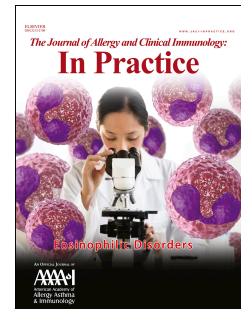


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Clinical Practice of Allergen Immunotherapy for Allergic Rhinoconjunctivitis and Asthma: An Expert Panel Report

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Clinical Practice of Allergen Immunotherapy for Allergic Rhinoconjunctivitis and Asthma: An Expert Panel Report

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Abbreviations: AA, allergic asthma; AAAAI, American Academy of Allergy, Asthma & Immunology; ACAAI, American College of Allergy Asthma & Immunology; AIT, allergen immunotherapy; AR/C, allergic rhinitis with or without conjunctivitis; CSACI, Canadian Society of Allergy and Clinical Immunology EAACI, European Academy of Allergy and Clinical Immunology; EBM, evidence-based medicine; EEC, environmental exposure chamber; EMA, European Medicines Agency; EoE, eosinophilic esophagitis; FDA, US Food and Drug Administration; HDM, house dust mite; INCS, intranasal corticosteroids; RDBPC, randomized, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick testing; WAO, World Allergy Organization.

Abstract

Allergen immunotherapy (AIT) reduces symptoms and medication use associated with allergic rhinitis with or without conjunctivitis and allergic asthma. Although several AIT guidelines exist, there remain unanswered questions about AIT that are relevant to everyday practice. Our objective was to prepare an evidence-based overview addressing the practical aspects of AIT in clinical practice based on published evidence and the experience of international experts in the field. Topics covered include interpretation and translation of clinical trial data into everyday clinical practice (e.g., allergen doses and treatment duration), assessment of risk and treatment of local and systemic allergic reactions, recommendations for improvement of AIT guidelines, and identification of appropriate data for seeking regulatory approval, to name a few. Many informational gaps in AIT practice need further evaluation as products and practices evolve.

Introduction

Allergen immunotherapy (AIT) significantly reduces symptoms and medication use associated with allergic rhinitis with or without conjunctivitis (AR/C) and allergic asthma (AA).^{1, 2} Two modes of AIT administration are in general use, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT; drops or tablets). Although several AIT guidelines exist,³⁻¹¹ there remain unanswered questions about AIT that are important for everyday practice. Our objective was to prepare an evidence-based overview that addresses the practical aspects of AIT in clinical practice based on published data and the experience of international experts in the field (see **Supplemental section for Methods**).

1. What does evidence-based medicine (EBM) of AIT mean for the practicing allergist?

Key takeaway: EBM should guide AIT practices when it is available. Documented available EBM should be considered when selecting AIT products. Practicing allergists should be informed and educated on the levels of EBM for AIT.

- Evidence-based medicine (EBM) is the standard for providing safe and effective treatment for any medical condition, including AR/C and AA.
- Over the decades, most AIT products have been marketed without being evaluated in appropriate clinical trials.^{12, 13} In some countries, non-standardized extracts and extracts that have not been studied in clinical trials are prescribed.
- The World Allergy Organization (WAO) and European Medicines Agency (EMA) have recommended criteria based on evidence obtained in randomized, double-blind, placebo-controlled (RDBPC) trials that may be used to support product claims regarding efficacy in adults and children, sustained effects, and disease-modifying effects for AR/C and AA.^{12, 14} The US Food and Drug Administration (FDA) has not published any formal guidance document specifically for AIT approval or product claims. However, internal FDA regulatory practices are in place.
- RDBPC trials have been conducted for SLIT-tablets that are available in many countries worldwide.^{13, 15-28}
- The clinical and methodological design quality of many of the older SCIT and SLIT-drop clinical trials is not equivalent to those of more recent studies due to lack of extract standardization, inappropriate trial design, incomplete reporting, inconsistent clinical outcomes, and/or limitations related to data from a single-center or small sample sizes.²⁹⁻³³
- The European Academy of Allergy and Clinical Immunology (EAACI) AIT guidelines for AR/C recommend that only AIT products with clinically documented supporting efficacy should be prescribed, with the exception of AIT for rare allergens.¹¹ No such guidance exists in the US for currently used allergen extract products; most allergen products have not been studied for efficacy. The EAACI recommendations only apply to Europe and have not been embraced by allergists in the US or by the FDA. The FDA has removed a number of commercially available extracts from the market for which there was insufficient evidence for efficacy. The extracts that remain on the market in the US

have sufficient evidence for efficacy for the FDA to allow them to remain on the market, but the quality of evidence is not the same as that currently needed for new product approval.

- A “class effect” of SCIT or SLIT products for a particular allergen cannot be assumed. Evidence of efficacy of a particular allergen cannot be extrapolated and used as clinical evidence for individual products (see section on Class Effect).¹² Clinical evidence needs to be obtained for each individual product.
- The expert panel, academics, and practicing physicians recommend that selection of AIT products be evidence-based when such evidence is available; however, we recognize that it will not be practical or feasible to evaluate all commercial extracts for SCIT and SLIT-drops in DBPC trials. Guidelines/recommendations on suggested doses for extracts that have not been robustly evaluated are available, but should be considered with caution as their efficacy may not be well proven.⁵

2. How can AIT guidelines be improved?

Key takeaways: Globally harmonized guidelines are needed to set common practice standards and improve AIT product development. Awareness and implementation of AIT guidelines may be improved by providing an abbreviated “handbook” of the major topics. As new evidence becomes available, future revisions of existing guidelines should add standardized protocols for extract labeling, handling treatment interruptions and re-initiation, multiple allergen administration, in-season initiation, and treatment of adverse events, as well as expanding information regarding patients with AA. Real-world experience and input from patients should also be considered in guideline development.

- There are many different regional, academic, and professional AIT practice guidelines which may confuse allergists, regulators, and patients when practices across regions vary for the same AIT products. We propose global harmonization of professional guidelines to set common standards for the practice of AIT. Many regional guidelines are not regularly updated and the expert panel recommends that local practices be based on international guidelines, with exceptions made when local medical practices and available AIT products (i.e., alum-precipitated vs aqueous extracts) substantially differ.
- Complexity, strength of evidence of recommendations, clear and simple statements, “user-friendliness”, and transparency appear to influence guideline implementation.³⁴ Guidelines that have the best compliance among healthcare practitioners are those that are well-supported by EBM, easy to follow, and compatible with existing norms and values in clinical real life settings.³⁵ Thus, we propose that in addition to the full guidelines a shortened “handbook” or executive summary of the key takeaways be developed that is simple, concise, and easy to read and understand for healthcare professionals, patients, and stake holders. The Canadian Society of Allergy and Clinical Immunology (CSACI), the American College of Allergy Asthma & Immunology (ACAAI), the WAO, and EAACI have developed handbooks/pocket guides.³⁶⁻³⁹

- Standardizing AIT extract labels, dosing schedules (both build-up and missed-dose schedules), and protocols for treating AIT-related systemic reactions would be helpful for improving workflow and safety. We propose that AIT guidelines include supplemental standardized protocols for labeling of SCIT or SLIT-drop extract vials (including vial colors), treatment of systemic reactions, and treatment of local reactions. The simultaneous use of more than one SLIT-tablet, use of concomitant biologics and AIT, AIT during pregnancy, in-season initiation, and re-initiation of AIT following a break in treatment should be addressed in future guidelines. Enhanced guidelines for multiallergen mixtures in American Academy of Allergy, Asthma & Immunology (AAAAI)/ACAAI Practice Parameters would be helpful in the United States where use of SCIT multiallergen mixtures is common practice.
- Guidelines should highlight practical aspects of treating children and adults with AIT. A number of large pediatric SLIT-tablet trials have been conducted^{15, 25, 26, 40, 41} and SLIT-tablets may have a unique and favorable role over SCIT in younger patients. A survey of parents indicated that they preferred SLIT over SCIT for children because of the ease of use and low risk of severe side effects,⁴² whereas children may want to avoid injections.⁴³
- When AIT is being considered in patients with AA, SLIT-tablets may have a more favorable safety profile than SCIT. More emphasis needs to be placed on severe or uncontrolled asthma as a risk factor for severe systemic reactions with AIT since 75% of surveyed practitioners in North America reported prescribing SCIT to patients with uncontrolled asthma.⁴⁴ A trend suggesting an increase in the number of SCIT-related fatalities (n=5) was observed between 2015 and 2017.⁴⁵ New EBM guidelines need to be developed examining the use of SCIT in patients with asthma of different severities.
- We propose that meta-analysis for AIT should include only RDBPC studies which are similar in AIT product, disease, age group, and clinical outcomes. Clinical and methodological heterogeneity should be noted in any published report; therefore, caution in the interpretation of meta-analysis should be taken.
- Since patient preference is a key component in decisions regarding AIT (i.e., SCIT vs SLIT), we recommend that patient views should be represented in AIT guideline development. Patient opinion and preference studies should also be considered during guideline development. Shared decision-making tools are now available for AIT⁴⁶⁻⁴⁸ and should be promoted in guidelines.

3. How should clinical trial data be interpreted and translated into everyday practice?

Key takeaway: Interpretation of clinical trial data is complicated by the complexity and lack of standardization in symptom and medication scoring systems, allergen exposure variations, lack of a well-defined and validated clinically meaningful effect, and a substantial placebo effect. Effects of an AIT treatment on patient-reported outcomes may be more relevant to everyday practice. Efficacy data for a specific AIT product obtained in well-controlled adult trials may be bridged to children by supplementing with smaller pediatric trials.

- The primary efficacy endpoint in the majority of newer AIT trials is the combined symptom and medication score, which is requested by regulatory agencies worldwide.¹⁴ However, many different symptom and rescue medication scoring algorithms have been used in AIT trials, which makes comparison of efficacy based on actual scores among trials and AIT products virtually impossible.^{49, 50} The magnitude of AIT efficacy should be based on the percentage reduction or minimal score point difference of symptom and medication scores in the active versus placebo groups over a well-defined period during relevant allergen exposure.⁵¹ The reference point for the reduction of symptoms typically is the time of the peak pollen season as defined by pollen counts; however, another reference point, namely the time of peak symptoms in placebo treated subjects, could also be considered as it may more accurately describe clinical efficacy.⁵² The point estimate based on the actual numeric score difference and relative percentage difference compared with placebo should both be reported. In seasonal pollen trials, pollen counts should be reported to allow interpretation of the magnitude of efficacy as low pollen seasons will tend to reduce the treatment signal.
- Using change from baseline is not possible for AIT trials of seasonal AR/C because treatment needs to begin several weeks or months before the pollen season begins. The WAO recommends against using scores from a previous pollen season as a baseline because of variations in pollen exposure from season to season.⁵¹ Change from baseline (i.e., before treatment randomization) in symptom scores is often used for placebo-controlled pharmacotherapy trials (for both seasonal and perennial AR/C) where no treatment induction period is needed. Care needs to be taken not to compare efficacy of pharmacotherapies measured by change from baseline with efficacy of AIT measured by difference from placebo at the trial endpoint.
- The minimal clinically relevant difference for active AIT treatment was first defined as 20% more than placebo.⁵¹ The WAO-recommended 20% is arbitrary based on relative reduction observed in older AIT trials,⁵³ with no suggestion of 20% representing a clinically meaningful difference. The WAO 20% definition is not validated and does not take into account modern principles of AIT trial design and conduct. Nevertheless, the 20% improvement versus placebo has become a “standard” threshold when considering the efficacy of an AIT product and was used in the power analysis for sample size calculations in at least one SLIT-tablet pivotal trial.¹⁶ Percentage improvements versus placebo for SCIT, SLIT-tablets, and pharmacotherapies have been calculated in three meta-analyses and demonstrated comparable percentage improvements with SLIT-tablets and SCIT to intranasal corticosteroids (INCS) for seasonal AR/C.⁵⁴⁻⁵⁶ Furthermore, AIT trials allow rescue medication use in both the active and placebo groups, which would presumably result in less symptoms and underestimation of the comparative improvement. Environmental exposure chamber (EEC) trials are of interest as pharmacotherapy is withheld before challenge; therefore, the optimal treatment effect on symptom reduction using a validated nasal symptom score algorithm (4 nasal symptoms scored on a 0-3 scale) may be assessed without the potential impact of pharmacotherapy and confounding environmental triggers. EEC data results may vary among different chamber sites. In general, EEC data may be used for dose determination and onset of effect but as of yet are not accepted for primary phase 3 verification of efficacy of AIT

without a field study. Conjunctival and nasal provocation testing are other options for initial efficacy and dose finding AIT studies.

- Other definitions for a clinically meaningful effect of AIT treatment exist beyond a 20% improvement versus placebo in efficacy scores.⁵⁷ The EMA defines a 1.0 score difference as the clinically meaningful effect. The minimally important difference in the nasal symptom score (max=12 for 4 nasal symptoms) for house dust mite (HDM) AR/C has been determined to be a change from baseline of at least -0.90 units in adults and children. The US FDA requires at least a point estimate of 15% difference from placebo with a 95% CI upper limit of at least -10% for the primary endpoint.^{14, 57} However, it is not clear if a mean 15% to 20% improvement or statistically significant improvement in combined symptom and medication score is clinically meaningful. Unfortunately, there are currently no simple, objective methods in clinical practice that can establish clinically important improvement for the individual patient. Hence, it must be a medical judgment to be discussed with the patient. Studies are needed to determine what a clinically meaningful result would be from a patient's perspective.
- For the clinician, patient-reported outcomes other than symptom/medication scores may be more important and easier to interpret. For example, patient global assessments often detect changes that may be missed by specific symptom score questions.⁵⁸
- Although changes in allergen specific IgE and IgG levels pre- and post- treatment do not correlate with clinical efficacy, they may at least demonstrate that the AIT product demonstrates an immune effect. It is undetermined if intra-nasal immune changes following AIT may be useful for assessment of efficacy.⁵⁹
- Patient selection criteria such as disease severity, skin test criteria, and baseline allergen-specific IgE levels may impact the magnitude of efficacy outcomes in AIT trials.^{16, 60, 61}
- Outcomes that rely on patient subjectivity, such as the scoring of AR/C symptoms, are highly susceptible to the placebo effect. In SLIT-tablet trials where free rescue medication is provided throughout the trials, placebo subjects may show up to 50% improvement at the end of the trial. A meta-analysis of randomized, placebo-controlled AIT trials found that a placebo effect contributed to 39% of the overall treatment effect.⁶² This observation is likely due to increased compliance with rescue medication (i.e. antihistamines, INCS, oral corticosteroids), symptom awareness, and the Hawthorne effect. To reduce the impact of patient subjectivity on AR/C treatment outcomes, measures based on more objective outcomes are desirable. However, no objective measure (e.g. skin test, serum IgE or IgG₄) has been found to be a consistent biomarker of efficacy and none have been validated or recommended for clinical practice.
- A common question that arises in interpreting AIT trial data is whether adult data can be extrapolated to apply to children. There are a number of reasons to consider that adult AIT efficacy data can be appropriately extrapolated to children: 1) AIT is dosed similarly in adults and children; 2) AIT has the same mechanism of action in adults and children; 3) the pathophysiology of AR/C is the same in adults and children; and 4) SLIT-tablet trials demonstrate comparable efficacy between adults and children.^{15, 16, 21, 24-28, 41, 63, 64} Young children who have immune systems still under development may actually see a greater

impact from AIT, such as less subsequent development of new allergen sensitizations and asthma.^{65, 66} The FDA supports the contention that effectiveness of a drug can be reasonably assumed from well-controlled adult trials if the disease course and drug effects are sufficiently similar in adults and children. Therefore, it is our opinion that adult efficacy data from well-controlled AIT trials can be extrapolated to children by conducting smaller bridging trials for the same AIT product.⁶⁷ Robust safety data in children would require a large trial.

4. What are the risk factors and treatment for systemic allergic reactions and anaphylaxis?

Key takeaway: Systemic allergic reactions can occur with SCIT and at a much-reduced frequency with SLIT-drops and SLIT-tablets. The risk is likely increased by certain patient or treatment-related factors. Life-threatening or fatal anaphylaxis is rare. SLIT is generally viewed as being safer than SCIT. Available EBM for safety of SLIT supports at-home administration. Clinics should be prepared to treat anaphylaxis and patients with asthma should be assessed for asthma control before each SCIT injection. Prescribing of SCIT and SLIT should be limited to physicians with adequate training and expertise in the treatment of allergic respiratory diseases.

- Systemic allergic reactions are a well-recognized adverse event associated with AIT.^{68, 69} Because most fatal anaphylactic reactions begin within 30 minutes after SCIT injections, all patients must be observed for 30 minutes following each SCIT injection.^{5, 11, 70} Nevertheless, approximately 15% of systemic allergic reactions (predominantly Grade 1 [mild] and 2 [moderate]) to SCIT injections begin after 30 minutes.⁴⁵ A 30-minute observation period is also required following the first dose of SLIT-tablets.⁷¹⁻⁷⁴ Known risk factors for severe systemic allergic reactions have been determined for SCIT and have been previously reviewed.^{45, 69, 75-77} The small number of systemic allergic reactions associated with SLIT-drops and SLIT-tablets has made determination of risk factors difficult, but symptomatic uncontrolled asthma, dose, and accelerated schedules (SLIT-drops) have been identified as factors in the few cases associated with anaphylaxis.⁴ A systematic review of AIT trials did not find an increased risk of systemic, serious, or severe reactions when SCIT or SLIT were initiated during pollen season.⁷⁸
- An analysis of SCIT injection visits from 2013 to 2016 in the United States found that systemic allergic reactions occurred in 0.6% of patients receiving SCIT; most were mild-to-moderate in severity.⁴⁵ The rate of severe, potentially life-threatening anaphylaxis (Grade 4 [severe] systemic allergic reaction) was 0.00062% of injection visits and approximately 0.005% of patients treated with SCIT.⁴⁵ The systemic allergic reaction rate for SLIT-tablets has been reported between 0.06% and 0.4%.^{72, 79} Very few cases of anaphylaxis have been reported with SLIT and to date there have been no fatalities.^{4, 44, 80, 81} SLIT is generally viewed as having a better safety profile than SCIT.^{4, 82} Available EBM for the safety of SLIT, supports at-home administration.
- Severe uncontrolled asthma considerably increases the risk of severe systemic allergic reactions and is a contraindication for AIT.^{5, 11} However, SCIT is routinely administered to patients with well-controlled asthma with an acceptable safety profile.¹ The safety and tolerability of ragweed, timothy grass, and HDM SLIT-tablets have been demonstrated in patients with well-controlled and partially controlled AA.^{79, 83, 84}

- Use of premedication (i.e., antihistamines, INCS, leukotriene receptor antagonists, oral corticosteroids) in clinical trials has been shown to reduce the rate of systemic allergic reactions during SCIT;⁸⁵⁻⁸⁷ however, in a large survey of SCIT in the United States, use of premedication did not have an impact on the rate of systemic allergic reactions.⁸⁸ Omalizumab has been shown to decrease the frequency and severity of reactions to rush SCIT in patients with AR/C and cluster build-up SCIT in patients with asthma.^{89,90}
- Premedication to prevent systemic allergic reactions to SLIT for inhalant allergens has not been fully established.
- In the United States, the FDA requires a prescription of SLIT-tablets to be accompanied by a prescription for self-injectable epinephrine.⁷¹⁻⁷⁴ This requirement was made mandatory when trial and market experience with SLIT-tablets were limited and therapy was intended for home administration. No other countries with approved SLIT-tablets require an accompanying epinephrine prescription. For SCIT, the necessity of the patient to carry self-injectable epinephrine is decided at the discretion of the prescribing physician.
- The CSACI suggests that exercise be avoided for at least 2 hours before or after SCIT injections because increased hemodynamics may lead to the occurrence of adverse events.³⁶ The German/Swiss/Austrian guidelines also advise against physical exertion, whirlpools or saunas, or alcohol use shortly before a SCIT injection and for the rest of day.⁶ In Japan, patients are also advised to avoid consuming alcohol and taking a Japanese-style bath before SCIT or SLIT-tablets and for approximately 2 hours after. There are no robust scientific data to support these recommendations for SCIT and SLIT-tablets.
- SCIT injection should be postponed if the patient has uncontrolled asthma, fever, or a respiratory infection.³⁶ SCIT dosage should be adjusted if a patient reports a delayed reaction after their last SCIT injection.
- Because of the risks for systemic allergic reactions, the expert panel recommends that the prescribing of SCIT and SLIT be limited to physicians with adequate training and expertise in the treatment of allergic respiratory diseases.

5. What are the risk factors and treatment for local allergic reactions?

Key takeaway: Local allergic reactions to SCIT and SLIT are common. Local allergic reactions to SCIT can be reduced or treated with oral antihistamines and other methods. Local allergic reactions to SLIT are self-limiting and rarely need medical treatment. SLIT-tablets are contraindicated in the United States in patients with a history of eosinophilic esophagitis.

- Local allergic reactions of short duration are expected with natural allergen extracts.⁹¹ Local allergic reactions with SCIT are itching, swelling, and redness at the injection site.⁵ The most common local allergic reactions to SLIT-drops and tablets involve the oral mucosa and include oral pruritus, throat irritation, ear pruritus, and lip and tongue swelling.^{4,81,92} The frequency of local allergic reactions to SCIT and SLIT decreases over time.^{93,94}

- When a local allergic reaction to SCIT does occur, cool compresses or topical corticosteroids can be applied.⁵ Oral antihistamines can also be given for a few days to treat and reduce the size of local reactions to SCIT.^{5, 86} Local allergic reactions to SLIT are self-limiting and rarely need medical treatment. The expert panel recommends daily use of oral antihistamines for 1 to 2 weeks, if necessary, for patients experiencing mild or moderate local allergic reactions to SLIT. For more severe local swellings, treatment may be discontinued or the next dose can be administered under observation along with oral antihistamine premedication. For patients who experienced local allergic reactions the previous season with co-seasonal SLIT-tablet treatment, the expert panel recommends oral antihistamines when treatment is reinitiated each season.
- Induction of eosinophilic esophagitis (EoE) after oral immunotherapy is well-known for food allergy, occurring in 2.7% of patients.⁹⁵ The hypothesis is that exposure of the esophageal mucosa to pollen allergens in some sensitized patients induces eosinophilia, but evidence for this hypothesis is contradictory.⁹⁶ Patients with EoE and seasonal allergies may have worsening of their EoE during pollen season. One case of EoE determined as likely associated with treatment with a pollen SLIT-drop formulation has been published. A history of EoE is a contraindication to SLIT-tablets only in the United States,⁷¹⁻⁷⁴ although to date there has been no established causal link between SLIT-tablets and EoE. The expert panel recommends that if EoE occurs, the event should be treated, documented (by histology if possible), and SLIT-tablet treatment discontinued. SLIT-tablets should not be prescribed to patients with clinical and histologically confirmed EoE until further safety data are available.

6. What data should be used for regulatory approval of AIT products?

Key takeaway: Regulatory approval processes for AIT products have become more stringent in recent years but vary widely among countries which may affect AIT product availability and product claims. Most regulatory agencies now require high-quality evidence of manufacturing quality, efficacy, and safety for approval and to support product claims.

- **Table 1** cites the SCIT and SLIT formulations that are regulatory approved for AR/C, AA, sustained-effects, and disease-modification.
- Countries around the world have varying differences in AIT regulatory approval processes which have evolved in the last 20 years.^{97, 98} Similarities among the approval processes include the requirement of market authorization and authorization based on the finished product.⁹⁷ Some of the key regulatory differences worldwide include the necessity of authorization for diagnostic allergens vs immunotherapy allergens, separate authorizations for pollen vs non-pollen derived-extracts, and allowance of named patient products (exclusively non-approved/non-registered products manufactured in accordance with a prescription for an individual patient).⁹⁷ In addition, the data requirements, such as the definition of a clinically meaningful difference and consideration of data from EEC trials, as well as dose selection, vary worldwide. Today, for new AIT products most regulatory agencies require that the pharmaceutical company provide evidence for high quality manufacturing, efficacy, and safety based on pre-clinical, and phase I-III trials. Only products with a positive benefit/risk ratio will be granted approval. Registration trials should be performed by using a RDBPC design. The primary endpoint must reflect

both symptom severity or presence/absence of symptoms and intake of rescue medication. Key secondary endpoints typically assess efficacy for the individual components of the combined symptom-medication endpoint. Many regulatory agencies require replicate trials.

- In years past, allergen extracts used in the diagnosis and treatment of AR/C were not subject to regulatory approval and many products were marketed without documentation of efficacy and safety. Current SCIT products in the US have been grandfathered in under manufacturers' licenses for allergenic extracts for diagnostic use and have not been validated in clinical development programs assessing efficacy and safety. Therefore, no promotional claims on safety and efficacy of these products can be made. In the last 20 years, AIT products have become categorized as medicinal products and are now subject to Good Clinical Practice⁹⁹ and regulatory approval. As such, regulatory authorities now require evidence of efficacy and safety for new marketing authorization of AIT products. It is also common regulatory practice that after obtaining an adult indication the license holder must conduct a clinical development program for children ages 5 years and up and may seek a waiver for children less than 5 years of age.
- Natural allergen exposure is highly variable, therefore, EEC trials that provide regulated exposure to allergens can be useful in determining efficacy, onset, and optimal dosing of an AIT product.¹⁰⁰ EEC trials also have the added advantages of shorter durations and the need for fewer subjects. The EMA AIT trial guidance recommends provocation tests (i.e., allergen exposure in EECs) be used for dose-finding.¹⁴ The WAO also endorses the use of provocation trials to find optimal dosing.¹² The FDA accepts data generated by EEC trials to determine onset of action and dose, although data from EEC trials are not currently accepted by any regulatory authority as conclusive evidence for efficacy and safety of an AIT product.¹⁴ EEC may be considered as potential bridging trials in "hybrid" development programs and could lead to faster approval if EECs are used to bridge adult data with pediatric data or between ethnic subgroups. However, methods of priming or exposure are not standardized among EECs, leading to potential discrepancies in outcomes from chamber to chamber.
- Selection of the approved dose of SLIT-tablets in the United States, Australia, and Europe was based on the highest dose that demonstrated safety and gave the most consistent effect across multiple endpoints. There has been no demonstrable evidence of a higher risk for systemic allergic reactions or anaphylaxis with higher doses of SLIT-tablets. A different regulatory approach is used in Japan where the lowest efficacious dose of SLIT-tablet is selected as the appropriate dose for clinical use.
- The EMA AIT trial guidance recommends a sustained clinical effect be demonstrated by "maintenance of significant and clinically relevant efficacy during 2 to 3 treatment years" and long-term efficacy and disease-modifying effect by "sustained significant and clinically relevant efficacy in post-treatment years".¹⁴ The EMA Pediatric Development Committee has stated that AIT drug developers have to select one allergen product out of their portfolio to be evaluated for long-term, disease-modifying efficacy in adults and children (3 year treatment period and 2 year post-treatment follow-up).¹⁰¹ If long-term effects are established in both adults and children for one allergen by one allergen product it is not required to establish long-term effects for another allergen as long as the

drug formulation is the same.¹⁰¹ The Pediatric Development Committee acknowledges that this process is a compromise and will not address the antigenic differences among different extracts. The WAO recommends that claims of sustained effects be based on at least one appropriately sized RDBPC trial of 3 years duration and a disease-modifying effect be based on symptom monitoring in trials with a blinded follow-up of at least 2 consecutive years after AIT discontinuation.¹² When considering an indication of sustained effect in post-treatment years, the FDA uses the same criteria to determine the clinically meaningful difference as that used for the primary efficacy endpoint (at least a point estimate of 15% difference in the combined symptom and medication score from placebo with a 95% CI upper limit of at least -10%).

- The preventative effects of SCIT and SLIT on the development of AA, particularly in patients with HDM AR/C, has been shown in several studies.^{102, 103} Large real-world studies have shown that grass SLIT-tablets and birch AIT reduce the risk of AA development.¹⁰⁴⁻¹⁰⁶ Systematic reviews and meta-analysis concluded there was either no statistically significant evidence or only low-grade evidence to support the contention that AIT reduces future sensitizations, although the lack of high quality, well-powered randomized controlled trials was noted and such trials are needed.^{103, 107} The impact of AIT on the development of new allergen sensitizations and asthma may be greater in younger children.

7. What dose ranges of allergens can be expected to be efficacious?

Key takeaway: AIT efficacy is dependent on allergen dose and treatment duration. Standardized extracts to common allergens are available, but dose justification and efficacy data for some of these allergens are lacking. All approved SLIT-tablets have standardized allergen content, potency estimates, and dose recommendations based on dose-ranging trials.

- Several AIT trials have failed to demonstrate a statistically significant clinical effect. One possible explanation for at least some trials is that the potency of allergen content in the extracts used was too low and not based on dose-ranging trials.^{31, 108, 109} Efficacy is not a function of accumulated dosing over time¹¹⁰ and it is now well established that the efficacy of AIT is time- and dose-dependent with the clinical and immunologic response related to the individual dose,¹¹⁰ and the persisting improvement after stopping treatment related to the duration of treatment.¹¹¹ Effective dose ranges must be established based on clinical outcomes for each allergen product and cannot be extrapolated from a category or groups of allergens. A two-fold change in dose may lead to an ineffective dose. Thus, a minimal and maximum dose should be established.
- Use of the terms “high” or “low” dose is only relevant when comparing identical allergen preparations used within a given study and when the doses are defined relative to a common reference standard.¹¹²
- Information on the standardized and regulatory-approved extracts available in the United States, Germany, Australia, and Japan is readily available and represent various geographic regions. These extracts are shown in **Table 2**. “Standardized” means that the extract is labelled in units that are associated with biologic activity and each released lot of the extract meets specifications regarding potency.⁹⁷ “Non-standardized” means the extract is labelled in units that are not associated with potency (e.g., weight/volume or

protein nitrogen units) or clinical effect. Non-standardized extracts are used as “named patient products” in some countries or as part of individualized patient treatment sets.

- Currently there are no standardized extracts for SCIT in the United States or Canada for molds, mouse, rat, cockroach, dog, tree, and most weed pollens.^{36, 113}
- Many of the SCIT studies predate the standardization of extracts. However, meta-analyses have concluded that SCIT results in statistically significant reductions in seasonal AR/C symptoms and medication use in selected patients.^{114, 115} Based on the limited available data, the potential range of doses that may be efficacious for maintenance SCIT in the United States are shown in **Table 3**.^{5, 116} It is known that the extracts in Europe and the United States differ in potency, allergen content, and adjuvants;¹¹⁷ therefore, extrapolation of dosing data from extracts in the United States to extracts in other countries (and vice versa) is questionable and not supported by clinical trial data.
- Compounding allergen extract mixtures is common practice in the United States. The efficacy and safety of extract mixtures has not been rigorously studied (see section 11).
- Approved SLIT-tablets are standardized for allergen content and potency and have well-documented dose- and time-dependent treatment effects.^{16, 17, 23, 118-121}
- Approved SLIT-tablets are either freeze-dried or compressed, which differ in terms of disintegration, allergen release, and allergen bioavailability in the oral cavity.^{122, 123} These differences in tablet formulation may have important implications in that the nominal strengths of SLIT-tablets are not comparable unless the tablets are identical in formulation and allergen composition.¹²³ SLIT-tablets that differ with regard to allergen composition and/or formulation are not interchangeable,¹²³ and clinical efficacy must be established for each individual product.
- Off-label use of SLIT-drops prepared from commercial SCIT allergen extracts is widely practiced in the United States.¹²⁴ With one exception,¹²⁵ SLIT-drops have not been rigorously studied in RDBPC studies in North America and this form of administration does not meet today’s standard of safe and effective AIT practice, which should be based on the principles of EBM. We cannot support this practice and it is not endorsed by the AAAAI/ACAAI Joint Task Force.¹²⁶ It cannot be assumed that dosing of SLIT-drops using potency equivalent to SLIT-tablets for a given allergen will be effective.¹²⁶

8. How long should AIT be administered and when is onset of effect?

Key takeaway: In patients responding to treatment, a minimum of 3 years is recommended to achieve long-term efficacy, but treatment should be discontinued after 1 year in non-responsive patients. Benefits of SLIT-tablets may be observed in as little as 4 to 8 weeks after maintenance dosing is begun. Significant clinical and immunologic response to SCIT has been observed on reaching maintenance dosing after 5 weeks using a cluster regimen. There are currently no biomarkers or other measures of response, which remains an unmet need in AIT.

- Depending on up-dosing schedule, the time needed to see a response to SCIT is variable. There is general consensus among guidelines and a review of the literature that AIT should be administered for a minimum of 3 years to achieve long-term efficacy.^{5, 6, 11, 111}

The EAACI AIT guidelines recommend treatment with HDM SLIT-tablet for at least 1 year for the short-term treatment of HDM AR/C.¹¹ Two HDM trials (one prospective open-controlled trial with SCIT and one prospective, controlled trial with SLIT-drops) have shown some additional benefit with 4 or 5 years of treatment versus patients receiving 3 years of treatment.^{127, 128} In our experience, there are patients who require long-term continuous treatment to maintain benefit, but there is no published data to support this observation.

- With SCIT, improvement can be demonstrated soon after maintenance dose.⁵ Significant clinical and immunologic response to SCIT has been observed on reaching maintenance dosing after 5 weeks using a cluster regimen.¹¹⁰ In EEC studies, the onset of action of 5-grass SLIT-tablet and HDM SLIT-tablet based on statistically significant improvements in symptom scores vs placebo were found to be 1 month and 2 months, respectively.^{120, 121} In field data found that for timothy grass and HDM SLIT-tablet, onset of action was observed by weeks 8 and 14, respectively.^{129, 130}
- The AAAAI/ACAAI practice parameters recommend that discontinuation of AIT should be considered if no improvement is apparent after 1 year of maintenance therapy⁵ and German/Swiss/Austrian AIT guidelines state that if there are “no signs of success” after 1 year to a maximum of 2 years, treatment should be reconsidered.⁶ This brings up the question of how to know if a patient is responding to treatment? Currently this is assessed by patient reported decreases in symptoms and symptom-relieving medication use. In addition, considering the implications for cost and adherence, future work needs to be continued to better identify responders/non-responders to AIT products. Thus, in vivo and in vitro biomarkers of response and identification of responders/non-responders are a key unmet need in AIT. At this point in time the expert panel cannot recommend any biomarkers of AIT efficacy or safety.

9. Is there a class effect of AIT products?

Key takeaway: A class effect for efficacy among AIT products cannot be assumed, although all AIT products have the potential to induce local and systemic allergic reactions. Ideally, each AIT product needs to demonstrate claims for efficacy, safety, disease-modifying effects, and long-term effects based on clinical trial data. Only AIT products with documented efficacy and safety should be used.

- Clinical trials conducted for various AIT products demonstrate a great degree of heterogeneity. In addition, numerous differences exist in the preparation and content of extracts for AIT,¹³ which precludes an assumption that efficacy and safety demonstrated for a specific AIT product can be applied to other AIT products (class effect).
- Nevertheless, there has been an inappropriate practice of prescribing AIT products based on assumptions of class effect. Examples of inappropriate assumption of a class effect apply to long-term efficacy, disease modification, and appropriateness in subgroups of patients (i.e., concomitant asthma). The fallacy of attributing a class effect to AIT products has been recognized by several experts, regulators, the WAO, and EAACI; current guidelines recommend using products that have been individually evaluated for efficacy and safety.^{11, 12, 131, 132}

- All AIT products have the potential to induce local and systemic allergic reactions (see sections on systemic allergic reactions and local allergic reactions).

10. How can diagnosis of clinically relevant allergens be improved?

Key takeaway: The accuracy of identifying clinically relevant allergy needs to be improved. Molecular-based diagnostics may be useful for identifying AIT targets, but there are barriers to its use.

- For AIT, it is essential to precisely determine the causal allergens since it is only recommended for patients who have demonstrated evidence of allergy to clinically relevant allergens.^{5, 11} However, the present diagnostic methods of allergen sensitivity have the potential for clinically false positive results due to cross-reactive allergen epitopes, carbohydrate cross-reactive determinants, or in some cases, trace amounts of histamine in the allergen extracts.^{133, 134} While intradermal testing is recommended in situations where high sensitivity is needed to exclude life threatening sensitizations (i.e., drug and venom), use of this method for inhalant allergens may result in positive tests which are not clinically relevant and also may have systemic effects.
- Cross-reactivity among allergens is a complicating factor of interpreting results from traditional skin prick testing (SPT) or in vitro serum-specific IgE testing.^{135, 136} Medical history is not always able to clarify the clinical relevance of sensitivities.
- Patients who are sensitized to more than one allergen based on SPT or in vitro serum-specific IgE testing (polysensitized) may require more in-depth testing, such as nasal provocation tests, to determine if more than one of the sensitized allergens is clinically relevant (polyallergic).¹¹ Many clinicians do not have the capability for nasal provocation testing and extracts for such a procedure are not available/authorized in all countries. Conjunctival provocation tests can also be used to confirm allergen sensitization; however, these tests are not standardized and are not available to many practicing allergists. Also, because of the priming effect, a single nasal or ocular challenge may not reveal a clinically relevant allergen. Patient history is the most critical factor in determining the most clinically relevant allergen sensitivities.
- Standardization of procedures and extracts used in provocation tests are needed. The expert panel encourages AIT manufacturers to register products for provocation tests. A European method for nasal provocation testing has been recommended but needs to be evaluated worldwide.¹³⁷
- Molecular diagnostic platforms are available in multiplex arrays that can detect specific IgE for up to 157 allergen extracts and 125 molecular components from as little as 100 µl of serum or plasma. "Component-resolved diagnosis" can provide more specific information as to genuine (specific sensitivity to the primary allergen that drives the IgE response) versus cross-reactive (secondary sensitivity to an allergen that shares structural similarity with the primary allergen) sensitivities.^{138, 139} Cross-reactive sensitivities may occur among allergens from closely related species (i.e, Northern pasture grasses) or among allergens from different species that share proteins with conserved functions (i.e., pathogenesis-related [PR]-10 proteins).¹³⁹ Component-resolved diagnostic technology needs further assessment for approval to gain use in all world markets and is not yet

approved by some regulatory authorities (e.g., US FDA). Cost and time needed to run the arrays may also be barriers to use in daily practice.

- Use of recombinant hybrid molecules for SPT may be a potential tool for diagnosing true sensitivities from cross-reactivity in certain patients, but not as a rule in general clinical practice.¹⁴⁰ Recombinant molecules may allow for better standardization of allergen specific IgE assessment platforms.

11. Should multiple allergens be mixed for AIT?

Key takeaway: Multiple allergen AIT may be effective, but mixing of non-homologous allergens for SCIT and SLIT-drops may affect efficacy and safety. Use of one well-characterized and standardized allergen within the homologous allergen group is recommended by most members of the expert panel.

- Practitioners around the world have differing opinions on the use of mixing multiple non-homologous allergen extracts for SCIT in polyallergic patients. In Europe and Asia, most practitioners choose to treat polyallergic patients with a single allergen for the allergic sensitization that is considered to be clinically most relevant, preferably selecting a representative allergen within a homologous allergen group. In contrast, practitioners in the United States administer SCIT for all of a patient's relevant allergens, either in a mixture or as separate extracts. The AAAAI and CSACI guidelines state that it is reasonable to choose one pollen for treatment from within a highly cross-reactive group (i.e., homologous groups).^{5, 36} An example is timothy grass for Northern pasture grasses. European AIT guidelines recommend that patients who are polyallergic for homologous allergens receive AIT as either a single homologous allergen or a mixture of homologous allergens.¹¹
- Use of component-resolved diagnosis provides evidence of genuine sensitizations,^{138, 139} which helps avoid including irrelevant allergens in AIT mixtures.
- Mixing of allergens into a single AIT administration has its reservations in regard to safety. If a patient has an adverse reaction to an allergen mixture, the extract that caused the reaction cannot be isolated and proper precautions taken for future administrations. When mixing allergens, one needs to consider IgE cross-reactivity within homologous groups to avoid excessive potentially unsafe cumulative amounts of an allergen group and to reduce dilution of potency.^{5, 116, 141}
- Evidence from RDBPC studies evaluating the efficacy of AIT allergen mixtures, particularly with more than 2 non-homologous allergens or mixtures, are limited and the results are uncertain. More recent RDBPC data for multiallergen mixtures that meet today's standards for EBM has not been derived. Thus, efficacy trials using more than 2 extracts are needed for SCIT. An expert workgroup panel has published recommendations for a trial design to evaluate seasonal monotherapy versus multiallergen SCIT.¹⁴²
- As efficacy of AIT appears to be time and dose-dependent (different formulations may require different doses), the relative allergen doses achieved with multiallergen AIT due

to dilution might be lower and therefore less effective. The US Immunotherapy Practice Parameters 3rd Update recommend methods for preparing mixed allergen vials that achieve final maintenance doses within the estimated ranges of therapeutic efficacy.⁵

- Mixing with non-standardized extracts is complicated by different manufacturing practices and allergen concentrations among products.¹¹⁶ This practice is not evidence-based.
- Consensus among the expert panel regarding the use of non-homologous multiallergen mixtures for SCIT was not reached, with recommendations divided primarily along the regional practices mentioned above. There are three options: 1) to use one well-characterized and standardized allergen within the homologous allergen group for SCIT (i.e., timothy grass for Northern grasses, birch for trees with Bet v 1 homologues as major allergen) or 2) to use mixtures of homologous allergens (e.g. grass pollen) or 3) to use mixtures of non-homologous allergens. Members agree that the numbers of allergens for SCIT should be reduced as much as possible by taking into account known patterns of aeroallergen homology and cross-reactivity. Few trials of multiallergen SLIT-drops have been conducted and there is no solid evidence of efficacy.
- There are currently no marketed SLIT-tablets that contain multiple allergens that are not within the same homologous group (i.e., the 5-grass SLIT-tablet) and no trials have examined the efficacy of treatment with multiple non-homologous allergens via SLIT-tablets. Evidence suggests that simultaneous administration of two SLIT-tablets or SLIT-drops/SLIT-tablets from 2 non-homologous allergens is well-tolerated after a sequential dosing period.¹⁴³⁻¹⁴⁶
- The majority of RDBPC trials for SLIT-tablets, SLIT-drops, and SCIT in the last decade have included large proportions of polysensitized subjects. The success of most of these trials suggests that multisensitization does not interfere with the efficacy of single allergen AIT as long as the respective allergen is considered to be clinically relevant. Subgroup analysis of monosensitized and polysensitized subjects has confirmed efficacy of AIT in both populations.^{84, 147}

12. How can adherence to AIT be improved?

Key takeaway: Shared decision making, regular follow-up visits or other reminder mechanisms (i.e., phone calls, mobile app), education regarding initial local allergic reactions, and clinic flexibility may be key factors to improving adherence to AIT.

- Like most medical treatments, adherence to AIT can be low.^{148, 149} Discontinuation rates ranged from 6% to 84% for SCIT and 21% to 93% for SLIT.¹⁵⁰ Adherence to 3 years of treatment is approximately 30% for SCIT and SLIT-tablets.¹⁵¹ Barriers to AIT adherence generally include adverse events, health insurance coverage, cost, unrealistic expectations on time course, and perceived ineffectiveness.^{149, 152-155} Inconvenience of office visits is a specific barrier for SCIT adherence, whereas cost is a major reason for early discontinuation of SLIT.^{149, 155} In some countries, access to AIT prescriptions can be problematic and interfere with AIT initiation.

- There are a number of ways that adherence to AIT can be improved. Shared decision making appears to be key in this process.¹⁵⁵ The prescriber and patient should carefully consider the appropriateness of and preference for SCIT vs SLIT and the willingness and ability of the patient to be adherent. The prescriber should educate on the importance of adherence and determine if previous non-adherence to other daily medications will be relevant to SLIT.
- Education on potential initial local allergic reactions has been shown to decrease early discontinuation of SLIT.¹⁵⁶
- Short course SCIT, including modified allergens and immune adjuvants, are under development to attempt to enhance safety, maintain efficacy and improve adherence.¹⁵⁷ These products have much shorter treatment courses, generally a few weeks, thereby enhancing the opportunity for adherence. None of these products are currently approved in the US but some are available on a named patient basis in Europe. Similarly, accelerated build-up SCIT strategies may improve adherence as patients experience relief from symptoms in a shorter time period than conventional build-up.¹⁵⁸
- Reminder mechanisms (i.e., phone calls, text reminders, mobile apps) may improve adherence.
- Patient's perceived benefit and satisfaction with AIT are important for adherence.¹⁵⁴ Thus, regular follow-up visits should be conducted to reassess efficacy, tolerability, satisfaction, and adherence. Adherence could potentially be improved by providing flexible clinic hours to receive injections and availability to answer questions in between follow-ups, reinstitute treatment, or adjust SCIT dosing. As an alternative to follow-up visits, many allergists use telephone contact to help improve adherence.¹⁵⁴ Patients receiving SCIT are seen at least once a month during maintenance yet adherence still remains a problem.

Conclusions

Guidelines for AIT are lacking in some areas relevant to everyday allergy practice. There are still many gaps in AIT practice that need further evaluation as products and practices evolve. It is the intent of this panel to provide evidence-based recommendations that address the practical aspects of AIT in clinical practice. Key takeaways from the recommendations are shown in **Table 4**.

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Table 1. Indications for which at least one registered AIT product is approved by at least one regulatory agency. “Yes” indicates an approved product is available. “No” indicates an approved product is not available. It cannot be assumed that different AIT products for the same allergen have similar effects. Named patient products that have not received marketing authorization are available in some countries but are difficult to verify and are therefore not included. The information in this table must be interpreted with caution as some of the older approved SCIT and SLIT-drop products have not been evaluated based on full clinical development programs (phases I-III).

Allergen	Formulation	AR/C Symptoms		AA Symptoms		Sustained Treatment Effect		Disease-Modifying Effect	
		Adults	Children	Adults	Children	Adults	Children	Adults	Children
Grass	SLIT-tablets	Yes	Yes	No	No	Yes*	Yes*	Yes*	Yes*
	SLIT-drops	No	No	No	No	No	No	No	No
	SCIT-natural	Yes	Yes	Yes	Yes	Yes [†]	Yes [†]	Yes [†]	Yes [†]
	SCIT-allergoid	Yes	Yes	Yes	Yes	Yes [†]	Yes [§]	Yes	Yes [§]
Ragweed	SLIT-tablets	Yes	No	No	No	No	No	No	No
	SLIT-drops	No	No	No	No	No	No	No	No
	SCIT-natural	Yes	Yes	No	No	No	No	No	No
	SCIT-allergoid	No	No	No	No	No	No	No	No
Cedar	SLIT-tablets	Yes	Yes	No	No	No	No	No	No
	SLIT-drops	Yes	Yes	No	No	No	No	No	No
	SCIT-natural	No	No	No	No	No	No	No	No
	SCIT-allergoid	No	No	No	No	No	No	No	No
Tree	SLIT-tablets	Yes	No	No	No	No	No	No	No
	SLIT-drops	Yes	No	Yes	No	No	No	No	No
	SCIT-natural	Yes	Yes	Yes	Yes	Yes [†]	Yes [†]	Yes [†]	Yes [†]
	SCIT-allergoid	Yes	Yes	Yes	Yes	No	No	Yes [¶]	Yes [¶]
HDM	SLIT-tablets	Yes	Yes	Yes	No	No	No	No	No
	SLIT-drops	No	No	No	No	No	No	No	No
	SCIT-natural	Yes	Yes	Yes	Yes	No	No	No	No
	SCIT-allergoid	No	No	No	No	No	No	No	No

AA, allergic

asthma; AR/C, allergic rhinitis with or without conjunctivitis; HDM, house dust mite; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

*Indicated for long-term effect and disease-modifying effect for AR/C for some SLIT-tablets.

[†]In patients with allergic rhinoconjunctivitis, indicated for long-term prevention of asthma and bronchial hyperreactivity.

[‡]Long-term effect for 6 years.

[§]Long-term effect, prevention of new sensitizations, and improvement of asthma symptoms and lung function for 12 years.

[¶]Indicated for prevention of new sensitizations.

^{||}Indicated for prevention of asthma

Table 2. Availability of standardized and regulatory-approved SCIT and SLIT extracts in the United States, Germany, Australia, and Japan.

Allergen Source	United States		Germany		Australia		Japan	
	SCIT Extract	SLIT	SCIT Extract	SLIT	SCIT Extract	SLIT	SCIT Extract	SLIT
Pollen								
Short ragweed	+	Tablet	-	Tablet	-	-	-	-
Mugwort	-	-	+	-	-	-	-	-
Glasswort	-	-	+	-	-	-	-	-
Bermuda grass	+	-	-	-	+	-	-	-
Northern grasses	+	Tablet (5-grass mix)	+	Tablet (5-grass mix)	+	Tablet (5-grass mix)	-	-
		Tablet (timothy grass only)		Tablet (timothy grass only)		Tablet (timothy grass only)		
Honeygrass	-	-	+	-	-	-	-	-
Meadow weed grass	-	-	+	-	-	-	-	-
Meadowbark grass	-	-	+	-	-	-	-	-
White ostrich grass	-	-	+	-	-	-	-	-
Ruchgrass	-	-	+	-	-	-	-	-
Rye pollen	-	-	+	-	-	-	-	-
Pointed oat	-	-	+	-	-	-	-	-
Oat pollen	-	-	+	-	-	-	-	-
Barley pollen	-	-	+	-	-	-	-	-
Wheat pollen	-	-	+	-	-	-	-	-
Plantain	-	-	+	-	-	-	-	-
Birch	-	-	+	Drops Tablets	-	-	-	-
Alder	-	-	+	Drops (mixed with birch and hazel)	-	-	-	-
Hazel	-	-	+	Drops (mixed	-	-	-	-

				with birch and alder)				
Cypress	-	-	-	-	-	-	-	-
Japanese cedar	-	-	-	-	-	-	+	Drops
HDM	+	Tablet	+	Tablet	+	Tablet (2 manufact urers)	+	Tablet Tablet (2 manufac turers)
Epithelia								
Cat hair	+	-	-	-	-	-	-	-
Cat pelt	+	-	-	-	-	-	-	-

HDM, house dust mite; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Table 3. Standardized allergen extracts available in the United States and ranges for potential effective doses for SCIT maintenance.^{5, 116}

Allergen Source	Extract	Potency Labeling	Potential Effective Dose Range per Dose*
Pollen	Short ragweed	1:10, 1:20 w/v and 100,000 AU/mL	6-12 µg of Amb a 1 or 1,000-4,000 AU
	Bermuda grass	10,000 BAU/mL	300-1,500 BAU
	Kentucky bluegrass	BAU/mL	1,000-4,000 BAU
	Perennial ryegrass	BAU/mL	1,000-4,000 BAU
	Orchard grass	BAU/mL	1,000-4,000 BAU
	Timothy grass	BAU/mL	1,000-4,000 BAU
	Meadow fescue grass	BAU/mL	1,000-4,000 BAU
	Redtop grass	BAU/mL	1,000-4,000 BAU
	Sweet vernal grass	BAU/mL	1,000-4,000 BAU
	<i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i>	3,000, 5,000, 10,000, and 30,000 AU/mL	500-2,000 AU
Epithelia	Cat hair	5,000 and 10,000 BAU/mL	1,000-4,000 BAU
	Cat pelt	5,000 and 10,000 BAU/mL	1,000-4,000 BAU

AU, allergen units; BAU, bioequivalent allergen units.

*Due to variability in allergen content among standardized extracts (AU/BAU) from different manufacturers, dosing may vary and must be individually assessed. The estimated effective SCIT dose ranges cannot be extrapolated to effective doses of SLIT-drops.

Table 4. Key takeaways for AIT clinical practice from the expert panel.

Question	Key takeaway
1. What does evidence-based medicine (EBM) of AIT mean for the practicing allergist?	<i>EBM should guide AIT practices when it is available. Documented available EBM should be considered when selecting AIT products. Practicing allergists should be informed and educated on the levels of EBM for AIT.</i>
2. How can AIT guidelines be improved?	<i>Globally harmonized guidelines are needed to set common practice standards and improve AIT product development. Awareness and implementation of AIT guidelines may be improved by providing an abbreviated “handbook” of the major topics. As new evidence becomes available, future revisions of existing guidelines should add standardized protocols for extract labeling, handling treatment interruptions and re-initiation, multiple allergen administration, in-season initiation, and treatment of adverse events, as well as expanding information regarding patients with AA. Real-world experience and input from patients should also be considered in guideline development.</i>
3. How should clinical trial data be interpreted and translated into everyday practice?	<i>Interpretation of clinical trial data is complicated by the complexity and lack of standardization in symptom and medication scoring systems, allergen exposure variations, lack of a well-defined and validated clinically meaningful effect, and a substantial placebo effect. Effects of an AIT treatment on patient-reported outcomes may be more relevant to everyday practice. Efficacy data for a specific AIT product obtained in well-controlled adult trials may be bridged to children by supplementing with smaller pediatric trials.</i>
4. What are the risk factors and treatment for systemic allergic reactions and anaphylaxis?	<i>Systemic allergic reactions can occur with SCIT and at a much-reduced frequency with SLIT-drops and SLIT-tablets. The risk is likely increased by certain patient or treatment-related factors. Life-threatening or fatal anaphylaxis is rare. SLIT is generally viewed as being safer than SCIT. Available EBM for safety of SLIT supports at-home administration. Clinics should be prepared to treat anaphylaxis and patients with asthma should be assessed for asthma control before each SCIT injection. Prescribing of SCIT and SLIT should be limited to physicians with adequate training and expertise in the treatment of allergic respiratory diseases.</i>
5. What are the risk factors and treatment for local allergic reactions?	<i>Local allergic reactions to SCIT and SLIT are common. Local allergic reactions to SCIT can be reduced or treated with oral antihistamines and other methods. Local allergic reactions to SLIT are self-limiting and rarely need medical treatment. SLIT-tablets are contraindicated in the United States in patients with a history of eosinophilic esophagitis.</i>
6. What data should be used for regulatory approval of AIT products?	<i>Regulatory approval processes for AIT products have become more stringent in recent years but vary widely among countries which may affect AIT product</i>

	<i>availability and product claims. Regulatory agencies now require high-quality evidence of manufacturing quality, efficacy, and safety for approval and to support product claims.</i>
7. What dose ranges of allergens can be expected to be efficacious?	<i>AIT efficacy is dependent on allergen dose and treatment duration. Standardized extracts to common allergens are available, but dose justification and efficacy data for some of these allergens are lacking. All approved SLIT-tablets have standardized allergen content, potency estimates, and dose recommendations based on dose-ranging trials.</i>
8. How long should AIT be administered?	<i>In patients responding to treatment, a minimum of 3 years is recommended to achieve long-term efficacy, but treatment should be discontinued after 1 year in non-responsive patients. Benefits of SLIT-tablets have been observed in as little as 4 to 8 weeks after maintenance dosing is begun. Significant clinical and immunologic response to SCIT has been observed on reaching maintenance dosing after 5 weeks using a cluster regimen. There are currently no biomarkers or other measures of response, which remains an unmet need in AIT.</i>
9. Is there a class effect of AIT products?	<i>A class effect for efficacy among AIT products cannot be assumed, although all AIT products have the potential to induce local and systemic allergic reactions. Ideally, each AIT product needs to demonstrate claims for efficacy, safety, disease-modifying effects, and long-term effects based on clinical trial data. Only AIT products with documented efficacy and safety should be used.</i>
10. How can diagnosis of clinically relevant allergens be improved?	<i>The accuracy of identifying clinically relevant allergy needs to be improved. Molecular-based diagnostics may be useful for identifying AIT targets, but there are barriers to its use.</i>
11. Should multiple allergens be mixed for AIT?	<i>Multiple allergen AIT may be effective, but mixing of non-homologous allergens for SCIT and SLIT-drops may affect efficacy and safety. Use of one well-characterized and standardized allergen within the homologous allergen group is recommended by most members of the expert panel.</i>
12. How can adherence to AIT be improved?	<i>Shared decision making, regular follow-up visits or other reminder mechanisms (i.e., phone calls, mobile app), education regarding initial local allergic reactions, and clinic flexibility may be key factors to improving adherence to AIT.</i>

Supplemental Information*Method of development*

The list of authors was compiled based on their known clinical expertise in various areas related to AIT. A list of potential topics and questions was developed under the direction of Moises A. Calderon and topics were discussed during teleconferences with all available authors. Authors provided initial feedback on each topic, which was then developed into a preliminary draft by the medical writer. In addition to the expertise of the authors, non-systematic literature reviews were conducted to provide supplemental information on the AIT topics/questions. All authors were assigned specific topics to review, based on their expertise. The final document was read and approved by all authors for submission.