most childhood wheezing resolves without sequelae, some will progress to comprise the majority of children and adults with persistent asthma.[84,87-92] National and international guidelines reflect the established relevance of early-life atopic risk factors in predictive indices for persistent asthma in later childhood.[93,94] Numerous well-executed studies in different locales identify atopy as a major risk factor for persistent asthma in symptomatic toddlers, in particular aeroallergen sensitization in the preschool years.[82,84,95-97] Aeroallergen sensitization with persistent exposure in the homes of symptomatic toddlers predicts asthma persistence, pulmonary dysfunction, and exacerbations and is believed to have a causal role.[98-100] Allergen-driven immune responses and inflammation are believed to affect lung growth and differentiation during this critical developmental period, leading to clinically persistent asthma by the lower school years.[101] Because the strongest predictors of persistent asthma appear to be the establishment of inhalant allergen sensitization by 2 to 3 years of age, intervening to prevent the effects of allergy in the lungs at the earliest point of development should be an important clinical research objective.

There is evidence that AAIT can be effective in preventing asthma in school-aged children. Children at this age with allergic rhinitis and physiologic findings consistent with asthma have increased risk of clinical asthma within several years. In the Preventive Allergy Treatment (PAT) study 54% of children with bronchial hyperresponsiveness to methacholine and 92% of children with reactivity to isocapnic hyperventilation of cold air but without asthma symptoms at enrollment reported a doctor's diagnosis of asthma in the subsequent 2 years.[102] In the same study children with allergic rhinitis but without asthma at enrollment were randomized to treatment with grass and/or birch SCIT and symptomatic medication or medication alone for 3 years. At the end of the 3 years of treatment, children who were treated with SCIT had an odds ratio of 2.52 (95% CI, 1.3-5.1) of not having asthma compared with those receiving medication alone. Additionally, there was improvement in bronchial hyperresponsiveness outside the season in year 3 for those children treated with SCIT (odds ratio, 2.78; 95% CI, 1.2-6.3), an effect that persisted at least to year 7.[4,74] Even rhinitis alone constitutes a major risk factor for the development of asthma: in the German Multicenter Allergy Study birth cohort, for example, 25% of children with allergic rhinitis at age 5 years had wheezing within the next 2 years.[103] Therefore school-aged children with allergic rhinitis could be another appropriate target for an asthma prevention study.

In discussing which form of immunotherapy would be most appropriate for the proposed trial, the workgroup came to the conclusion that SCIT was the best choice for a number of reasons: (1) SCIT might be more effective than SLIT in treating rhinitis, and although systemic allergic reactions are clearly more frequent with SCIT, serious reactions occur rarely (approximately 1/25,000 injection visits based on a population of older children and adults)[102,104]; (2) unlike the PAT study using SCIT, treatment with SLIT in the Grazax Asthma Prevention trial decreased symptomatic asthma but did not decrease the time to asthma diagnosis[105]; (3) the only perennial allergen with efficacy data in SLIT is HDM, and a wider array of allergens might need to be covered; and (4) it is easier to assess compliance with therapy by using SCIT.

The trial proposed below represents the workgroup's highest-priority trial, but an additional trial proposal (Fig E3 and Table E3) on the prevention of asthma in older children with established allergic rhinitis can be found in this article's Online Repository at www.jacionline.org.

**Proposed clinical trial concept.** SCIT in atopic preschool children at high risk for persistent asthma.

**Study objectives.** The primary objective of this study is to determine whether AAIT can prevent persistent asthma and/or

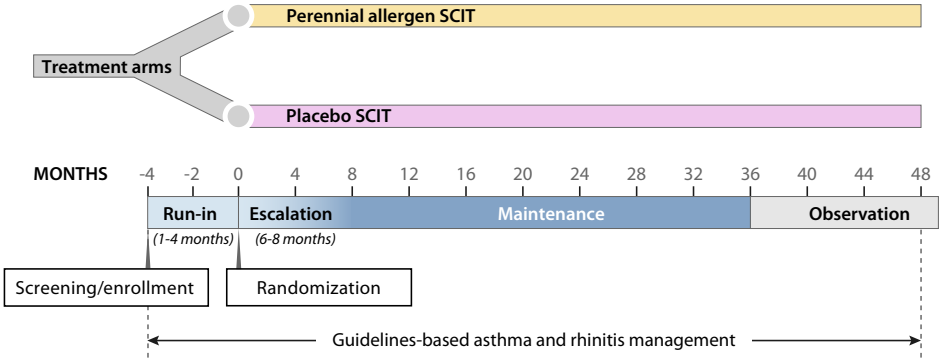


**FIG 3.** Workgroup 3: Allergen immunotherapy for the prevention of asthma trial concept. A study schematic for a randomized, double-blind, placebo-controlled longitudinal study of perennial allergen SCIT administered for 3 years to allergic toddler-age children at high risk for asthma followed by a 1-year observation period is shown.

reduce asthma severity by school age when administered during preschool years in high-risk children.

**Study design.** For the study design, see Fig 3 and Table IV.[106-108]

**Discussion.** This trial was designed to address whether AAIT can alter the progression of recurrent wheezing/childhood asthma in atopic toddlers by using the perennial allergens that are thought to drive this disease. The trial addresses a public health concern and unmet need in asthma prevention.

There are numerous feasibility considerations. Effective allergen dose and safety of AAIT in toddlers have not been determined. In the AAIT updosing phase, SCIT administration is more complicated than SLIT, and more adverse events occur. However, SCIT has the advantage of ensured administration because it is given in the clinic, and during the lengthy maintenance dose phase, the frequency of SCIT administration can be reduced to once every 4 weeks. The effectiveness of the specific allergen extracts, including lots, doses, and compatibility and sustained potency when combining allergens in multiallergen SCIT extracts, would need to be established. Of note, in a recent study by Grier et al[109] extracts in mixtures that contained 5 common sources of indoor allergens (cat, dog epithelia, dog dander, *Dermatophagoides farinae*, and cockroach mix) possessed favorable stabilities and mixing compatibilities, which supports the practice of combining these products in the same patient treatment formulations for SCIT.

Statistical sample size estimates were based on the earlier described PAT study.[75] Two years after SCIT discontinuation, the SCIT-treated children in the PAT study had significantly less asthma compared with the control group, as diagnosed based on clinical symptoms (20% vs 43%). By using these estimated asthma rates, the binary primary end point of the proposed trial could be tested with 100 participants per arm or a total sample size of 200 to obtain 90% power. This sample size accounts for a 15% loss to follow-up/discontinuation rate.

Enrolling more participants would strengthen the power of the study and might be necessary to adequately test additional hypotheses. For example, one conceptual concern about aiming to prevent persistent asthma in at-risk toddlers with indoor allergen sensitization and recurrent respiratory symptoms is that they might already have established persistent asthma that could be immutable to allergy pathway therapeutics, such as AAIT. Because of this concern, one could include participants with a broad range of lower respiratory tract symptoms to determine whether baseline disease severity affects the efficacy of AAIT intervention and to allow stratification of participants with intermittent/mild versus moderate/severe respiratory disease at study entry.

It is unclear whether levels of allergen to which sensitized subjects are exposed in their daily lives affect the response to AAIT. Although AAIT has demonstrated efficacy to high seasonal allergen exposure, as well as perennial allergen challenge, most AAIT clinical trials have not assessed efficacy in the context of high chronic exposure level. If a larger number of participants were to be enrolled in the proposed trial, the effect of chronic home allergen exposure as a modifier of the preventive efficacy of AAIT could also be addressed. However, because perennial allergen exposure outside of the home (eg, schools) contributes to asthma symptoms and disease severity, it is plausible that such public exposures are sufficient to drive asthma in sensitized children regardless of exposure in the home.[110]

The children in this proposal would be sensitized to allergens causally related to asthma development and severity: HDM, cat, dog, and cockroach allergens.[99,100] There is also strong supportive evidence for the importance of fungal and mouse allergens; however, significant work with extract development would be necessary before they could be included in such a study. Although focusing on 1 perennial allergen in monosensitized at-risk toddlers (eg, HDM or cockroach in inner-city children) is appealing as a proof-of-concept study, it does not adequately address the breadth of common allergen exposures causally related to asthma or the public health burden.

## Workgroup 4: Dosing strategies and duration of allergen immunotherapy

**Charge.** Workgroup 4 was charged with proposing a study design to determine the optimal dosing of allergen and optimal duration of treatment, with the goal of achieving maximal effectiveness with an acceptable safety profile.

**Background and recommendations.** AAIT has been used successfully for more than a century; however, many important questions remain related to practical issues that are

**TABLE IV.** Workgroup 3: Allergen immunotherapy for the prevention of asthma trial concept—Synopsis of key elements of the recommended trial concept

| | |
|---|---|
| Study type/description | Randomized, double-blind, placebo-controlled longitudinal study of SCIT administered for 3 years to allergic toddler-age children at high risk for asthma, followed by a 1-year observation period |
| Overall study objective | Evaluate the effectiveness of perennial allergen SCIT for the prevention of persistent asthma and/or reduction in asthma severity by school age |
| Primary study objectives | To determine whether SCIT with perennial allergens in preschool children at high risk for asthma prevents the development of persistent asthma and/or reduces asthma severity 1 year after the cessation of AAIT |
| Secondary and/or exploratory study objectives | *To determine whether SCIT with perennial allergens*:<br>● Is safe in preschool children at high risk for asthma<br>● Prevents the development of asthma and/or reduces asthma severity during SCIT treatment<br>● Reduces the prevalence and severity of allergic rhinitis during and after completion of treatment<br>● Reduces the development of new allergen sensitizations (neosensitization)<br>● Has effects on immunologic outcomes (antibody, T-cell, and basophil activation responses to treatment)<br>● Has effects on biomarkers of allergic inflammation<br>*Analyze covariates to determine patterns of response* |
| Study population age | 2-3 y |
| Key inclusion/exclusion criteria | *Key inclusion criteria*:<br>● At least 3 episodes of cough or wheeze in the prior year or a diagnosis of or treatment for asthma<br>● Sensitization based on SPT responses and sIgE levels to at least 1 of the following: HDM, CT, DG, or CR<br>*Key exclusion criteria*:<br>● Severe or unstable asthma<br>● Other chronic respiratory diseases (other than allergic rhinitis)<br>● History of anaphylaxis or receiving medications that might interfere with treatment of anaphylaxis<br>● Prior treatment with allergen immunotherapy or therapy with antiallergy/asthma biologics |
| Sample size | Two hundred participants (100 per arm) |
| Interventions and comparators | *Participants will be randomized to receive the following*:<br>● Allergen SCIT for 3 years (dose escalation and maintenance), including all of the above perennial allergens to which the participant is sensitized (allergens should be dosed in a range anticipated to be effective and not in admixtures that could lead to degradation) OR<br>● Placebo for allergen SCIT<br>All participants will receive conventional, guidelines-based asthma and rhinitis management by using standardized algorithms, such as that of the Inner-City Asthma Consortium Asthma Control Evaluation and Treatment (ACET) program.[106] |
| Primary outcomes | ● Asthma diagnosis at end of the 1-year observation phase<br>● Asthma severity: in children with asthma, using the CASI[107,108] at the end of the 1-year observation phase |
| Secondary and/or exploratory outcomes | ● Number and severity of systemic allergic reactions attributed to SCIT vs placebo<br>● Occurrence of other adverse events for SCIT vs placebo<br>● Asthma diagnosis at the end of the treatment phase<br>● Asthma severity in children with asthma at the end of the treatment phase<br>● Time to first asthma exacerbation<br>● Lung function outcomes at the end of treatment and at the end of the 1-year observation phase<br>● Diagnosis of allergic rhinitis at the end of treatment, as well as at the end of the 1-year observation phase<br>● Severity of allergic rhinitis at the end of treatment, as well as at the end of the 1-year observation phase<br>● Neosensitization: number of new allergen sensitizations to a relevant panel compared with baseline<br>● Markers of allergic inflammation (eg, peripheral blood and airway eosinophilia, type 2 cytokines, or other inflammatory molecules) at the end of treatment, as well as at the end of the 1-year observation phase<br>● Allergen-specific IgE, IgG, $IgG_4$, and T-cell responses<br>● Basophil activation responses at the end of treatment and the end of the 1-year observation phase |
| Duration (per participant) | Approximately 4 years: 3 years of SCIT and 1 year of follow-up |

*ACET*, Asthma Control Evaluation and Treatment; *CASI*, Composite Asthma Severity Index; *CR*, cockroach allergen; *CT*, cat allergen; *DG*, dog allergen; *SPT*, Skin prick test.

critical to ensuring the most efficient and effective use of this treatment modality. Two key questions still to be adequately addressed include identifying the optimal allergen dose level and treatment duration.

*Optimal allergen dose level.* Very low-dose allergenic extract administration is ineffective, although efficacy generally increases with higher doses. However, incrementally higher doses of SCIT and, to a lesser degree, SLIT might be associated with higher risk of adverse reactions. The "highest tolerated" dose has often been considered the most effective dose level, although there are few data on allergen doses that reflect the peak of the dose-response curve. Furthermore, determining a precise "optimal" allergen dose relevant to all patients might not be possible because of unique complex sensitization patterns among subjects sensitized to multiple allergenic components that are represented in a single allergen extract.

Dose-response studies of AAIT for respiratory disorders are few, with published studies exhibiting wide variation in study

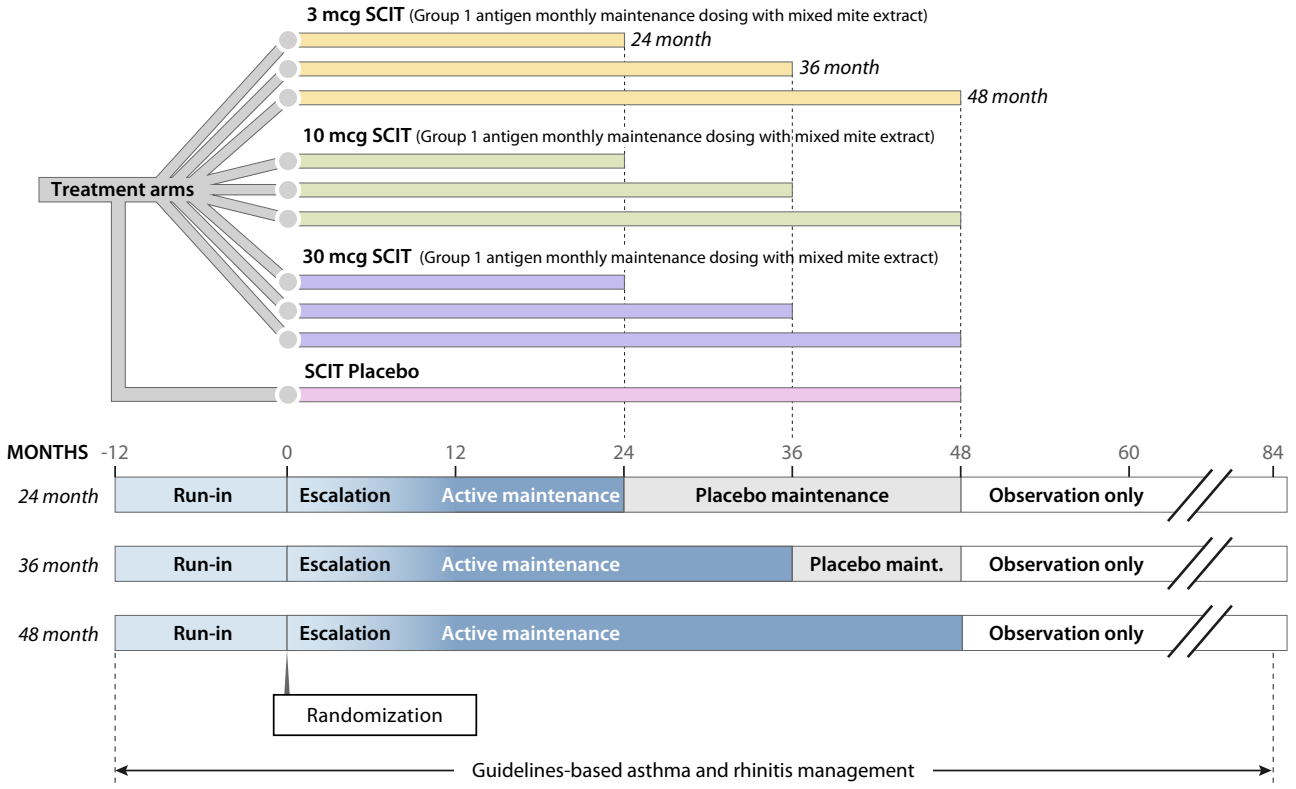


**FIG 4.** Workgroup 4: Optimal immunotherapy dosing and duration trial concept. A study schematic for a randomized, double-blind, multiarm, placebo-controlled trial of HDM SCIT for patients with mild-to-moderate stable allergic asthma is shown. Three dose levels of mixed HDM are given for 2, 3, or 4 years.

design and many reports lacking ideal randomization and/or control group allocations. Further complicating this area of research is the lack of universally accepted or reported metrics that can be used to describe and compare extract potencies.[111] However, studies of SCIT using standardized extracts for cat,[112,113] dog,[114] ragweed pollen,[115] and grass pollen[6] suggest that clinically effective maintenance doses typically range between 5 and 20 μg of the major allergen.[56] Effective dose levels and dose-response relationships for HDM immunotherapy have been less apparent in the limited number of published studies.[116,117]

*Optimal duration of allergen immunotherapy.* Some studies have indicated that sustained remission of symptomatic allergic respiratory disease is at least partially dependent on the duration of SCIT maintenance. One study of HDM SCIT demonstrated a statistically significant correlation between duration of immunotherapy and length of sustained efficacy.[118] Another prospective study of HDM SCIT found that 3 and 5 years of active treatment yielded similar sustained clinical improvements for many rhinitis and asthma outcomes. However, compared with 3 years of treatment, 5 years of continuous treatment resulted in slightly improved rhinitis symptom scores at 5 years after treatment.[119]

Unfortunately, there are no known clinical or laboratory markers that reliably predict which patients will have long-term benefit. Therefore the decision of when to stop immunotherapy is empirical and based on limited observational studies.[120] In accordance with international consensus recommendations, a common practice is to consider a minimal duration of 3 years of immunotherapy in those who have an initial beneficial response to treatment.[121]

*Benefits of further studies on AAIT dose level and duration.* Studies focused on establishing an optimal dose level and duration of AAIT that also quantify the effect size and duration of clinical benefit beyond treatment discontinuation are needed to confidently prescribe this treatment modality. This information is not known for many allergens, including whether incremental benefit might be realized by using doses somewhat greater than those commonly recommended. Because the vast majority of patients with allergic asthma have concomitant rhinitis, whereas the reverse is not true, the proposed trial has the potential to provide valuable dosing and duration information relevant to both disorders. However, investigation of higher-than-traditional allergen doses is associated with a degree of heightened risk, which is of particular importance to those with asthma. To minimize this risk while still allowing evaluation of the safety of the dosing regimen, enrollment in the proposed trial should be restricted to adult participants with a history of stable mild-to-moderate asthma and without a history of potentially life-threatening asthma episodes or anaphylactic reactions.

In addition, properly designed trials can provide an opportunity to validate candidate clinical and laboratory surrogate biomarkers that correlate with long-term clinical efficacy and are measurable early in the course of therapy. Such biomarkers have the potential of greatly enhancing the efficiency of future trials in which clinically based outcomes, and especially duration of effect,

**TABLE V.** Workgroup 4: Optimal immunotherapy dosing and duration trial concept—Synopsis of key elements of the recommended trial concept

| | |
|---|---|
| Study type/description | Randomized, double-blind, multiarm, placebo-controlled trial of HDM SCIT for mild-to-moderate stable allergic asthma |
| Overall study objective | To determine the optimally effective HDM allergen maintenance dosing level and optimal duration of SCIT maintenance |
| Primary study objectives | To determine the relative clinical efficacy and duration of effect for allergic asthma using 3 dose levels of HDM SCIT given for 2, 3, or 4 years in HDM-sensitive adults with allergic asthma |
| Secondary and/or exploratory study objectives | ● To determine the safety of increasing maintenance allergen dose in relation to increased effectiveness<br>● To determine the relative clinical efficacy and duration of effect for allergic rhinitis using 3 doses of HDM SCIT given for 2, 3, or 4 years in HDM-sensitive adults<br>● To identify early laboratory and/or clinical surrogate markers that are predictive of clinical efficacy and duration of posttreatment effect on allergic asthma and/or rhinitis |
| Study population age | 18-55 y (Inclusion of children aged 6-17 y can be considered pending an acceptable safety profile of high-dose HDM dosing among an adult population initially enrolled.) |
| Key inclusion/exclusion criteria | *Key inclusion criteria*:<br>● Asthma of at least 2 years' duration<br>● Sensitization based on SPT responses and sIgE levels to *D pteronyssinus*, *D farinae*, or both<br>● Requirement for NAEPP treatment steps 2-4, as determined after a 1-year run-in period of standardized asthma medication management<br>*Key exclusion criteria*:<br>● Requirement for NAEPP treatment step 5 or greater as determined after a 1-year run-in period of standardized asthma medication management<br>● More than 1 course of systemic steroids during the run-in period<br>● History of asthma hospitalization in the previous 2 years<br>● History of life-threatening asthma exacerbation requiring intubation, mechanical ventilation, or hypoxic seizure<br>● History of anaphylaxis with moderate of severe respiratory or cardiovascular involvement<br>● $FEV_1$ <70% of predicted value after a 1-year run-in period of standardized asthma medication management<br>● Other chronic respiratory diseases (other than allergic rhinitis)<br>● History of anaphylaxis or receiving medications that might interfere with treatment of anaphylaxis<br>● Allergen immunotherapy within the last 5 years<br>● Therapy with antiallergy/asthma biologics in the prior year<br>● Sensitized to and in regular contact with an animal or sensitized to pests and living in an infested home |
| Sample size | One thousand three hundred participants randomized into 10 arms of equal size |
| Interventions and comparators | ● SCIT with mixed HDM extract at monthly maintenance doses of 3, 10, or 30 μg (group 1 antigen) for a duration of 2, 3, or 4 years of active therapy (9 arms) OR<br>● Placebo SCIT for 4 years (1 arm)<br>● All participants to receive conventional, guidelines-based asthma management and rhinitis management using a standardized algorithm, such as that of the Inner-City Asthma Consortium ACET program[106] |
| Primary outcomes | ● CASI scores averaged over 4 quarterly assessments during months 12 to 24 (allergen dosage outcome)<br>● CASI scores averaged over 3 consecutive years (12 quarterly assessments) after completion of AAIT (duration outcome) |
| Secondary and/or exploratory outcomes | ● Number and severity of systemic allergic reactions attributed to SCIT vs placebo<br>● Occurrence of other adverse events in SCIT vs placebo<br>● TCRS averaged over 4 quarterly assessments during the first year after initiation of maintenance dosing and 3 consecutive years after completion of AAIT<br>● Surrogate markers for prediction of efficacy and duration of AAIT effect evaluated as change from baseline with assessments at 1 year after achieving maintenance dose and at completion of active treatment<br>● HDM SPT response<br>● HDM sIgE, sIgG, and $sIgG_4$<br>● IgE-facilitated allergen-binding assay<br>● Basophil or mast cell activation assays<br>● T-cell regulatory responses<br>● Allergen-specific T cells and activation status<br>● HDM nasal challenge—induced symptoms and nasal peak inspiratory flow reduction (to be considered in a subset of each treatment arm) |
| Duration (per participant) | Eight years: 1-year run-in period, 4 years of maintenance SCIT (active, placebo, or some combination), and 3 additional years of observation |

*ACET*, Asthma Control Evaluation and Treatment; *CASI*, Composite Asthma Severity Index; *NAEPP*, National Asthma Education and Prevention Program; *sIg*, specific immunoglobulin; *SPT*, Skin prick test.

would otherwise only become evaluable after prolonged observation periods and perhaps lengthy courses of AAIT administration.

**Proposed clinical trial concept.** A comparison of effect size and posttreatment duration of effect for 3 dose levels of HDM subcutaneous allergen immunotherapy after treatment for 2, 3, or 4 years in adults with allergic asthma.

**Study objectives.** The objectives of this study are (1) to determine the allergen dose level for AAIT that provides maximal effectiveness while maintaining a favorable safety profile and (2) to determine the duration of maintenance AAIT necessary to maximize the potential for persistent posttreatment clinical efficacy.

**Study design.** For the study design, see Fig 4 and Table V.[106]

**Discussion.** This trial has the potential to establish the standard for addressing maintenance dose levels and duration of AAIT. Although designed to address the efficacy of SCIT, the protocol could be adapted for HDM SLIT. However, there remains considerable concern over long-term adherence rates with SLIT, a problem that might be compounded in a lengthy trial in which ascertainment of allergen dosing over an extended duration will be critical for intention-to-treat and per-protocol analyses.

Basic questions regarding optimal AAIT dose and duration remain for both asthma and allergic rhinitis. The AHRQ summary assessment of AAIT for asthma includes a high level of evidence supporting the efficacy of AAIT in asthma symptom improvement but a low level of evidence to support efficacy for other key asthma outcomes, such as medication requirements and asthma progression.[1] The primary outcome suggested for the proposed trial is the Composite Asthma Severity Index, which integrates asthma medication requirements, asthma control, and lung function metrics. A high proportion of HDM-sensitized asthmatic patients are expected to have concomitant nasal symptoms, and rhinitis is considered a key secondary outcome.

The primary end point for comparing doses is a mean of 4 quarterly assessments, yielding an anticipated SD of 2.01 based on data provided by Wildfire et al.[122] Because 0.5 was deemed the minimum clinical difference, we assumed a difference in Composite Asthma Severity Index score of 0.5 between the lowest and highest doses (and a difference of 0.25 for adjacent doses). Then, accounting for a loss to follow-up rate of 20%, 130 participants per arm are needed to provide 80% power to test a dose effect in an ANOVA, for a total of 1300 in the trial. This corresponds to 390 subjects per dose cohort and likewise 390 per duration cohort. However, because the primary end point for testing the duration effect is based on 12 measurements over 3 years, the SD is reduced to 1.89, yielding 85% power to detect analogous treatment differences.

Assessment of the optimal dose and duration of AAIT in a single trial necessitates a large, complex, and lengthy protocol that will require substantial resources and might raise feasibility concerns. Two protocols separately focused on optimal dose and optimal duration of AAIT might be worth consideration. Although the current design is very efficient if the effects of dose and duration are additive, it also provides some data on dose/duration combinations. Furthermore, additional analytic complexity is introduced because of the inherent seasonal nature of asthma exacerbation. Although a year-long run-in period is proposed to provide an optimal baseline observation period, statistical methods accounting for the anticipated seasonally related differences in this primary outcome measurement might allow shortening of the run-in period.

Additional questions and practical challenges related to the optimal dosing and duration of therapeutic allergenic extracts will remain, including the following:

- determining threshold dose levels and dose-response curves reflecting optimal efficacy for allergenic extracts other than HDM;
- translating the results of such trials into clinical practice by establishing standardized dosing strategies based on major allergen content and relevant biomarkers for patients with suboptimal responses to traditional dose levels. (Such strategies might inform clinicians when progressively higher doses of extract are likely to be safe and clinically superior, as opposed to situations in which safety problems of dose escalation outweigh incremental benefit.);
- establishing whether threshold and optimal AAIT dosing varies by clinical indication (ie, allergic rhinitis, conjunctivitis, and asthma);
- establishing whether optimal dosing strategies vary by age;
- determining whether AAIT dosing levels or duration of therapy affect the likelihood of risk for progression of allergic rhinitis to asthma or sensitization to additional allergens[4,73]; and
- determining whether the rapidity of AAIT dose escalation or the frequency of maintenance dose administration (eg, weekly, biweekly, or monthly, etc) affect the safety, efficacy, or duration of benefit.

## REFERENCES

1. Lin SY, Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Ward D, et al. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Rockville (MD): Agency for Health Care Research and Quality; 2013.
2. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341:468-75.
3. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129:717-25.e5.
4. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.
5. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. Pediatr Allergy Immunol 2017;28:18-29.
6. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, Group UKIS. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:319-25.
7. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. J Allergy Clin Immunol 2014;133:751-8.
8. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. JAMA 2016;315:1715-25.
9. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial. JAMA 2017;317: 615-25.
10. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74.

11. Bousquet J, Michel FB, Malling HJ. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized clinical trials. Am J Respir Crit Care Med 1995;152:1737-8.
12. Calderon MA. Meta-analyses of specific immunotherapy trials. Drugs Today (Barc) 2008;44(suppl B):31-4.
13. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Clin Immunol 2011;127:30-8.
14. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. Clin Exp Allergy 2011;41:1263-72.
15. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Med 2014;12:71.
16. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med 2015;175:1301-9.
17. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. Clin Ther 2000;22:329-41.
18. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol 2012;157:288-98.
19. Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma—a placebo controlled study. Ann Allergy Asthma Immunol 1999;82:485-90.
20. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922-32.
21. Keles S, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. J Allergy Clin Immunol 2011;128:808-15.e7.
22. Tahamiler R, Saritzali G, Canakcioglu S, Ozcora E, Dirican A. Comparison of the long-term efficacy of subcutaneous and sublingual immunotherapies in perennial rhinitis. ORL J Otorhinolaryngol Relat Spec 2008;70:144-50.
23. Antunez C, Mayorga C, Corzo JL, Jurado A, Torres MJ. Two year follow-up of immunological response in mite-allergic children treated with sublingual immunotherapy. Comparison with subcutaneous administration. Pediatr Allergy Immunol 2008;19:210-8.
24. Pfaar O, Calderon MA, Andrews CP, Angjeli E, Bergmann KC, Bonlokke JH, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future—an EAACI Position Paper. Allergy 2017;72:1035-42.
25. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 2015;135:1494-501.e6.
26. Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. Clin Exp Allergy 2010;40:242-50.
27. Ellis AK, Frankish CW, O'Hehir RE, Armstrong K, Steacy L, Larche M, et al. Treatment with grass allergen peptides improves symptoms of grass pollen-induced allergic rhinoconjunctivitis. J Allergy Clin Immunol 2017;140:486-96.
28. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2016;138:1631-8.
29. Zieglmayer P, Nolte H, Nelson HS, Bernstein DI, Kaur A, Jacobi H, et al. Long-term effects of a house dust mite sublingual immunotherapy tablet in an environmental exposure chamber trial. Ann Allergy Asthma Immunol 2016;117:690-6.e1.
30. Anto JM, Bousquet J, Akdis M, Auffray C, Keil T, Momas I, et al. Mechanisms of the Development of Allergy (MeDALL): introducing novel concepts in allergy phenotypes. J Allergy Clin Immunol 2017;139:388-99.
31. Zoratti EM, Krouse RZ, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, et al. Asthma phenotypes in inner-city children. J Allergy Clin Immunol 2016;138:1016-29.
32. Acquistapace F, Agostinis F, Castella V, Kantar A, Novembre E, Perrone MR, et al. Efficacy of sublingual specific immunotherapy in intermittent and persistent allergic rhinitis in children: an observational case-control study on 171 patients. The EFESO-children multicenter trial. Pediatr Allergy Immunol 2009;20:660-4.
33. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol 2011;127:64-71, e1-4.
34. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61:1162-72.
35. Calderon M, Essendrop M. Specific immunotherapy with high dose SO standardized grass allergen tablets was safe and well tolerated. J Investig Allergol Clin Immunol 2006;16:338-44.
36. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;118:434-40.
37. Tabatabaian F, Casale TB. Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT). Allergy Asthma Proc 2015;36:100-4.
38. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 2010;125:131-8, e1-7.
39. Esch RE, Bush RK, Peden D, Lockey RF. Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. Ann Allergy Asthma Immunol 2008;100:475-81.
40. TePas EC, Hoyte EG, McIntire JJ, Umetsu DT. Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals. Ann Allergy Asthma Immunol 2004;92:25-31.
41. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:802-9.
42. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. J Allergy Clin Immunol 2010;126:969-75.
43. Norman PS, Lichtenstein LM. The clinical and immunologic specificity of immunotherapy. J Allergy Clin Immunol 1978;61:370-7.
44. Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 2006;97:141-8.
45. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2010;12:CD002893.
46. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011;66:740-52.
47. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31.
48. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102:558-62.
49. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013;131:1342-9.e6.
50. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol 2011;127:72-80, e1-2.
51. Ciprandi G, Incorvaia C, Puccinelli P, Scurati S, Masieri S, Frati F. The POLISMAIL lesson: sublingual immunotherapy may be prescribed also in polysensitized patients. Int J Immunopathol Pharmacol 2010;23:637-40.
52. Larenas Linnemann DE, Blaiss MS. Selection of patients for sublingual versus subcutaneous immunotherapy. Immunotherapy 2014;6:871-84.
53. Creticos PS. Sublingual Immunotherapy for Allergic Rhinoconjunctivitis and Asthma. Waltham (MA): UpToDate; October 2015.
54. Migueres M, Davila I, Frati F, Azpeitia A, Jeanpetit Y, Lheritier-Barrand M, et al. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. Clin Transl Allergy 2014;4:16.
55. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334:501-6.
56. 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(suppl):S1-55.
57. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol 2007;120:1338-45.
58. Calderon MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. J Allergy Clin Immunol 2012;129:929-34.
59. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus

combination in a multiallergen extract. J Allergy Clin Immunol 2009;124:150-6, e1-5.
60. Bahceciler NN, Galip N, Cobanoglu N. Multiallergen-specific immunotherapy in polysensitized patients: where are we? Immunotherapy 2013;5:183-90.
61. Durham SR, Leung DY. One hundred years of allergen immunotherapy: time to ring the changes. J Allergy Clin Immunol 2011;127:3-7.
62. Marogna M, Spadolini I, Massolo A, Zanon P, Berra D, Chiodini E, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. Ann Allergy Asthma Immunol 2007;98:274-80.
63. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. J Allergy Clin Immunol 2009;123:763-9.
64. Nelson HS. Specific immunotherapy with allergen mixes: what is the evidence? Curr Opin Allergy Clin Immunol 2009;9:549-53.
65. Massie T. Statistical review: biologics license application of Oralair. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM393025.pdf. Accessed February 22, 2019.
66. Passalacqua G. The use of single versus multiple antigens in specific allergen immunotherapy for allergic rhinitis: review of the evidence. Curr Opin Allergy Clin Immunol 2014;14:20-4.
67. Esch RE. Specific immunotherapy in the U.S.A.: general concept and recent initiatives. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 2003;(94):17-23.
68. Calderon MA, Eichel A, Makatsori M, Pfaar O. Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials. Curr Opin Allergy Clin Immunol 2012;12:249-56.
69. Grier TJ, Converse LM, Rekkerth DJ, Renahan KE. Math-free guides for glycerin and allergens at variable subcutaneous injection volumes: how's my dosing? Update. Ann Allergy Asthma Immunol 2016;116:455-60.
70. Turkeltaub PC. Use of skin testing for evaluation of potency, composition, and stability of allergenic products. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 1994;(87):79-87; discussion 114-7.
71. Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman PS. A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. J Allergy Clin Immunol 1982;70:343-52.
72. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016;137:444-51.e8.
73. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
74. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.
75. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006;61:855-9.
76. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
77. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med 2016;374:1435-43.
78. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 2002;288:963-72.
79. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. J Allergy Clin Immunol 2001;108:509-15.
80. Bufford JD, Reardon CL, Li Z, Roberg KA, DaSilva D, Eggleston PA, et al. Effects of dog ownership in early childhood on immune development and atopic diseases. Clin Exp Allergy 2008;38:1635-43.
81. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J Allergy Clin Immunol 2014;134:593-601.e12.
82. O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, et al. Early-life home environment and risk of asthma among inner-city children. J Allergy Clin Immunol 2018;141:1468-75.
83. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ 3rd, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. Am Rev Respir Dis 1992;146:888-94.
84. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.
85. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116:571-7.
86. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667-72.
87. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005;172:1253-8.
88. Godden DJ, Ross S, Abdalla M, McMurray D, Douglas A, Oldman D, et al. Outcome of wheeze in childhood. Symptoms and pulmonary function 25 years later. Am J Respir Crit Care Med 1994;149:106-12.
89. Horak E, Lanigan A, Roberts M, Welsh L, Wilson J, Carlin JB, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. BMJ 2003;326:422-3.
90. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195-9.
91. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
92. Bacharier LB. The recurrently wheezing preschool child-benign or asthma in the making? Ann Allergy Asthma Immunol 2015;115:463-70.
93. National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. U.S. Department of Health and Human Services; 2007. Available at: https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed February 22, 2019.
94. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA) 2015. Available at: https://ginasthma.org/wp-content/uploads/2016/01/GINA_Report_2015_Aug11-1.pdf. Accessed February 22, 2019.
95. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162:1403-6.
96. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004;114:1282-7.
97. Garden FL, Simpson JM, Mellis CM, Marks GB, Investigators C. Change in the manifestations of asthma and asthma-related traits in childhood: a latent transition analysis. Eur Respir J 2016;47:499-509.
98. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet 2006;368:763-70.
99. Institute of Medicine. Committee on the Assessment of Asthma and Indoor Air. Clearing the Air: Asthma and Indoor Air Exposures. Washington (DC): National Academy Press; 2000:xvi, 438.
100. Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine. Environ Health Perspect 2015;123:6-20.
101. Plopper CG, Smiley-Jewell SM, Miller LA, Fanucchi MV, Evans MJ, Buckpitt AR, et al. Asthma/allergic airways disease: does postnatal exposure to environmental toxicants promote airway pathobiology? Toxicol Pathol 2007;35:97-110.
102. Ferdousi HA, Zetterstrom O, Dreborg S. Bronchial hyper-responsiveness predicts the development of mild clinical asthma within 2 yr in school children with hayfever. Pediatr Allergy Immunol 2005;16:478-86.
103. Rochat MK, Illi S, Ege MJ, Lau S, Keil T, Wahn U, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. J Allergy Clin Immunol 2010;126:1170-5.e2.
104. Nelson HS. Subcutaneous immunotherapy versus sublingual immunotherapy: which is more effective? J Allergy Clin Immunol Pract 2014;2:144-51.
105. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF, et al. Results from the 5-year SQ grass SLIT-tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2018;141:529-38.e13.
106. Kercsmar CM, Sorkness CA, Calatroni A, Gergen PJ, Bloomberg GR, Gruchalla RS, et al. A computerized decision support tool to implement asthma guidelines for children and adolescents. J Allergy Clin Immunol 2019;143:1760-8.
107. Moller C, Bjorksten B, Nilsson G, Dreborg S. The precision of the conjunctival provocation test. Allergy 1984;39:37-41.
108. Krouse RZ, Sorkness CA, Wildfire JJ, Calatroni A, Gruchalla R, Hershey GKK, et al. Minimally important differences and risk levels for the Composite Asthma Severity Index. J Allergy Clin Immunol 2017;139:1052-5.

109. Grier TJ, Hall DM, Duncan EA, Gada SM. Allergen stabilities and compatibilities in immunotherapy mixtures that contain cat, dog, dust mite, and cockroach extracts. Ann Allergy Asthma Immunol 2015;115:496-502.
110. Grant T, Aloe C, Perzanowski M, Phipatanakul W, Bollinger ME, Miller R, et al. Mouse sensitization and exposure are associated with asthma severity in urban children. J Allergy Clin Immunol Pract 2017;5:1008-14.e1.
111. Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on "dose-response relationship in allergen-specific immunotherapy". Allergy 2011;66:1345-59.
112. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. J Allergy Clin Immunol 2003;111:155-61.
113. Nanda A, O'Connor M, Anand M, Dreskin SC, Zhang L, Hines B, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol 2004;114:1339-44.
114. Lent AM, Harbeck R, Strand M, Sills M, Schmidt K, Efaw B, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. J Allergy Clin Immunol 2006;118:1249-56.
115. Creticos PS, Marsh DG, Proud D, Kagey-Sobotka A, Adkinson NF Jr, Friedhoff L, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 1989;84:197-205.
116. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993;91:709-22.
117. Olaguibel JM, Tabar AI, Garcia Figueroa BE, Cortes C. Immunotherapy with standardized extract of *Dermatophagoides pteronyssinus* in bronchial asthma: a dose-titration study. Allergy 1997;52:168-78.
118. Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy 1996;51:430-3.
119. Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol 2011;127:57-63, e1-3.
120. Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? Ann Allergy Asthma Immunol 2007;98:416-26.
121. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 2015;136:556-68.
122. Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, et al. Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. J Allergy Clin Immunol 2012;129:694-701.