Title

AAAAI/ACAAI Joint Task Force on Practice Parameters: 2026 Allergen Immunotherapy Practice Parameter Update

Corresponding Author:
Dennis K. Ledford, MD, FAAAAI, FACAAI
Mabel and Ellsworth Simmons Professor of Allergy/Immunology
Morsani College of Medicine
University of South Florida and
Section Chief, Allergy/Immunology
James A. Haley VA Hospital
dledford@usf.edu
dennis.ledford@va.gov
(813) 601-7492

Authors

AAAAI/ACAAI JTF Allergen Immunotherapy Practice Parameter Panel
Dennis K. Ledford, MD (Co-Chair); Anne K. Ellis, MD, MSc, FRCPC (Co-Chair); Dana V. Wallace, MD; Tolly Epstein, MD, MS; David I. Bernstein, MD; Christopher W. Calabria, MD; Joseph P. Forester, DO; Désirée E.S. Larenas-Linnemann, MD; Yvonne L. Hsieh, MD; Michael Nelson, MD, PhD; Amber M. Patterson, MD; Aarti Pandya, MD; Punita Ponda, MD; Anitha V. Shrikhande, MD; Jody R. Tversky, MD

The AAAAI/ACAAI Joint Task Force on Practice Parameters: David B.K. Golden, MD; Marcus S. Shaker, MD, MS; Jonathan A. Bernstein, MD; Caroline C. Horner, MD; Jay A. Lieberman, MD; Matthew A. Rank, MD; Julie Wang, MD; Giselle S. Mosnaim, MD, MS; Anne K. Ellis, MD, MSc, FRCPC; Elissa M. Abrams, MD, MPH, FRCPC; Dennis K. Ledford, MD; Katherine Anagnostou, MD; Anil Nanda, MD; Derek K. Chu, MD, PhD

Allergen Immunotherapy

Preface

Allergen immunotherapy (AIT) is the original biologic therapy enabling specific immune modulation of a pre-existing immune response. Vaccination for infection was the first biologic therapy to induce an immune response in the absence of a prior immunity. Over the more than 100 years of AIT use, research has demonstrated that the empiric approach of administering increasing doses of allergen solutions, also called extracts, induces a variety of beneficial immunologic changes, provided the diagnosis of IgE-mediated sensitivity is correct, the specific allergen is administered, and an effective dose of the allergen is provided in each maintenance dose. Empiricism dominated AIT for its first 50 years of use, and the original premise of developing a protective immune response to a 'toxin' in the allergen solution was incorrect. Despite these limitations, careful clinical observations of allergic patients receiving treatment with allergen vaccines of appropriate potency have confirmed clinical benefit. The double-blind studies, starting with Frankland and Augustin in 1954, provided evidence of AIT's efficacy, albeit for only a limited number of allergens.[1]

AIT is a cornerstone of allergy and immunology practice in North America, the audience for this updated practice parameter (PP). The Allergen Immunotherapy Committees of both the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) were instrumental in initiating this effort and in completing the work. The Joint Task Force (JTF) for Practice Parameters (JTFPP) is grateful for the contributions from the members and leadership of these two committees.

This 4th update of the Allergen Immunotherapy Practice Parameter (AIT PP) is not intended to be a comprehensive review of the science and practice of AIT. Rather, this is an update from the time literature was gathered for the last parameter published in 2011.[2] Although this update emphasizes evidence published since 2010, the writing group (WG) considered the totality of available evidence across all publication periods. Greater weight was given to more recent studies with higher methodological quality, larger sample sizes, and clinically relevant outcomes, particularly when earlier evidence was limited, heterogeneous, or of lower certainty. The intention is to bring new information to the clinician in the recommendations. A few topics, such as cat, dog, and other animal AIT, not covered in detail in the last parameter, are reviewed using publications earlier than 2011. The WG felt that clinicians need more granular recommendations for these allergens despite the limited new literature. There is some duplication of the JTF 2017 AIT PP update which focused on US Food and Drug Administration (FDA) approved sublingual allergen immunotherapy (SLIT)-tablets (SLIT-T).[3]

This PP does not address food immunotherapy, oral or sublingual, or stinging-insect immunotherapy, as these will be or have been addressed in other PPs. There is some reference to the oral food immunotherapy literature for comparative and contextual purposes (grading scales, cofactor considerations for systemic reactions [SRs], future direction comparisons), but no recommendations for oral immunotherapy (OIT). This PP is not focused on allergy diagnosis, though there is some discussion, as AIT cannot effectively be applied without a correct diagnosis. The allergic diseases treated with AIT and discussed in this PP are:

- **Allergic rhinitis (AR):** An IgE-mediated inflammatory disease of the nasal mucosa triggered by allergen exposure and characterized by rhinorrhea, nasal congestion, sneezing, and nasal pruritus.
- **Allergic conjunctivitis (AC):** An IgE-mediated inflammatory condition of the conjunctiva caused by allergen exposure, presenting with ocular pruritus, erythema, tearing, and chemosis.
- **Allergic asthma (AA):** A chronic inflammatory airway disease in which allergen sensitization and IgE-mediated immune responses contribute to variable airflow obstruction, bronchial hyperresponsiveness, and respiratory symptoms.
- **Atopic dermatitis (AD):** A chronic, relapsing inflammatory skin disease associated with epidermal barrier dysfunction and immune dysregulation, characterized by pruritus and eczematous lesions.

Each section of this PP addresses a specific domain of AIT, including patient selection, efficacy, safety, and administration considerations, and relies on the published evidence relevant to that domain. Evidence related to harms, risks, and treatment burden is reviewed in dedicated safety sections for subcutaneous allergen immunotherapy (SCIT) and SLIT, respectively, to avoid unnecessary repetition and to allow a focused discussion of adverse events (AEs), contraindications, and practical burdens of AIT. There is some unavoidable duplication, particularly among patient selection, efficacy, and safety. This document is a traditional PP rather than a formal GRADE guideline; recommendations are informed by a comprehensive review of the literature, the quality and consistency of the available evidence, and the consensus judgment of the work group.

Some clinicians may question why there is little information related to the traditional practice of multi-allergen SCIT, the most common AIT option utilized in North America. The reason is there have been very few studies investigating multi-allergen SCIT since 2010. Many of the recommendations may seem less confident than the clinical results from the perspective of many experienced specialists utilizing ‘high-dose’ SCIT. This is due to limited or a lack of new evidence, so we recommend a shared decision-making discussion, communicating the lack of robust evidence, but the decision made by the clinician and patient may be influenced by the clinician’s experience and the patient’s preferences and values. Our intention is that the recommendations, even when conditional and based on limited evidence, will serve as the starting point of the shared decision-making process.

The WG’s preference was to only use evidence based upon research with products available in North America. Because of the limited studies performed with traditional aqueous allergen extracts, information from studies using modified allergen extracts, primarily from Europe, are cited to provide evidentiary structure, though extrapolated, to a specific recommendation.

Almost all AIT studies use statistical analyses with p-values rather than the more relevant clinical analyses of effect size. The clinician should keep in mind that patient-reported outcomes, the primary instruments used in AIT studies, should be interpreted with reference to clinically meaningful change on validated instruments rather than mathematical or statistical differences. In several sections of this PP, treatment effects from randomized trials and meta-analyses are reported as standardized mean differences (SMDs), which express the magnitude of the

treatment effect in units of standard deviation, allowing comparison across studies with different outcome scales. Although interpretation of SMDs has limitations, values of approximately 0.2 are generally considered small effects, approximately 0.5 moderate effects, and 0.8 large effects. In interpreting these results, readers should also assess whether the 95% confidence interval (CI) crosses zero, as CIs that include zero indicate that a statistically significant treatment effect cannot be confirmed.

The organization of the PP is to initially provide information related to the improved understanding of the mechanisms by which AIT achieves clinical efficacy and a brief review of biomarkers. The first major section is devoted to patient selection that overlaps with the next section devoted to efficacy. The final four sections address safety, AIT administration considerations, alternative methods for AIT, and the future of AIT. The WG included some calls to action, particularly regarding the importance and necessity for registries of large cohorts of multi-allergen AIT-treated patients using a standardized before-and-after measure of efficacy. This need is paramount, since randomized, double-blind, placebo-controlled (RDBPC) trials using currently available extracts are unlikely to be performed, making registries the only reasonable means of securing evidence of the efficacy of multi-allergen SCIT and SLIT.

Reference is made to dose, potency, concentration, allergen content, and allergen cross-reactivity. These are confusing terms, particularly when referring to non-standardized allergen extracts. There is great heterogeneity in the various ways of assessing SCIT or SLIT vaccine potency or effective dose. This variability limits the ability to compare studies. Dose is defined by the volume of the concentrated extract, by biologic units, or by the mass of a specific allergen in the maintenance injection or sublingual application. Bioequivalent allergy units (BAUs) are based upon skin test reactivity in an assemblage of highly sensitized individuals. The methodology was developed by the FDA's Center for Biologics Evaluation and Research. This type of standardization is not used outside of the US. Allergy units (AU) for house dust mite (HDM) extracts in the US is generally equivalent to BAU; but historically, the standard was developed prior to the technique that defines BAU, so the term AU was retained. However, AU is used outside of the US and is usually based upon a manufacturer's standard. Potency refers to the amount of allergen capable of degranulating mast cells by allergen-specific IgE (sIgE) cross-linking, usually defined by skin testing or challenge. This is not equivalent to a mass unit but generally reflects the amount of allergen that is extracted when raw material is mixed with the extraction solution and the likelihood of mast cell degranulation. Mass units are generally used for the major allergen in the extract, and in the US, this is used for the standardization of ragweed. Outside of the US, manufacturers may use internal assays to determine the mass of the major allergen. Cross-reactivity refers to different allergen extracts containing structurally similar allergens. The result is a single member of the cross-reacting group could be used to provide the dose sufficient for treatment of all in the group or smaller amounts (possibly a subtherapeutic dose) of each member of the group could be combined to provide a final therapeutic dose for the group. Cross-reactivity is prevalent among the seasonal pollen allergens, particularly the Northern pasture grasses and certain trees.

Methods

The work group was composed of members of the AAAAI and ACAAI Allergen Immunotherapy Committees, two JTFPP co-chairs (AE, DL), and invited members based upon geography, expertise and contributions to the JTF 2011 AIT PP. Conflicts of interest were reviewed and

vetted. Questions were developed by the work group related to aeroallergen SCIT and SLIT. These questions were subsequently reviewed by the JTFPP, who offered suggestions. The questions were divided into 6 topic clusters:

1. Patient selection
2. Efficacy
3. Safety
4. Vial preparation and administrative considerations
5. Alternative methods for AIT
6. Future directions of AIT

Subgroups were formed based upon interest and experience of the work group members and search strategies were recorded and performed related to the topic, with articles added about which individual work group members were aware. Actionable responses to the questions were developed based upon the evidence and a strength of recommendation and quality of evidence were determined by consensus. Systematic reviews and GRADE methodology are universally accepted as the ideal standard to inform clinical decision-making. This PP is not a GRADE document, but the WG strove to adopt as many qualities as possible in the language and separate the strength of the recommendation from the certainty of the evidence. The strength of the recommendation is either 'Recommend' or 'Suggest'. The specific searches were repeated by authors in the Spring of 2026 to be certain new publications had not occurred since the first search.

Recommendation rating scale[4]

Strong = recommended
• Desirable effects outweigh undesirable effects • Most patients would want this course of action • Most clinicians would implement these recommendations in patient care • Most policy makers should agree to follow these recommendations
Conditional = suggested
• Most patients would want this course of action, but many may not • Most clinicians would consider this course of action but would review the clinical situation to see if other options are also appropriate and involve the patient in shared decision-making, including patient preferences and values • Policy makers will likely agree to follow these recommendations but may require additional information from stakeholders

Deviations from recommendations and suggestions are appropriate in specific clinical situations, as the PP provides the starting point for the shared decision-making process and does not define the practice of AIT. A strong recommendation does not mean this course of action is always the most appropriate, but a rationale should be documented as to why an alternative is selected.

The certainty of evidence was determined by consensus of the work group using the following criteria:[5]

- High: Further research is very unlikely to change the confidence in the recommendation.
- Moderate: Further research is likely to affect the confidence of the balance of effects and may change the recommendation.
- Low: Further research is likely to change the recommendation.
- Very low: The estimate of the effect is very uncertain.

The literature for AIT generally does not provide effect size but relies on other statistical approaches. Thus, the strength of evidence assignment depended primarily on the WG assessment.

The first draft of the PP was reviewed by the members of the JTFPP, and the authors of each section replied to these critiques. The assembled document was then presented for review by the JTFPP, followed by the public, the general membership of our specialty societies, and designated representatives of the AAAAI and ACAAI, who served as peer reviewers for the Annals of Allergy Asthma and Immunology, the journal predetermined for publication. The WG is most appreciative of the editorial assistance provided by Erin P. Scott.

What is New?

Compared to the JTF 2011 AIT PP,[2] the current PP introduces some new concepts (e.g., SLIT treatment of AD), provides updated information on safety, and addresses some topics in greater detail than the 2011 PP. The major newer topics and recommendations are summarized in **Table 1**. The largest differences between 2011 and 2026 are the addition of more information about SLIT, as most of the research since 2010 has focused on SLIT. There are recommendations about the off-label use of FDA SCIT approved extracts for SLIT-liquid (SLIT-L) as well as FDA-approved SLIT-T. In addition, there are AIT recommendations related to incrementally older and younger patients and patients with comorbidities such as autoimmune disease, cardiovascular drug treatment, immunodeficiency, and malignancy. The importance of asthma in contributing to serious SRs with SCIT is emphasized with the updated AAAAI/ACAAI North American Immunotherapy Surveillance Study (NAISS). Documenting asthma control at the time of AIT prescription and at the time of administration is emphasized, ideally with the use of a validated instrument. AIT for controlled, severe asthma is discussed, emphasizing the safety of SLIT but recognizing SCIT could be utilized with proper monitoring. There are recommendations about alternative AIT, particularly intra-lymphatic immunotherapy (ILIT). Finally, there is a call to action for the development of real-world multi-allergen data for SCIT and SLIT using validated patient reported instruments. This is likely the only way to provide high-quality evidence for multi-allergen AIT.

Table 1. What is new.

Topic	Discussion	Recommendation Numbers
Oligo- and multi-allergen SLIT-T and SLIT-L	Use of more than one SLIT-T and dosing of SLIT-L	#45, #46, Table 8
AD	Treatment with HDM SCIT and SLIT-T	
Asthma	Treatment with SCIT and SLIT	#57, #58, #59, #85, #86
Age extension	Children 4 years of age and adults over 65 years	#4, #5

Comorbidities and cofactors	Autoimmune disease, malignancy, eosinophilic esophagitis, immunodeficiency, mouth ulcerations, exercise, upper respiratory infections, gastroenteritis	#9, #10, #11, #26, #78, #79, #80, #81, #82, #83
Animal allergy	Dog, horse and laboratory animal AIT	#17, #18
Accelerated schedules	Use of cluster and rush schedules	#69, #70, #71, #72
Local reactions and large local reactions	Importance in decision making related to next dose of AIT as well as strategies to reduce occurrence	#47, #48, #49, #50, #51
Reducing risk for SRs from SCIT	Strategies ranging from standardized assessments for asthma control, adjustments during peak pollen season, importance of staff training and documented consent	#52, #53, #54, #55, #56, #57, #58, #59, #60, #61, #62, #63, #64, #65, #66
Vial preparation	Aseptic technique and resources to fulfill USP Chapter <797>, Section 21 (the 'Allergy Exception')	#95
Transport of allergen vials	SCIT administration outside of the prescribing specialist's clinic	#95,#96
ILIT	Issues related to unapproved immunotherapy and learning health networks to advance the field of AIT	#98, #99
AIT and biologic therapy	A discussion of combining AIT with biologics in general and omalizumab in particular to control asthma and reduce the risk of SCIT	#73

AD, atopic dermatitis; AIT, allergen immunotherapy; HDM, house dust mite; ILIT, intralymphatic immunotherapy; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy; SR, systemic reaction.

Glossary

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Patient selection for SCIT and SLIT

Diagnosis of atopic diseases prior to AIT

The diagnosis of atopic disorders is based on a history consistent with IgE-mediated symptoms, appropriate physical exam findings and the presence of relevant sIgE, defined by either skin testing (ST), via skin prick testing (SPT) and/or intradermal/intracutaneous testing (IDT), or by in-vitro testing (i.e., measurement of sIgE). Sensitivity and specificity for SPT has been reported to be 85% and 77% respectively,[6] and SPT is well tolerated and safe.[7] Intradermal testing may be helpful if the patient has a negative SPT, but the clinical history suggests high pre-test probability of allergy to a specific allergen or group of allergens. However, given the decreased specificity of IDT (69%),[6] increased false positives, and risk of adverse reactions, broad, indiscriminate IDT is not advised. Moreover, there is only one very small study from 1994 showing benefit of SCIT/SLIT for inhalant allergens identified with IDT.[8]

The sensitivity and specificity of serum sIgE assays are comparable to that of SPT for respiratory allergens.[9] *In-vitro* testing modalities have some advantages over ST including numerical quantitation, safety, lack of drug interference (antihistamine therapies suppressing ST reactivity), and potential of long-term storage of serum specimens as a reference.[10] Potential disadvantages include cost and lack of immediate results in the majority of clinical settings. The two commonly available *in-vitro* methods for measuring clinically significant allergens are detection of sIgE to the whole allergen and sIgE to unique components of an allergen. This latter method is commonly referred to as component-resolved diagnostics (CRD) or molecular allergy diagnosis. The ability to distinguish between sIgE to unique allergenic components allows allergists to better identify true allergen sensitization vs cross-reactivity.[11] CRD is gaining increased recognition in the diagnosis of inhalant, food, and insect venom allergens and can also be useful in detecting sensitization involving minor allergen components. In some cases, sensitization to a certain molecular allergen is linked to a higher risk of more severe allergic reactions. CRD may offer the future potential of developing improved, targeted AIT.[12, 13] For IgE-mediated disorders, ST is considered the preferred testing modality with *in-vitro* sIgE testing being an appropriate complementary or alternative testing modality. Also, all trials showing efficacy with SCIT/SLIT selected the patients based on SPT, sometimes complemented with sIgE or challenge tests.

Finally, there is a small group of patients with symptoms consistent with AR, but a negative ST and absent systemic sIgE, while reacting to nasal provocation testing (NPT) with the clinically suspected aeroallergen. These local AR patients may benefit from SCIT/SLIT; many, but not all of them, develop systemic sIgE with time.[14, 15]

Initiation of AIT - general considerations

Biomarkers

1. **Recommendation: We suggest against the use of immunologic markers or biomarkers such as sIgE, SPT, or sIgG4 quantification to predict or assess the clinical efficacy of SCIT/SLIT.**

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Since the JTF AIT PP 3rd update[2], a wide range of possible biomarkers have been studied, and many of them differentiate between allergic and non-allergic individuals, between treated and untreated allergic subjects, and between immunologic responses within- and outside-season or in pre- and post-allergen-challenge. Several also differentiate between SCIT/SLIT responders and non-responders or correlate with combined symptoms and medication score (CSMS) improvement. However, very few biomarkers predict patients' response to SCIT/SLIT before therapy initiation or within months of initiation. Furthermore, only one of these evidence-based tests is clinically feasible. The specific to total serum pre-SCIT/SLIT IgE ratio may be promising, but only one Italian study, using a non-validated visual analog score (VAS) score as efficacy readout, showed that a (sIgE)/(total IgE) ratio higher than 0.162 had a good sensitivity and specificity to predict response to treatment.[16] So, even though the landscape of biomarkers is broad and many could successfully be linked to SCIT/SLIT efficacy (**Table 2** and **Table 3**), there are currently no biomarkers for use in clinical practice.

Patient selection is optimally based on a clear clinical history of symptoms correlating with exposure (difficult with perennial allergen exposure) and the documentation of sIgE with a positive SPT (generally defined as a wheal diameter ≥3mm larger than the negative control). A few clinical trials use ≥5mm wheal as positive cut-off for the SPT, others add serum sIgE (varying from class 2, ≥0.35 kU/L, up to >0.7 kU/L). However, comparative evidence on these serum cut-off values or classes, showing patients with higher levels fare better with AIT, is lacking. Other trials even include response to allergen-challenge as a mandatory inclusion criterion. Although intuitively higher cut-off values for SPT and requiring greater *in vitro* sIgE values would select more sensitive patients, potentially more likely to benefit from SCIT/SLIT, applying these criteria in clinical practice would exclude the potential benefit of SCIT/SLIT for patients who are historically very sensitive but with less skin test reactivity or sIgE.

Table 2. Parameters that have been shown to be related to responders vs non-responders on treatment or biomarkers related to symptom-medication score improvement per patient.

Parameter	**Ref.**
***In vivo* biomarkers**	
SPT reduction	Boonpiyathad et al, 2019[17]
FeNO reduction (28 ppb)[a]	Hoshino et al, 2020[18]
Serum specific IgE	
Reduced IgE-allergen interactions (as also expressed below under FAB inhibition)	Shamji et al, 2012[19]
Rise in IgE blocking factor	Schmid et al, 2021[20]
IgG and IgA responses	
Serum antibodies not related to SCIT or SLIT efficacy Local nasal specific IgA_1 in SLIT is related to TNSS	Shamji et al, 2021[21]
Specific IgE -facilitated allergen binding/blocking factor	

Rise in specific IgG4 serum blocking activity	Shamji et al, 2019[22]
Rise in specific IgG4 nasal fluid blocking activity	
Inhibition of CD23-dependent IgE-facilitated allergen binding (IgE-FAB)	Shamji et al, 2012[19]
Basophil activation	
Basophil sensitivity decrease	Schmid et al, 2021[20]
Cytokines and chemokines	
Periostin decrease of 30.9 ng/mL[a]	Hoshino et al, 2020[18]
Increase in musculin, in PBMC harvested T-cells	Iinuma et al, 2022[23]
Increase in gene expression of PIK3R1 in several Tcells	Fan et al, 2023[24]
Increase in serum IL-10, IL-35, and TGFb	Zeng et al, 2023[25]
Cellular markers	
C1Q of PBMC harvested DCs, increase	Zimmer et al, 2012[26]
STAB1 of PBMC harvested DCs, increase	
Activated specific … (increase) - FOXP3+Helios+ Treg cell - IL-10+ Treg cells - IL-10+IL-22+ Treg cells - IL-22+ Th cells	Boonpiyathad et al, 2019[27]
Reduction in dysfunctional Der p 1-specific Treg cells ILT3+CD4+CD25+FOXP3+	
% of Treg, Breg and Tfr, increase	Zeng et al, 2023[25]
%HDM-specific IgG4+ B-cells, plasmablasts, increase	Boonpiyathad et al, 2019[17]
Breg cells: IL-10+ Bregs and dual-positive IL-10+IL-1RA+ , increase	Boonpiyathad et al, 2019[17]; Pointner et al, 2022[28]
IL-10+ CTLA-4+ ILCs[b], increase	Boonpiyathad et al, 2021[29]
Lin-CD127-CD161+CRTH2+ ILC2s, decrease	

Breg, regulatory B cell; CLTA-4, cytotoxic T lymphocyte-associated protein 4; C1q, complement component 1; DC, dendritic cells; FAB, facilitated allergen binding; FeNO, fractional exhaled nitric oxide; IL, interleukin; IL-1RA, IL-1 receptor antagonist; ILC, innate lymphoid cell; ILC2, group 2 ILCs; ILT3, immunoglobulin-like transcript 3; PBMC, peripheral blood mononuclear cells; ppb, parts per billion; SPT, skin prick test; STAB1, stabilin-1; Tfr, follicular regulatory T cell; TGF, transforming growth factor; Th, T helper; TNSS, total nasal symptom score; Treg, regulatory T cell.

[a]Cut-off values for change in parameters with best area under the curve receiver operating characteristic.

[b]Unclear if these are exhausted IL-10-producing ILC2s, or regulatory ILCs.

Table 3. Parameters that could serve as possible predictive biomarkers pre-SCIT/SLIT.

Parameter	**Ref.**
Specific IgE	
Pre-SCIT/SLIT specific IgE/total IgE ratio higher than 0.162	Di Lorenzo et al, 2009[16]

Cytokines and chemokines	
Pre-SLIT, serum miRNA exosomes: has-miR-24-3p, decreased at baseline	Cao et al, 2023[30]
Pre-SLIT, serum miRNA exosomes: serum has-miR-128-3p, increased at baseline	
Pre-SCIT serum CXCL13, increased	Cheng et al, 2022[31]
Other	
Pre-SCIT/SLIT metabolomics: linolenic acid and arachidonic acid, higher in responders	Xie et al, 2021[32]
Pre-SCIT/SLIT metabolomics: lactic acid, ornithine, sphingosine, creatinine, higher in non-responders	

CXCL13, C-X-C motif ligand 13; miRNA, microRNA.

2. Recommendation: We recommend specialists should initiate a shared decision-making conversation to discuss the value of AIT for patients with AR, AA, and/or moderate to severe AD and who remain symptomatic despite disease management who want to reduce medication use, or who want a potentially disease-modifying treatment.

Strength of Recommendation: Strong
Certainty of Evidence: Low

AIT is indicated for patients with AR, AC, and/or AA who cannot achieve control of symptoms with allergen avoidance and medications, who do not want to take long-term medications, who have experienced adverse side effects from medications, and/or who desire the potential to prevent or reduce the severity of comorbid conditions.[5, 33] AIT reduces disease severity and improves quality of life (QoL) in patients with AD[34] and may be considered in patients with moderate to severe disease.[35-37] See the Efficacy section of this PP for recommendations with specific indications and qualifiers per disorder.

Initiation or continuation of SCIT/SLIT requires a shared decision-making discussion incorporating risks, benefits, and patient preferences.[38] The risk discussion is particularly important in patients with medical co-morbidities (e.g. cardiovascular conditions, advanced age, or difficult to control asthma) or who receive medications that may impair response to epinephrine and/or increase severity of anaphylaxis (e.g. beta-blockers or angiotensin converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARBs]). The 2024 JTF Anaphylaxis PP states SCIT/SLIT is not contraindicated in such patients, but a shared decision-making discussion should be documented.[39]

While the treating physician's experience and expertise may impact their willingness/comfort to offer AIT to patients with potential complicating comorbid conditions,[40] the decision to treat with AIT should be made after a detailed discussion between the patient and treating physician concerning the risks, benefits and logistics of AIT (i.e., shared decision-making).[5, 41]

Adherence

3. Recommendation: We recommend a documented shared decision-making discussion prior to AIT on the risks and benefits of AIT and the patient's preferences.

Strength of Recommendation: Strong
Certainty of Evidence: Low

Adherence to both SLIT and SCIT is generally poor in multiple real-world studies. Careful selection of patients will maximize successful completion of the 3-5 years of SCIT/SLIT, thereby providing the best chance at achieving desired, evidence based, clinical outcomes. Multiple studies have documented that over half of the individuals initiating AIT abandon treatment before completion of the prescribed 3-5 years of treatment due to multiple factors.

Table 4. Factors that may affect adherence: problems and possible solutions.[42, 43]

Variables	Specialist potential action	SCIT[a]	SLIT[a]
Lower patient understanding of treatment, adverse effects & administration schedule	Good patient-physician communication. Re-confirm if everything was understood. Offer repeated information in several ways: verbal, written, video, social media, etc. Use technology tools for reminders.		
Lower perceived efficacy of initial treatment	Initial full explanation of when to expect some improvement: it is a long process; immunological changes take time (months!). Insist on continuation of control medication. When coming in for shots: staff reconfirms it takes time before improvement starts.		
Convenience	Some patients are better with SLIT (very adherent ones), some with SCIT, but time/travel is needed for the regular office visits. Offer patients the flexibility that they can always switch to the other route.		
AEs	Explain before starting which AEs to expect and what shall be done about them. Routinely interrogate about AEs on every (administration) visit.		
Cost/copays	Explain full administration schedule and how often payments should be made. Support where possible with insurance coverage. Propose the least expensive option. In some patients: start with only one vial, including the most reactive allergens.	Variable	Variable
Social factors: Health literacy	Use common language, use comparisons with things/situations about which people are acquainted. Repeat and repeat messaging.		
Income	See above in co-pays.	Variable	Variable
Housing	With unstable electricity, avoid liquid SLIT.		Liquid

Location	See below.		
Age	Elderly: give them more time. Repeat explanations. Children: once they can understand, also direct your explanations/questions to them, involve them.		
Patient-physician relationships	Have some method of possible, limited, communication in place, so patients feel supported. Encourage nurse/staff-patient interaction. Teach nurses/staff about AIT.		
Follow-up frequency	SCIT: offer cluster, rush or modified rush schedules for build-up.		
Location: distance and travel to and from house or work	When far away from the office: SLIT might be the better option. Involve GP closer to the patient's location for administration if possible		
Change of residence	Cooperate with colleagues. Let the patient know treatment can be continued in another office or administration route adjusted (change SCIT to SLIT).		
Travel for work or leisure	Explain to patients what you do when they come in late for a shot (not all is lost, high flexibility). When schedule is often missed: SLIT-T might be the better option. Another option is luster or rush build-up for SCIT and reinforce maintenance injections are monthly. SLIT-L may be difficult as cold-chain is needed.		Tablet Liquid

AE, adverse event; GP, general practitioner; SLIT-L, SLIT liquid; SLIT-T, SLIT tablet.
[a]Applies for SCIT or SLIT: the darker the grey, the stronger the variable applies for the administration route. The absence of shading indicates the variable applies equally.

Multiple barriers to adherence to SCIT/SLIT are reviewed in **Table 4**.[42, 44-46] For example, a retrospective Dutch pharmacy database study of 6,486 patients starting AIT between 1994 and 2009 (2,796 SCIT and 3,690 SLIT) had an overall 18% 3-year completion rate, with medians of 1.7 and 0.6 years, respectively ($p<0.001$).[47] Independent predictors of premature discontinuation included SLIT compared to SCIT, lower socioeconomic status, and younger age. In this study, 56% of the persistent patients (i.e., those who finished the 3-year AIT course) were never late in picking up their medication from the pharmacy.[47]

In another retrospective study of 555 patients discontinuing SCIT/SLIT for treatment of AR and/or AA, following factors for non-adherence were reported:[48]

- copayment for allergy injections and/or payment for allergen extract by health insurer (40%);
- inconvenience of travel (15%);
- change of residence (8%);
- concurrent health problems (5%);
- patient-perceived ineffectiveness (4%);
- patient-perceived lack of need to continue immunotherapy (2%);
- adverse effects from injection (local reaction, 1%;
- systemic allergic reaction (0.5%);

- trial of alternative medicine (0.1%).

One important factor that could contribute to improved AIT adherence is a shorter duration of the build-up phase.[44] Longer disease duration was associated with lower adherence, suggesting the value of initiating AIT as early as possible in the disease course.[49] Another study of 897 patients in the Military Healthcare System, without out-of-pocket expenses for treatment, reported only 34% completed 3 or more years of SCIT.[50] Male sex was the only factor associated with reaching the maintenance dose.[50]

There is a wide variability in reported adherence rates. A 2014 systematic review of adherence in SLIT prospective and database studies with different designs, including some testing interventions to enhance adherence, found that 55-82% of patients abandoned therapy before completing the recommended 3-5 years of treatment.[51] In contrast, a systematic review of 81 published SLIT RDBPC trials involving nearly 10,000 participants reported a low dropout rate of 14%, with minimal differences between active and placebo groups.[52] This illustrates the difference between nonadherence in clinical studies compared to real-world data.

It is difficult to compare factors and interventions impacting SLIT versus SCIT adherence due to differences in patient populations, allergen extracts (tablet, liquid, modified allergens, etc.), and study methodologies. Only a few studies have directly compared SCIT and SLIT adherence; SCIT adherence was superior.[53, 54] A systematic review of real-world SLIT for AR analyzed approximately 1600 abstracts and 32 manuscripts with approximately 64,000 patients.[55] While 26 studies reported persistence rates (patients continuing SLIT) ranging from 7-89% and 18 studies reported adherence rates (patients continuing and administering according to dose and schedule) ranging from 10-97%. As expected, studies with longer follow-up periods showed lower rates of adherence.[55]

Adopting patient-centered, proactive approaches to patient selection and management during treatment has improved adherence.[56] A recent study using Delphi consensus methodology led to the development of a validated questionnaire that can be used in shared decision-making.[57] It incorporates 6 patient factors: patient knowledge, barriers to patient adherence, patient behavior, future actions, treatment costs and final patient preferences.[57]

A recent review of factors adversely impacting SCIT/SLIT persistence, compliance, and adherence described erroneous expectation of effectiveness, adverse reactions, unrelated medical conditions, financial issues, and inconvenience (**Table 4**).[43]

AIT in older adults

4. Recommendation: We recommend that SCIT and SLIT be considered for adults with for AR, including those over 65 years of age, when they meet standard eligibility criteria.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

The JTF 2011 AIT PP did not provide a specific recommendation related to treatment of older adults with SCIT/SLIT.[2]

Since 2008, at least four RCTs have demonstrated the efficacy of either SCIT or SLIT for more mature adult patients with AR in various age groups beginning at age 60 years.[58-63] Doses in these studies were comparable to those used for younger adults and children. Adding to the evidence for SCIT efficacy in older adults, a study identified that three years of pre-seasonal grass SCIT treatment led to a 41% reduction in CSMS.[59] Related to SLIT, one study of 111 participants aged 60-75 years treated for three years with HDM SLIT-T demonstrated a 44% reduction in total nasal symptom score (TNSS) compared to 6% in the placebo group ($p<0.05$), and a 35% reduction in medication score (MS) vs no significant change with placebo ($p<0.05$).[58] Another study of 86 participants, aged 60-75 years, treated with HDM SLIT-L for two years, similarly demonstrated a significant reduction in symptom score (SS) and MS.[63] Efficacy in a randomized controlled trial (RCT) has also been demonstrated for 3-year treatment with grass SLIT-T in older adults.[60]

There is also recent evidence of sustained treatment effects in older adults. A prospective observational study of 109 patients with AR treated with 3 years of grass preseasonal SCIT demonstrated a sustained reduction in CSMS, improved QoL (more than twice the minimal important difference)[64] and persistence of serum grass sIg4 three years after discontinuation of SCIT.[62] A prospective study of 47 patients receiving HDM SLIT-L for three years in a RCT demonstrated three years after discontinuation a sustained reduction in SS, improvement in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and a persistence of HDM allergen-specific IgG4 (sIgG4).[61]

In aggregate, these studies support consideration of SLIT or SCIT for older adults who have an appropriate indication and lack significant comorbidities. However, participants were appropriately excluded if they had significant comorbidities that would increase the risk of adverse effects or impair treatment of AEs with epinephrine. Importantly, none of the studies identified a significant safety signal among treated patients. Multiple reviews since the JTF 2011 AIT PP have also concluded that treatment in this age group is safe and effective, even though it is very probable that several included individuals with mixed rhinitis, as non-allergic rhinitis, particularly vasomotor and atrophic rhinitis, is frequent in this age group.[65, 66] Overall, data remain limited for patients beyond age 70-75 years, and there is a paucity of data directly comparing outcomes in older patients to younger populations. All but one of the controlled studies reviewed were conducted at a single center, further highlighting the need for additional studies in this age group. In addition, there remains limited data for the treatment of AA in older adults.

AIT in children

5. Recommendation: We suggest the use of SCIT and SLIT in children with AR aged 4 years and older if they meet the other eligibility criteria.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

The JTF 2011 AIT PP summary statements 17 and 18 stated that SCIT is safe and effective in children as young as 5 years, possibly younger.[2] The 2017 JTF SLIT focused PP update also noted that there are FDA approved SLIT-T products judged to be safe and effective for use in children 5 years and older.[3] Subsequent studies confirm those findings and have added additional data supporting the efficacy and safety of SCIT and SLIT in young children.

Recent international consensus statements support the efficacy of SCIT in pediatric patients with allergic rhinoconjunctivitis (ARC).[67] A systematic review from 2013 that analyzed 13 RCTs (920 children) using SCIT for the treatment of pediatric AA and ARC showed that there was moderate quality evidence to support that SCIT improves AA and AR symptoms.[68] Since the JTF 2011 AIT PP there are only a limited number of SCIT studies with children younger than 5 years.[69] A prospective, single-center trail from China demonstrated safety and efficacy of HDM (Alutard™SQ, ALK) SCIT in 91 children younger than 5 years of age (mean age 4.13 years). Eightly-eight percent were diagnosed with AR and 12% with AA (Yang, Y., Ma, D., Huang, N., Li, W., Jiang, Q., Wang, Y., Wang, X., Yang, L., Zhu, R., 2021. Safety of house dust mite subcutaneous immunotherapy in preschool children with respiratory allergic diseases. Italian Journal of Pediatrics 47.. https://doi.org/10.1186/s13052-021-01046-z). The intended maintenance dose was 50-100,000 SQ (4.9-9.8 ug Der p 1). Twenty-six percent did not reach the target maintenance dose, primarily due to LRs. Despite this, efficacy, as reflected by combined symptom medication scores (CSMS), improved from 4.47 baseline to 1.94 in year one, 1.45 in year two, and 1.31 in year three. A randomized Italian study uinsg multi-allergen SCIT in 50 children younger than 4 years with asthma (23 standard of care, 27 SCIT + standard of care) did not demonstrate improvement in clinical asthma outcomes, although caregiver quality of life improved (de Vos, Gabriele, et al. "A randomized trial of subcutaneous allergy immunotherapy in inner-city children with asthma less than 4 years of age." *Annals of Allergy, Asthma & Immunology* 126.4 (2021): 367-377). Systemic reactions occurred in 22% (1.8% of all SCIT injections), but none were treated with epinephrine. The investigators concluded pre-school, inner-city children are exposed to multiple allergens and a larger study of SCIT in children younger than 4 years is needed to demonstrate efficacy. Most pediatric studies or SCIT trials enroll children 5 years and older or enroll adolescents.[69] However, there is no evidence or rationale to suggest that there are negative effects or differences in efficacy of AIT in children under the age of 5 years.[70] A retrospective chart review with 2927 children treated with pollen or HDM SCIT for at least one year showed a decrease in nasal symptoms with a favorable safety profile.[71] Other recent studies also continue to show post-cessation or long-term efficacy of SCIT in children.[72]

Since the JTF 2017 SLIT PP,[3] several SLIT trials and real-world studies have shown the efficacy of pollen and HDM SLIT in children.[73-77] In a real-world study of 335 children, SLIT was effective.[78] A multicenter RDBPC trial enrolled 1025 children between the ages of 5-17 years with ragweed AR or ARC found significant improvement in daily SS and daily MS with 28 weeks of daily ragweed SLIT compared to placebo.[79] Similarly, pooled data from studies of timothy grass SLIT showed a favorable safety profile in children.[80] Other studies have confirmed no significant differences in safety and efficacy of SLIT between children and adults.[81-83] Use of SLIT for AC and ARC was reported in a meta-analysis of 13 RCTs in children, demonstrating improvement in eye symptoms, particularly in pollen-induced AC, but not in HDM-induced AC.[84] Another systematic review and meta-analysis that included 16 pediatric studies, including abstracts, reported improvements in TNSS and total MS with the use of HDM SLIT (tablets and liquid), although the authors cautioned about monitoring for AEs.[85]

For studies that combined SCIT and SLIT, there is similar evidence of efficacy in children. In 2017, a meta-analysis of 160 studies that included 135 RCT studies showed the efficacy of SCIT and SLIT in both adults and children.[86] Subgroup analysis in this study of 12 RCT that only included children also showed a significant improvement in short-term CSMS (SMD -0.25 (95% CI: -0.46, -0.05]) for both SLIT and SCIT, and the meta-analysis also included four available studies that assessed long-term efficacy, one of them included children.[86]

6. Recommendation: We suggest aeroallergen SCIT and SLIT to prevent the development of AA in children with AR.

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

Since the JTF 2011 AIT PP,[2] a large study (GAP) that randomized 812 children with AR and without AA to receive a timothy grass SLIT-T versus placebo found a reduction in ARC symptoms and medication use after 3 years of treatment, as well as a significant reduction in risks of development of AA requiring medical treatment.[87] However, the trial did not show a reduction in the proportion of children with onset of asthma as defined by a combination of asthma symptoms, medication, and lung function measurements.[87] A short-term benefit preventing patients with AR from developing AA was noted in a meta-analysis that included 17 RCTs and 15 controlled-before-after trials (prospective but not randomized) treated with SCIT and SLIT (tablet and liquid) showed short-term efficacy (RR 0.40 [95%CI: 0.29, 0.54]), short-term being defined as within 2 years after the completion of treatment.[88] Sustainability of that benefit beyond the 2 years was unclear. Likewise, there was a short-term reduced risk of new allergen sensitization, although this was not confirmed in the pre-specified sensitivity analysis; and there was no long term (>2 years) reduction of new sensitivities.[88] A real-world population-based cohort study with 1,739,440 patients, including 2586 adolescents with coincident asthma, found that those treated with SLIT (tablet or liquid) or SCIT with AA were less likely to have progression of asthma severity from GINA step 1 to GINA step 3.[89] Another large systematic review that included 18 long-term observational or RCT studies with 1049 children and 10,057 adults found that there was low-grade level evidence supporting the use of AIT in the prevention of new allergen sensitization.[90] Another smaller study found no benefit of HDM SLIT on prevention of new sensitization when 37 children who received SLIT-L were compared to 184 patients receiving only pharmacotherapy.[91]

Overall, a recent pooled analysis of 33 studies found favorable, similar evidence for primary, secondary, and tertiary prevention of new sensitizations, reduction of allergic disease onset and progression, and immunomodulatory changes with both SCIT and SLIT (tablet and liquid).[92] However, higher-quality studies are needed.

7. Recommendation: We recommend the same dose, dosing schedules, and duration for AIT in children as those used for adults.

Strength of Recommendation: Strong
Certainty of Evidence: Low

There are no head-to-head RCTs comparing dosing efficacy and safety of SCIT or optimal length of treatment between adults and children. SCIT dosing typically uses identical dosing

strategies and schedules for adults and children. With this practice, there is no evidence that efficacy is any lower or AEs any greater or more severe in children, although other guidelines do not recommend treatment of children under the age of 2 years.[70] One US report described higher rates of grade 1 and 2 SRs in a retrospective study of 270 children when compared to adults.[93] Another report described higher adverse reactions in 344 children treated with SCIT under the age of 12 years ($p<0.001$).[94] Finally, there is a paper describing more LRs and SRs in children.[72] However, larger studies have not confirmed these findings.[70, 86, 95, 96] A real-world pediatric prospective survey of 1563 pediatric patients undergoing SCIT or SLIT found a 1.53% SR rate, with the majority of reactions not severe.[97] For SLIT, a study that specifically looked at efficacy, safety, and immunological parameter changes found no influence of body weight on outcomes in children.[98]

For length of treatment, data are summarized in detail in the section on length of treatment in this document (see Efficacy section). However, specifically, a study of 81 children randomly assigned to receive HDM SCIT for either three or five years found a significant decline in VAS at year three (70%, $p=0.001$) and rhinitis global score (44% improvement; $p=0.002$).[99] At year five, there was an additional 30% decrease in AR VAS global score, but no significant change at five years compared to three years in other parameters.[99] Another study looking at the long-term efficacy of HDM SCIT in 130 children demonstrated positive results, with a decrease in the TNSS, CSMS, VAS, and RQLQ during 3 years of SCIT and for 2 years after discontinuation (5 years from initiation of AIT).[100] Other studies have shown efficacy up to 3-7 years after discontinuation.[101, 102] For SLIT, the JTF 2017 SLIT focused PP did not suggest different dosing or a modified length of treatment for children.[3]

AIT for patients with chronic urticaria

8. Recommendation: We suggest no adjustment to the dose of SCIT or SLIT for the treatment of AR and/or AA in patients with co-existing CSU.

Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

There is a paucity of data regarding the efficacy or safety of SCIT or SLIT for AR or AA in patients with co-morbid chronic spontaneous urticaria (CSU). From a practical standpoint, administration of SCIT or SLIT in patients with uncontrolled CSU may limit the clinician's ability to distinguish systemic reactions to SCIT or SLIT from CSU outbreaks, thus theoretically increasing safety concerns.

Although some cross-sectional studies suggest an increased prevalence of atopy in patients with CSU, the clinical relevance of this finding is unclear.[103-105] In the situation where recurrent urticaria is caused by aeroallergen sensitization, which represents a very small number of patients with recurrent urticaria, some case reports and uncontrolled case series suggest that SCIT may provide benefit.[106] Larger, well-controlled studies are needed.

AIT for patients with malignancy, immunodeficiency conditions, or autoimmune diseases

Malignancy

9. Recommendation: We suggest consultation with the patient's oncologist when initiating/continuing AIT in patients with comorbid cancer.
Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

There is no evidence suggesting a relationship between the development of cancer and concomitant allergic diseases.[107, 108] There is also no evidence that AIT increases the risk of cancer. Historically, cancer has been a relative contraindication to AIT.[109] However, long-term prospective database studies have demonstrated that in a group of patients who received AIT vs. those who did not, there may in fact be a decrease in the incidence of leukemia.[110] As for efficacy, there is no reason to believe that SCIT or SLIT in patients in remission of cancer is less effective, and a position paper did not consider a history of malignancy a contraindication to SCIT/SLIT.[70]

In a case series of patients with stage 1 cancers (4 patients with melanomas, 1 lung and 1 breast cancer), these individuals safely received concomitant SCIT while also receiving chemotherapy.[111]

In the AAAAI membership survey on contraindications to SCIT, 93% of the 1085 respondents did not consider cancer in remission a contraindication to starting SCIT, between 60-70% would prescribe SCIT in patients undergoing active treatment for cancer, and over 2500 patients with various cancers had actually been treated by the members.[112] Membership was more cautious on treating patients with a malignancy and concurrent cancer therapy, although 67% found this was not an absolute contraindication to SCIT. Furthermore, respondents reported experience in 720 patients.

Theoretically, the cytotoxic, immune suppressive, or immune modulating effects of various treatments for cancer and autoimmune conditions may impact the efficacy and possibly the safety of SCIT or SLIT. Data regarding coadministration of AIT with particular anti-cancer therapeutics are lacking. Given the wide variety of therapeutics used to treat malignancies and autoimmune conditions, consultation with the prescribing physician (oncologist, rheumatologist, etc.) may be necessary when co-administering SCIT or SLIT in such patients.

Immunodeficiency conditions

10. Recommendation: We suggest that AIT for AR and/or AA is an option for patients with primary or secondary immunodeficiencies.
Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

The JTF 2011 AIT PP suggested that AIT is a consideration in patients with immune deficiency and AR or AA.[2] This recommendation is unchanged. Data regarding the safety and efficacy of

SCIT/SLIT in patients with primary and secondary immune deficiencies are very limited. Preliminary studies in the 1990s suggested that SCIT may be effective and well-tolerated in patients with mild/moderate HIV disease, but more definitive studies have not been conducted.[113] Data from a 2006 survey of AAAAI members found that practitioners prescribed SCIT less often in HIV+ patients; only 40% of practitioners started patients with HIV on SCIT and 60% of practitioners continued SCIT when an AIT treated patient was found to be HIV positive.[114] A subsequent survey of 1085 AAAAI members published in 2016 found that approximately 80% of respondents would prescribe SCIT in patients with HIV without a diagnosis of AIDS, and approximately 50% of respondents would prescribe SCIT in patients with AIDS.[112] In that survey, 4.2% of respondents reported experiencing major safety problems in patients with AIDS receiving SCIT.[112] Based on the same survey, 70% of specialists would prescribe SCIT in patients who had undergone bone marrow or solid organ transplant.[112]

Intuitively, the specialist should consider the degree of immune deficiency based on blood cell counts and other relevant measures when determining whether a patient is a good candidate for immunotherapy. Patients whose general health precludes them from coming to the Allergy clinic to receive SCIT due to increased risk for infection may be better candidates for SLIT. A case-control study of 22 HIV+ positive patients on stable anti-retroviral therapy with undetectable HIV viral load and CD4 cell counts > 350 cells/mm^3 who received grass pollen SLIT-T found significant improvements in total combined rhino-conjunctivitis symptom scores plus asthma and medication scores (p=0.0001) as well as QoL (p=0.03) in the SLIT-treated group.[115] A case report of two HIV+ positive patients on anti-retroviral therapy with undetectable viral loads and normal CD4 cell counts found that birch pollen SLIT provided clinical benefit with no adverse effects on viral load or CD4 cell counts.[116] Safety and efficacy data are lacking regarding the use of SCIT or SLIT in patients with humoral immune deficiencies, including those on immunoglobulin replacement therapy. It is reasonable to consider SCIT or SLIT in atopic patients with humoral immune deficiency if they meet other criteria for immunotherapy.

Autoimmune disease

11. Recommendation: We suggest that AIT for AR and/or AA is an option for patients with comorbid autoimmune disease.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

The previous JTF 2011 AIT PP suggested that immunotherapy could be considered in patients with autoimmune conditions, on a case-by-case basis;[2] this recommendation is unchanged. There is no evidence to suggest that SCIT or SLIT promote the development of new autoimmune conditions. Previous concerns that aluminum-based adjuvants may trigger autoimmune or autoinflammatory diseases have been refuted.[117] Of note, North American SCIT formulations do not use aluminum. A population-based study from Denmark that included 10 years of data found that patients on SCIT (n=18,841) actually had a 14% lower incidence of autoimmunity than those on conventional medication therapies for rhinitis (n =428,484).[118] Similarly, a case-control study of 816 patients on SLIT and 1096 control patients found that the incidence of new autoimmune conditions was higher in the control group ($p<0.05$).[119]

Based on theoretical safety concerns, some consensus documents have recommended against prescribing SCIT/SLIT in patients with active autoimmune diseases.[70] Based on a survey of 1085 AAAAI members from 2016, 80-90% of respondents would prescribe SCIT in patients with autoimmune conditions.[112] In that same survey, 1.9% of respondents reported major safety problems in patients with autoimmune conditions, which was higher than most other patient groups (for example 0.6% in patients with hypertension).[112]

SCIT/SLIT may theoretically be less effective in patients treated with immunosuppressive medications. The specialist should consider the type and degree of immune modulation due to immunosuppressive medications when determining the likelihood that a patient will respond to SCIT or SLIT.

Efficacy of AIT

Introduction to efficacy of SCIT and SLIT

Seasonal allergic rhinitis (SAR) refers to AR that exhibits symptoms during a defined, specific pollen season, resulting from exposure to seasonal aeroallergens.[5] The same aeroallergen can be seasonal or perennial, depending on the climate/region; for example, grass pollen is perennial in South Florida. In contrast, perennial allergic rhinitis (PAR) is a form of AR with symptoms present year-round, typically triggered by indoor/perennial allergens (e.g., HDM, pets, cockroaches, and molds/fungi).[5]

Pre-seasonal AIT is generally initiated at least ~8 weeks (≈2 months) before the expected start of the pollen season; longer pre-seasonal durations of ~12–16 weeks (≈3–4 months) are commonly used in clinical trials and may enhance efficacy.[120] Co-seasonal AIT continues from the onset of the pollen season through the period of active allergen exposure, typically spanning ~4–12+ weeks, depending on the local pollen calendar and allergen type.[120]

The efficacy of SCIT and SLIT will be reviewed separately. The term “short-term efficacy” in this PP is limited to efficacy while the patient is receiving SCIT or SLIT or immediately upon termination of therapy. “Long-term efficacy” refers to efficacy that is sustained following discontinuation of therapy, usually reported as months or years after therapy is terminated. The recommendations referencing long-term efficacy are limited to 1-13 years following cessation of therapy. When reviewing the efficacy of SCIT and SLIT, the “onset of treatment” varies from study to study, as some authors indicate when the first treatment, e.g., injection, was administered, and others date the onset from when the maintenance dose was reached. The recommendations related to the duration of therapy for maximum efficacy should be interpreted as starting from the first maintenance dose; therefore, the build-up phase would not be included within the minimum of three years of SCIT or SLIT recommended for long-term efficacy.

Following the definition used by most of the large systematic reviews and meta-analyses cited in this update, a “single allergen” refers to a single category of allergen, e.g., grass, tree, weed, mold, cat, dog, and HDM. As such, a “single allergen” could contain more than one related allergen, often cross-reacting. “Multiple allergens” refers to an extract that combines more than one of these categories of allergens, e.g., timothy grass and HDM. Northern pasture grasses belong to the subfamily Pooideae of the Poaceae grass family. The Pooideae subfamily includes timothy, ryegrass, orchard, bluegrass, fescue, and sweet vernal. All these individual grasses contain highly cross-reactive allergens. When multiple members of this family are tested or included for AIT, they will be referred to as “Northern grasses”. The large Dhami 2017 systematic reviews and meta-analyses for AR and asthma using SCIT and SLIT AIT included fewer than 10% and 5% “multiple allergen” trials, for SCIT and SLIT, respectively.[86, 121] Likewise, the terms monosensitized and polysensitized as used in this document are those specified by the study authors, who may not always indicate if “monosensitization” describes a patient who has one major allergen and a few minor allergens or if the patient has a single sensitization. The WG used the sensitization terminology used by the study author, although the classification of “monosensitized” will vary based upon the number of allergens tested and the method of sIgE/SPT interpretation.

The terminology of "allergic rhinitis" rather than "allergic rhinoconjunctivitis" will be utilized in this document. While many patients with AR have symptoms of AC, most trials do not quantify eye symptoms, often using the TNSS to show symptom improvement. More than 80% of the articles cited in this document use the term "allergic rhinitis" rather than "allergic rhinoconjunctivitis," and the JTF Rhinitis 2020: A Practice Parameter Update uses the terminology "allergic rhinitis".[5] When reviewing individual trials in which the authors indicate that they have specifically studied an ARC population, this will be stated.

The type of study, e.g., randomized, double-blind, placebo-controlled, controlled, observational, etc., will be indicated based on the terminology used in the publication.

Within this document, SLIT-T refers to all SLIT-tablets, both FDA-approved and those that are not currently FDA approved. The recommendation applies to all countries that have the tablet available which will not always include the US. SLIT-L refers to SLIT liquid or drops, both mono- and multi-allergen, which are not approved for use in the US.

This document will provide the age range, e.g., for children or adolescents, as provided by the authors or the drug label. However, if only an age category, e.g., "children", is specified by the authors, that term will be used. When the certainty of evidence is the same for all age groups, such as children, adults, and older adults, a single recommendation will be made, for example, for SCIT or SLIT-T. When the certainty of evidence varies across different age groups, this will be indicated within one or more recommendations. When the certainty of evidence is predominantly supported by systematic reviews/meta-analyses that include both adults and children, but the authors provide no subset analyses by age, the recommendation will not indicate an age.

Efficacy of single-allergen SCIT

This section will focus on the short-term efficacy of single-allergen SCIT in treating AR and AA. Most SCIT studies have focused on treatment with pollen or HDM allergens. The studies using fungi and animal dander are separately reviewed at the end of this section. The use of SCIT for AD is also reviewed in this section. SCIT short-term efficacy studies published after 2010 (end of literature search for the JTF 2011 AIT PP update[2]) are predominantly from Europe and utilize either modified, peptide, or aluminum hydroxide-adsorbed extracts; these products are not commercially available in the US. In the US, specialists almost exclusively use unmodified, aqueous extracts for SCIT; however, in Europe, specialists mainly use aluminum hydroxide- (66.7%) or microcrystalline tyrosine- (16.7%) adsorbed allergen extracts.[122] Since 2010, only two US studies have examined the efficacy of SCIT with aqueous extracts, and both used biologics concurrently with SCIT.[123, 124]

Efficacy of SCIT for AR (pollen and HDM)

12. Recommendation: We recommend single-allergen SCIT for adults and children with SAR and PAR when there is evidence that a single allergen is the major cause of AR symptoms.

Strength of Recommendation: Strong

Certainty of Evidence: High for SAR in adults, Moderate for PAR in adults, Moderate for SAR in children, Moderate to Low for PAR in children

A review and meta-analysis of 160 randomized, blinded SCIT AR studies, published between January 1, 1981, and October 31, 2015, included 51 SCIT studies that reported short-term effects.[86] Of these, 16 studies, all published prior to 2010, could be pooled for a meta-analysis. SCIT short-term efficacy was demonstrated for SSs (16 studies; SMD -0.65; [95% CI: -0.86, -0.43]); MSs (16 studies; SMD -0.52 [95% CI: -0.75, -0.29]) and CSMS (15 studies; SMD -0.51 [95% CI: -0.66, -0.26]). Although the pediatric studies on short-term efficacy were limited, there was overall benefit for symptom reduction and a suggestion of benefit for medication reduction; the benefits in both symptom and medication use reduction were greater for SCIT compared to SLIT.[86] In the same systematic review,[86] of the 12 short-term efficacy studies published after 2009 (pollen-10; cat-1; mold-1), 9 used modified or peptide extracts (one from the US[125]) and 3 used aluminum hydroxide-adsorbed extract.[59, 125-135] Using this systematic review and meta-analysis,[86] the European Academy of Allergy & Clinical Immunology (EAACI) guidelines on the use of SCIT for AR concluded that the evidence supporting short-term use of SCIT for SAR was Grade A for adults and Grade B for children; for PAR for adults and children, the evidence was Grade B and C, respectively.[69] While both pre-/co-seasonal and continuous pollen SCIT were determined to have GRADE A evidence by the EAACI guidelines,[69] the current practice in the US of perennial SCIT for pollen is further supported by a RDBPC 3-year trial, which showed perennial SCIT was more effective than pre-seasonal SCIT (p=0.012).[133] There are no head-to-head comparisons of unmodified vs. modified allergens using a randomized placebo-controlled study design.[136] Furthermore, many types of modified allergen extracts, such as the use of adjuvants, recombinant allergens, modified hypoallergenic variants, allergen-derived T-cell or B-cell directed peptides, and mid-length peptides, have not been successful in phase III trials, nor have they achieved regulatory approval in either Europe or the US.[136]

In a systematic overview of systematic reviews (all published prior to October 3, 2015) on the efficacy of SCIT for AR, 17 systematic reviews met the inclusion criteria.[137] In this overview, the types of AIT varied: 4 studies were exclusively SCIT, 4 combined SCIT and SLIT, and 1 used several forms of AIT, including SCIT. Quality assessment used the Critical Appraisal Skills Programme quality assessment tool for systematic reviews.[138] In terms of quality, 8 studies were of high quality, 5 were of moderate quality, and 3 were of low quality. The authors concluded that there was moderate to strong evidence that both SCIT and SLIT can reduce SS and MS.[137] Furthermore, a review of meta-analyses having 5 or more RDBPC trials, compared the effect of SCIT to pharmacotherapy during the first pollen season and concluded that SCIT was equal to or superior to pharmacotherapy.[139]

In a 2026 meta-analysis of randomized trials of AIT for AA, AIT improved asthma symptoms compared with placebo (SMD, -2.19 [95% CI: -3.19, -1.19]; p<0.001), although heterogeneity was very high (I^2=96%).[140] For studies reporting asthma symptom outcomes, the point estimate was numerically greater for SCIT than for SLIT (5 SCIT studies vs 2 SLIT studies), with a significant effect for SCIT (SMD, -2.42 [95% CI: -3.54, -0.89]; p=0.001) but not for the SLIT subgroup (SMD, -1.68 [95% CI: -4.26, 0.90]; p=0.20); however, the direct comparison between routes was not significant (p=0.63), likely because of marked heterogeneity. AIT also reduced asthma medication use overall (SMD, -1.10 [95% CI: -1.76, -0.44]; p=0.001), and in this analysis, SCIT showed greater benefit than SLIT for medication reduction (6 SCIT studies vs 4 SLIT studies; SCIT SMD, -2.27 [95% CI: -2.94, -1.60] vs SLIT SMD, -0.19 [95% C: -0.63, 0.26]; p<0.00001 for subgroup difference). Symptom improvement was seen for both HDM and grass-pollen AA, with a larger numerical effect for HDM (SMD, -2.57 [95% CI: -4.13, -1.02]; p=0.001) than grass pollen (SMD, -1.08 [95% CI: -2.00, -0.16]; p=0.02), although the between-allergen difference was not significant (p=0.11). Age did not significantly influence symptom reduction (p=0.66). Forced expiratory volume in 1 second (FEV_1) also improved overall (SMD, 0.88 [95% CI: 0.39, 1.37]; p<0.001), but with high heterogeneity (I^2=89%). In the HDM subgroup, 7 RCTs showed a significant improvement in FEV_1 (SMD, 0.47 [95% CI: 0.10, 0.84]; p<0.001; I^2=81%). For pollen allergens, the meta-analysis did not provide a pooled grass-specific estimate, but the single grass-pollen trial identified in the review reported a significant improvement in FEV_1 (p=0.005) compared to placebo. Overall, these findings support AIT efficacy in AA and suggest a stronger signal for SCIT than SLIT, particularly for reduction in asthma medication use and, less definitively, for symptom control.[140, 141] Unfortunately for US allergists, this meta-analysis offers limited evidence for the efficacy of US aqueous extracts; five of the 28-29 studies used aqueous extract, and the only study conducted in the US failed to demonstrate a significant difference in CSMS for rhinitis compared with placebo.[142]

Several recent systematic reviews and meta-analyses have been conducted on subtypes of AR patients, non-conventional SCIT schedules, and modified allergen extracts. A systematic review and meta-analysis of RDBPC trials examined the efficacy of SCIT, using depigmented polymerized or aluminum hydroxide-adsorbed extracts, for local allergic reactions (LAR).[143] Four trials, a total of 134 patients, were included. The results showed significant improvement in CSMS (p<.001), SS (p=0.01), MS (p=0.02), and on the RQLQ (p=0.02).[143]

The efficacy of SCIT in older adults was demonstrated in a RDBPC trial involving 58 HDM monosensitized patients aged 65 years or older.[144] Two years of HDM allergoid extract resulted in a significant improvement in medication-adjusted scores (p<0.05), CSMS (p<0.05), and RQLQ.[144]

A systematic review of pediatric trials using accelerated SCIT schedules included two rush and 9 cluster trials.[145] The authors concluded that accelerated SCIT is clinically and immunologically efficacious with faster onset of effect than conventional schedules.[145]

In a RDBPC 3-year trial, perennial SCIT was more effective than pre-seasonal SCIT (p=0.012).[133] A systematic review and meta-analysis of RDBPC trials using depigmented-polymerized allergen extracts in adult and pediatric AR patients with or without asthma included 6 pollen and 2 HDM trials.[146] There was a significant improvement in CSMS (SMD, 1.9 [95% CI: 0.9, 2.8]) and RQLQ (SMD, 0.30 [95% CI: 0.10, 0.50]) compared to placebo, and the improvement was greater in those with more severe disease.[146]

A few noteworthy trials examined modified extracts and demonstrated clinical improvement. In a 2025 RDBPC phase III trial of SCIT using a glutaraldehyde-modified (allergoid) HDM extract (50,000 AU eq/mL; approximately 25,000 AU per monthly maintenance injection), 767 adults with HDM-induced ARC were treated for 1 year.[147] The primary endpoint, excluding ocular symptoms and using only nasal symptoms and medication scores (CSMS[n]), showed a non-significant treatment effect compared to placebo (mean difference −0.12 [95% CI: −0.26, 0.01]; p=0.0767), not meeting the prespecified minimal clinically important difference (MCID) of 0.25 points. Secondary endpoints were directionally consistent but not statistically significant, with confidence intervals crossing zero. A large proportion of patients had mild baseline disease (539/767), which likely attenuated the overall treatment effect. In the subgroup with moderate-to-severe symptoms (baseline daily nasal symptom score ≥2; n=228), a significant and clinically meaningful reduction in CSMS(n) was observed (−0.39 [95% CI: −0.64, −0.13]; p=0.0031), exceeding the MCID, with consistent improvements across secondary outcomes.[147]

Another 2025 pivotal phase III RDBPC trial of 555 adults with moderate-to-severe seasonal grass pollen AR showed that a short-course, pre-seasonal SCIT regimen of 6 injections of modified adjuvanted PQ Grass produced a clinically meaningful reduction in the peak-season $CSMS_{EAACI}$ score versus placebo (−0.27 points [95% CI: −0.42, −0.12]), representing a 20.3% relative improvement (p=0.0005).[148] Benefit was consistent across the full season and extended to symptom, medication, and quality-of-life outcomes, while treatment induced robust increases in blocking antibody responses. Adverse effects were mainly local and mild to moderate; 1 treatment-related anaphylactic event resolved without epinephrine or hospitalization. This study provides high-quality contemporary evidence supporting short-course grass SCIT for seasonal grass pollen-induced AR.[148]

Furthermore, in a 2025 pivotal phase III RDBPC trial, 298 adults with birch pollen-induced AR received 5 preseasonal injections of birch pollen allergoid T502 or placebo.[149] T502 significantly reduced the median CSMS during the peak birch pollen season by 33% versus placebo (0.67 vs 1.00; p=0.002), with additional improvements in daily SS (−30.4%; p<0.001), daily MS (−56.3%; p=0.045), and peak-season RQLQ (−31.5%; p<0.0001). No fatalities or serious AEs were reported.[149]

In summary, these three phase III trials conducted in 2025 provide additional evidence supporting the efficacy of short-course allergoid SCIT for seasonal pollen-induced AR.[147-149] However, currently there are no FDA approved allergoid SCIT extracts in the US.

In a RDBPC 3-week trial of 554 patients, 8 SCIT injections of rye grass peptide hydrolysates reduced the CSMS during peak (p=0.041) and for the entire (p=0.029) grass season, reduced the reactivity to the conjunctival provocation test (p<0.001), and improved the QoL global score (p=0.005).[150] In a 12-month observational study, using cluster up-dosing followed by monthly maintenance, a glutaraldehyde-modified HDM mixture (*D. pteronyssinus, D. farinae,* and *B. tropicalis*) demonstrated significant improvement in AR patients, both with and without asthma.[151] Efficacy of HDM allergoid extract SCIT in older adults was shown in an RDBPC trial of 58 HDM monosensitized patients > 65 years of age.[144] Two years of SCIT resulted in significant improvement in medication-adjusted scores (p<0.05), CSMS (p<0.05), and RQLQ.[144]

One study has examined the effect of combining biologics with SCIT.[123] In a DBPC parallel-group study of 103 grass SAR adults, patients were randomized to receive aqueous SCIT, dupilumab 600 mg loading dose followed by 300 mg every 2 weeks, aqueous SCIT + dupilumab. The two groups receiving aqueous SCIT were treated in an 8-week cluster protocol, with the goal of achieving the maintenance dose of 4000 BAU by 8 weeks and continuing with maintenance SCIT (q 2wks x 1, q 3 wks x 2) for an additional 8 weeks, with the last SCIT and dupilumab dose at week 16. After completion of the 8-week escalation phase, patients entered maintenance at the highest tolerated dose achieved and further escalation was not allowed. The SCIT maintenance dose of 4000 BAU was achieved by 61.5% of the SCIT + dupilumab group compared with 46.2% of the SCIT only group. There was no significant improvement in the TNSS area under the curve (AUC) (0-1 h) following nasal allergen challenge at week 17 in the SCIT + dupilumab group compared to the SCIT only group.[123]

SCIT studies have evaluated allergen products that differ not only in allergen source but also in the composition of major allergens, formulation, standardization method, potency nomenclature, and dosing schedule. In the US, injectable products used for SCIT are generally native liquid extracts. For selected standardized allergens, manufacturers assign potency by comparison with common Center for Biologics Evaluation and Research reference preparations, providing a shared US potency framework across manufacturers.[152] However, product labeling recommends assessment and a reduced starting dose when patients are switched to a product from a different manufacturer; reference-based potency standardization does not establish automatic patient-level dose-for-dose interchangeability.[153] In Europe, SCIT studies may use native liquid extracts, native depot extracts in which unmodified allergen is adsorbed to an adjuvant such as aluminum hydroxide or L-tyrosine, or chemically modified allergoids, which can be depigmented and polymerized and may also be depot-adsorbed. Native depot extracts and allergoids should not be considered synonymous: depot adsorption alters allergen release characteristics but does not chemically modify the allergen, whereas allergoids contain chemically modified allergen proteins.[154]

Accordingly, US AU/mL, BAU/mL, Amb a 1 units/mL; European SQ-U and index of reactivity (IR); and manufacturer-specific allergoid units, such as DPP, TU/TE, or AUeq, cannot be converted to a common clinical dose.[152, 155] Chemical modification, as in allergoids, may further reduce immediate IgE-mediated allergenic potency per unit mass. In a dose-response, skin-prick study comparing depigmented, glutaraldehyde-polymerized extracts of *Dermatophagoides pteronyssinus*, *Phleum pratense*, *Olea europaea*, and *Parietaria judaica*, the median freeze-dried mass required to produce a wheal equivalent in size to the histamine control (10 HEP) was 10.5-, 49.5-, 27.9-, and 178-fold greater, respectively, for the polymerized extracts than for the matched native extracts.[156] These findings characterize immediate cutaneous allergenicity for the tested products and do not establish a universal clinical dose-equivalence ratio. Thus, injection volume, nominal protein or precursor-extract mass, major allergen content, and manufacturer-specific potency units should not be interpreted as interchangeable measures of allergen dose or as evidence of dosing equivalence across products. Only testing native allergen extracts from different manufacturers simultaneously in the same lab[157] or in SPTs in the same patients can give an indication of how their allergen potency compares.[157-159] However, clinical safety and efficacy should ideally be assessed for each specific product, formulation, dose, and regimen,[154]

In previous practice parameters, a dosing table has always been included. When interpreting the recommended dose ranges, the reader should take into account that the maintenance dosing recommendations for the US HDM and grass pollen SCIT extracts are based on studies conducted with European aluminum hydroxide-adsorbed extracts from the 1990's, which have a different composition than the US extracts. This leads to the restrictions mentioned above. Thus, dosing ranges for the SCIT maintenance doses of these allergens should be considered with caution.

Efficacy of SCIT for AA (pollen & HDM)

13. Recommendation: We suggest single-allergen SCIT for patients with AA when a single allergen is likely the major contributor.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Single-allergen SCIT has been associated with reductions in asthma symptom burden and medication use, along with modest improvements in lung function, based on evidence derived primarily from RCTs in patients with mild to moderate AA.

A 2018 systematic review and meta-analysis reviewed 18 SLIT and 31 SCIT RCT trials.[160] Ten of these SCIT studies were published after 2010.[99, 161-169] In this systematic review, 31 RCTs were identified that addressed the efficacy of SCIT, of which 17 and 5 studies involved monosensitized and polysensitized patients, respectively. Two studies included both monosensitized and polysensitized patients, and 7 studies did not report the sensitization status. Single allergen SCIT was used in 28 trials of these RCTs, multi-allergen SCIT in 2 trials, and one study used both. SCIT reduced the use of long-term, asthma control medications (moderate strength of evidence); furthermore, SCIT reduced the use of quick-relief medications and systemic corticosteroids and improved the FEV_1 (low strength of evidence). The majority of studies in this systematic review included only patients with mild to moderate asthma; however, not all studies reported the severity of asthma or the degree of control.[160]

A 2017 systematic review and meta-analysis by Dhami et al.[121] found 98 randomized, double-blind, controlled SCIT AA studies published from the inception of the searched databases through October 31, 2015 that looked at efficacy based on SS and/or MS or CSMS as the primary outcome. The review included 54 SCIT studies that reported short-term effects of which only 9 (4 using aluminum hydroxide precipitate and 5 using modified allergens) were pooled for meta-analysis due to heterogeneity in approaches used to assess efficacy outcomes. Seven SCIT studies prior to 2010 were conducted in the US, but none could be pooled for meta-analysis due primarily to heterogeneity; no studies completed after 2010 were from the US. In the SCIT subset analysis, short-term effectiveness was demonstrated for SS (9 studies; SMD, -1.64 [95% CI: -2.51, -0.78]) and MS (7 studies; SMD, -1.65 [95% CI: -2.52, -0.79]); no studies reporting CSMS were included in the meta-analysis. The meta-analysis was limited to two short-term efficacy studies published after 2009, both of which used aluminum hydroxide-adsorbed extract. One HDM study reported significant improvement in SS ($p<0.05$ at 2 and 3 yrs); reduced dose of inhaled corticosteroids (ICS; $p=0.015$ at 2 yrs; $p=0.027$ at 3 yrs); and increased peak expiratory flow ($p<0.05$ at 2 and 3 yrs).[168] The second study using *Alternaria alternata* AIT,

reported improvement in CSMS in year 2 and 3 of the study (by 38.7% and 63.5%, respectively; p<0.001 for each) and in QoL (p<0.05).[130] For the entire systematic review, SCIT improved QoL and reduced allergen-specific airway hyperreactivity but did not have a consistent effect on asthma control, exacerbations, lung function, or nonspecific airway hyperreactivity.[121] When considering whether SCIT is less effective for patients with both AR and AA, Dhami concluded that there was no reduced efficacy of SCIT in patients with concurrent AR and AA compared to those having only AR.[121]

A systematic overview of 9 systematic reviews (SCIT-3; SLIT-4, both SLIT and SCIT-2) by Asamoah et al.[170] published prior to October 2015 concluded that both SCIT and SLIT can reduce SS and MS for asthma, but the effect on asthma control and lung function is inconsistent.

A 2015 systematic review and meta-analysis looked at the efficacy and safety of SCIT in HDM-sensitized patients with asthma,[171] including 19 RCTs, one of which was published after 2010.[172] They found that SCIT significantly reduced SS (p=0.004) and MS (p=0.001) compared to the control group.[171] However, at the end of 3 years of SCIT, the lung function was not significantly different in the SCIT-treated group compared to placebo (p>0.05).[171] In a 2012 study, SCIT-treated patients (n=10) had significantly lower SS and MS for asthma (p=0.03) and rhinitis (p=0.01) compared with placebo, whereas the improvement with SLIT was not significant.[172]

Three RDBPC 12-month HDM SCIT trials in adults with mild-to-moderate asthma have been reported from Cuba: one trial with *Blomia tropicalis* and two parallel trials with *D. pteronyssinus* and *D. siboney*.[173, 174] Maintenance doses were 6000 BU, corresponding to 12 mcg Der p 1 for *D. pteronyssinus*, 24 mcg Der s 1 for *D. siboney*, and approximately 60 mcg of the 12-21 kDa *B. tropicalis* allergen fraction containing Blo t 5, Blo t 21, Blo t 13, and Blo t 2. At 12 months, SSs in active-treatment groups were 20%-36.5% of placebo values and MSs were 13%-23% of placebo values, with reported p values <0.001.[173, 174]

In summary, SCIT effectively reduces symptoms and medication use but has not been shown to have a significant effect on asthma control, asthma exacerbations, lung function, or nonspecific airway hyperresponsiveness. Overall, the certainty of evidence supporting this recommendation is low, reflecting heterogeneity across studies, variability in outcome measures, and limitations in study design and reporting.

Efficacy of SCIT for AD (HDM)

14. Recommendation: We suggest considering HDM SCIT as an adjunct to optimized skin-directed therapy for patients with moderate-to-severe AD and clinically relevant HDM sensitization who remain inadequately controlled.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

The use of AIT has been suggested as an effective treatment for AD; however, historically, there has been a concern that AIT might worsen AD. Earlier European consensus guidance

stated that aeroallergen AIT may be considered in selected cases.[175] The recent update to the AD PP also recommends adding AIT (either SCIT or SLIT) for moderate-to-severe AD.[36]

The evidence for SCIT in AD is derived predominantly from trials of HDM extracts administered as an add-on to standard skin-directed therapy (See SCIT for AD evidence table in Appendix 1). In a 2023 systematic review and meta-analysis, AIT was associated with clinically important improvements in AD severity and AD-related QoL, with moderate-certainty evidence.[34] In prespecified subgroup analyses, pooled relative effect estimates did not differ significantly between SCIT and SLIT (P for interaction = 0.63). Because these were indirect subgroup comparisons rather than direct head-to-head trials, they neither establish equivalence between routes nor show that SCIT is more effective than SLIT or vice versa.[34] SCIT is associated with more treatment-related AEs than SLIT. Local AEs occurred in approximately 66% of SCIT recipients and 41% of control participants.[34] Systemic allergic reactions, which included immediate allergic reactions and delayed eczematous eruptions, occurred in approximately 11% with SCIT versus 8% with control, and AEs leading to discontinuation occurred in approximately 10% versus 7%, respectively.[34]

In a 2024 meta-analysis of HDM AIT (SCIT and SLIT) for AD, You et al.[176] found the likelihood of clinical response to be 1.7-fold overall (risk ratio [RR] 1.74 [95% CI: 1.46, 2.06]; I^2=0%). However, the pooled SCORing Atopic Dermatitis (SCORAD) reduction (-6.17 [95% CI: -8.11, -4.22]) did not reach the MCID of 8.70. The SCIT subgroup had a lower SCORAD mean difference (-5.93) than that of the SLIT subgroup (-7.22), indicating modest clinical efficacy. Across the pooled (SCIT and SLIT) analysis, the effect was larger in children than adults (RR 1.96 vs. 1.42).[176]

The multicenter, randomized dose-response trial by Werfel et al.[177] enrolled 89 adults with chronic HDM-sensitized AD and baseline SCORAD scores of 40 or greater. Participants received 1 year of weekly HDM SCIT with maintenance doses of 20, 2,000, or 20,000 SQ-U; the 20 SQ-U group served as a low-dose active comparator rather than a true placebo. SCORAD improved in all groups, but the combined higher-dose groups had a greater mean reduction than the low-dose group (-18.0 versus -10.0; p=0.0379), and higher doses were associated with reduced topical corticosteroid use (p=0.0007). However, attrition was substantial: only 51 of 89 randomized participants completed the 1-year SCORAD evaluation. Mild SRs occurred after fewer than 1% of injections.[177]

In a small, double-blind, placebo-controlled trial, Bogacz-Piaseczyńska and Bożek[178] enrolled adults with moderate-to-severe AD who were monosensitized to HDM and had IgE reactivity to both HDM extracts and the major components Der p 1 and Der f 1. After 12 months of SCIT with a *D. pteronyssinus/ D. farinae* extract, the active-treatment group showed greater improvement than placebo in Eczema Area and Severity Index, percentage body-surface area involved, investigator global assessment, medication score, and Dermatology Life Quality Index. An investigator's global assessment of clear or almost clear skin was achieved by 13 of 20 SCIT-treated participants (65%) compared with 4 of 14 placebo-treated participants (29%). The trial was small and enrolled a highly selected monosensitized population, so it does not establish that component testing predicts response or that a similar benefit will occur in broader AD populations.[178]

A larger RDBPC German trial of a depigmented polymerized HDM extract enrolled 168 adults with HDM-aggravated AD.[179] The primary analyses showed no statistically significant difference between SCIT and placebo in the area under the curve for total SCORAD or use of basic medication over 18 months. Among patients with baseline SCORAD greater than 50, post hoc analyses showed lower time-weighted SCORAD with SCIT than with placebo over the 18-month treatment period (median improvement, 21% in the intention-to-treat analysis; p=0.02). In a separate post hoc analysis restricted to September through February, when indoor heating is commonly used, the median improvement in time-weighted SCORAD was 18% with SCIT compared with placebo (p=0.02). This subgroup signal is hypothesis-generating but should not lead one to conclude that severe AD is a validated predictor of SCIT response.[179]

A retrospective, nonrandomized 3-year comparison of HDM SCIT plus pharmacotherapy (n = 164) with pharmacotherapy alone (n = 214) reported significantly greater reductions in SCORAD and pruritus VAS scores in the SCIT group.[180] Although the study reported benefit of longer treatment, because treatment allocation was not randomized and outcomes were not adjusted for all potential confounders, the study supports the feasibility of longer treatment but cannot establish sustained efficacy, prevention of new sensitization, or prevention of asthma.[180]

Evidence supporting pollen SCIT for AD is limited and of very low certainty. In a 4-year open, nonrandomized study, patients treated with grass pollen SCIT (n = 17) or grass-plus-mugwort SCIT (n = 6) had lower scores on the extent-and-severity-of-skin-inflammation index for AD than contemporaneous control patients who declined AIT; however, the small subgroups, self-selected controls, and use of a nonstandard AD outcome measure create substantial risk of bias.[181] In an uncontrolled 12-week study of 55 adults with clinically relevant birch pollen sensitization, co-seasonal birch SCIT was associated with a 34% median reduction in SCORAD and a 49% mean improvement in Dermatology Life Quality Index, but the absence of a comparator and short treatment duration preclude attribution of benefit to SCIT or assessment of sustained efficacy.[182] More recently, a comparative controlled study of 78 adults reported higher SCORAD-50 and SCORAD-75 response rates after one course of tree-pollen SCIT (n = 33) or grass-pollen SCIT (n = 21) than with standard AD treatment alone (n = 24); however, the study was not reported as randomized or blinded.[183]

Evidence is insufficient to recommend pollen SCIT specifically for the treatment of AD. When pollen SCIT is otherwise indicated for AR or asthma, any improvement in AD should be regarded as a potential additional benefit rather than an established treatment effect.

Overall, SCIT may therefore be considered as an add-on therapy in selected patients with moderate-to-severe AD and clinically relevant HDM allergy. The current data are insufficient to support routine SCIT for AD on the basis of sensitization alone, to extrapolate results across products or allergens, or to claim superiority over SLIT.[34, 177, 178, 182]

Efficacy of SCIT for fungal allergy

15. Recommendation: We suggest that fungal SCIT may be considered in select patients with fungal allergy.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

There are limited studies on the use of SCIT for AR and AA in patients with fungal allergy. A 2018 systematic review and meta-analysis reviewed 9 RCTs (including 6 SCIT studies) to determine the efficacy of fungal SCIT for AR and/or AA compared to pharmacotherapy/placebo for respiratory allergies (AR and/or AA).[184] Seven of the included studies used *Alternaria* allergen extract, with four showing a benefit. Two studies used *Cladosporium herbarum* allergen extract and were unable to demonstrate efficacy. Only two of the six SCIT studies found a greater reduction in SS and MS than in the comparator. Of the two SCIT studies published after 2010, one study, using a non-aqueous, standardized *Alternaria alternata* extract (Novo-Helisen Depot), with a maintenance dose of 8 mcg Alt a 1, showed a significant reduction in CSMS ($p<.001$) in children after three years of treatment.[130] Another study used a standardized *Alternaria* extract (ALK, 402, Denmark) for AA in children monosensitized to *Alternaria* and found no significant difference in SS or MS at the end of one year of treatment.[165] In a more recent 1-year RDBPC trial of SCIT using 0.37 mcg of the major allergen Alt a 1 isoform (UniProt P79085) vs. placebo in adults with AR, some having asthma, there was a significant improvement in CSMS.[185] In the two controlled *Cladosporium* SCIT studies, both from the 1980s (the same two as included in the 2018 systematic review), there was limited efficacy in reducing symptoms and/or medication usage, but only a small proportion of patients reached the maintenance dose due to SRs.[186-188] There have been no additional *Cladosporium* studies published since the 1980s.[188] There are no commercially available, standardized fungal allergen extracts in the US, and no recent studies using non-standardized aqueous fungal allergen extracts. Therefore, we have very limited evidence to support SCIT for *Alternaria* allergy and only a suggestion of benefit to support SCIT for *Cladosporium* allergy.[188]

The fungal source material used to prepare allergen extracts consists of numerous strains—up to 100 distinct strains in the case of *Alternaria alternata*. Each strain can produce varying allergenic profiles depending on the culture medium and environmental conditions. Allergenic components are found in the spores, mycelia, and metabolites secreted during the culturing process.[188]

The use of fungal extracts is further complicated by the fact that no commercial manufacturer lists the allergen content, for example mcg of Alt a 1. When studied, Alt a 1 in US extracts ranged from 0.04 to 2.75 mcg/ml, and various extract potencies by enzyme-linked immunosorbent assay inhibition varied 111-fold.[189] It is not recommended that fungal extract be combined with pollen, animal dander, cockroach, or HDM extract.[190, 191]

Efficacy of SCIT for animal dander

The JTF 2011 AIT PP recommended that the clinician consider including cat and/or dog SCIT when there is exposure.[2] Subsequently, the EAACI and British Society of Allergy and Clinical Immunology guidelines conclude that cat immunotherapy can be effective for AR.[192] This document will summarize the evidence for the efficacy of SCIT for cats, dogs, laboratory animals, and horses separately.

Efficacy of SCIT for cat allergy

16. Recommendation: We suggest cat allergen SCIT (using a minimum of 15 mcg of Fel d 1 per maintenance dose) for patients with AR and/or AA and symptoms upon exposure to cats.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Interpretation of cat allergen extract potency requires an understanding of the different unit systems used for standardization and labeling. The JTF 2011 AIT PP stated that the cat allergen maintenance dose should not be less than 15 mcg of Fel d 1.[2] In the US, cat allergen potency is measured in Fel d 1 units, and one unit was initially considered to be approximately 4 mcg of Fel d 1, but subsequently reported to be equivalent to 2.7 mcg Fel d 1.[193, 194] In the US, 10,000 BAU/ml of standardized cat extract is required to have 10-20 Fel d 1 units (approximately 27-54 mcg Fel d 1)/ml.

In a small RDBPC trial (n=28) comparing maintenance doses of 0.6, 3, and 15 mcg Fel d 1, the 15 mcg dose provided a significant immune response in both IgG4 and CD4+/IL-4+ PBMCs at 4 weeks[195] and a greater reduction in skin test response and symptoms upon nasal challenge at 1 year.[196]

Before 2011, the efficacy of using cat SCIT had been established with several small, short-term RDBPC trials. In a 3-month study using a maintenance dose of 15 mcg Fel d 1 (n=28), there was a decrease in conjunctival symptoms, conjunctival provocation sensitivity, and reduced peak flow response to cat exposure.[197] A 5-month trial, using a mean maintenance dose of 43,700 BU (approximately 87 mcg Fel d 1) showed a significant ($p=0.04$) reduction in cat sensitivity as demonstrated by a bronchial allergen challenge.[198] In an open-label extension of this study, there was further reduction in bronchial sensitivity at 12 months ($p=0.003$).[198] A 1-year study using 13 mcg Fel d 1 (n=28) demonstrated significant improvement in medication-symptom scores ($p<0.001$), SPT ($p<0.001$), and conjunctival ($p<0.001$) and bronchial provocation tests ($p<0.05$).[199] A non-randomized, DBPC 12-month study using 5 FDA units of Fel d 1 (approximately 20 mcg) showed a significant decrease in skin ($p<0.025$) and bronchial responses ($p<0.01$) to cat extract and an increase in sIgE ($p<0.01$) and sIgG4 ($p<0.001$) compared to placebo.[200] A 3-year observational SCIT study using cat extract (4.3 mcg Fel d 1 as a maintenance dose) established a significant reduction in response to cat extract bronchoprovocation ($p<0.01$).[201]

Following cat SCIT in patients with AA, allergen-specific bronchial provocation tests showed improvement in some,[199, 200, 202, 203] but not in all studies.[204, 205] Four of these studies also looked at non-specific bronchial provocation tests (bronchial hyperreactivity), and none showed a significant difference compared to placebo.[199, 200, 202, 204]

Since 2011, most cat SCIT-controlled trials have investigated peptides, neutralizing antibodies, or aqueous allergens combined with a biologic. In an RDBPC study, subjects underwent a titrated nasal challenge with cat extract before and after receiving 4 injections of 0.6, 3.0, or 15 mcg of Fel d 1-derived peptide antigen.[196] The results showed that 4 injections of Fel d 1-derived peptide antigen, administered 4 weeks apart, produced a dose-dependent improvement in nasal and ocular symptoms for one year following treatment completion in cat-allergic patients. While the patients were randomized according to the presence or absence of ongoing cat exposure, the results were not stratified by the degree of cat exposure.[196] However, the same peptide allergen failed to reach the primary endpoint in a phase III trial, with the CSMS not showing a significant difference between the active and placebo groups.[192, 206]

The passive administration of anti-Fel d 1 neutralizing sIgG antibodies to patients with cat allergy has been studied in a few, small, randomized trials. Cat-allergic (n=36 active, 37 placebo) patients who received a single 600 mg subcutaneous dose of a fully human anti–Fel d 1 monoclonal antibody (containing 300 mg each of REGN1908 and REGN1909), had improved nasal symptoms and showed suppression of FcεRI-mediated basophil activation and FcεRII (CD23)-mediated allergen-IgE binding on B cells, and reduced Th2 cytokines (IL-4, IL-5, and IL-13) in nasal fluid compared with placebo.[207] The serum concentration of REGN1908-1909 and the improvement in TNSS, the nasal symptom VAS (1-100), and peak nasal inspiratory flow were greatest at 8 days and remained statistically significant ($p<0.05$) compared to placebo when measured at day 29 and day 85 (last day of observation) but not at day 57.[207] The authors suggested that this may have been due to the dropout of 2 patients on day 57, increasing type 2 error. In a randomized trial, a single injected 600 mg dose of REGN1908–1909 administered to cat-allergic, mild asthmatics (n = 29 active, 27 placebo) significantly prevented reductions in FEV_1 ($p<0.05$) during cat exposure in an environmental exposure unit from day 8 to day 85 following administration.[208]

In a RDBPC, parallel-group design trial, 121 cat-allergic patients were randomized to receive standardized aqueous cat SCIT (4000 BAU maintenance dose) with or without tezepelumab 700 mg IV q 4 weeks for 48 weeks, with the primary efficacy assessment performed at week 52, approximately 4 weeks after completion of treatment.[124] SCIT was administered weekly using a cluster build-up protocol for 12 weeks, followed by monthly maintenance injections for weeks 12-48. At week 52, there was significant improvement in the primary endpoint, TNSS AUC (0-1 h), and in the TNSS peak (0-1 h) following nasal allergen challenge (NAC) in the SCIT/tezepelumab group compared to SCIT monotherapy; both groups showed improvement in these measurements compared to placebo. Following the 52-week primary assessment, the patients were observed for an additional 52 weeks. Using the same two TNSS measurements at 104 weeks, the improvement in SCIT monotherapy was no longer statistically different from that of the placebo. In the SCIT/tezepelumab, only the TNSS-peak (0-1 h after challenge) differed from placebo, but not the AUC. This study did not measure the effect of any of the treatments on daily symptoms and medication use.[124]

A retrospective review at a university-based allergy practice compared matched AA subjects (35 cat-allergic; 35 non-cat-sensitized) after 3 years of multi-allergen SCIT, including pollen, mold/fungi, HDM, dog, and cat (if allergic).[209] Cat-allergic patients, predominantly cat owners, had perennial, usually household, exposure to cat dander. Patients received standardized Greer cat hair extract, but the maintenance dose was not reported. Patients receiving SCIT containing cat allergen extract had a similar risk of asthma exacerbation compared to those with AA without cat sensitivity on SCIT. The authors concluded that AA with cat allergy and regular exposure do as well or better on cat SCIT as cat non-allergic, similarly ill, AA individuals receiving SCIT without cat allergen.[209]

Efficacy of SCIT for dog allergy

17. Recommendation: We suggest dog allergen SCIT (using a minimum of 15 mcg of Can f 1 per maintenance dose) for patients with AR and/or AA, who have symptoms upon exposure to dogs.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

The efficacy of dog SCIT has not been established to a high degree of certainty either before or after the JTF 2011 AIT PP update publication.[2] A review of dog allergens and dog extract composition will provide insight into the complex and unresolved issues surrounding the efficacy of dog SCIT. Dog hair or pelt extracts are not standardized, and potency is reported as w/vol or protein nitrogen units (PNU) per milliliter. Commercial crude (native) dog allergen extract is composed of many different dog proteins, including some of the 7 named dog component allergens (**Table 5**); however, the manufacturer does not list these on the vial label.[210] While component testing is commercially available for Can f 1, 2, 3, 5, these have not been characterized or quantified in crude extracts used for skin testing or for SCIT. Furthermore, Can f 1 is the only component that is routinely quantified for acetone precipitated (AP) and ultra-filtrated (UF) dog extract. The overall potency of dog allergen extract can vary by up to 1000-fold, and the amount of each component can vary between different lots from the same manufacturer.[211, 212]

Historically, there has been concern that commercial dog extracts may be contaminated with other allergens, such as cat and HDM.[213] A recent study using ELISA assays found that AP dog was not contaminated with *Alternaria*, ragweed, German cockroach, HDM, rye grass, or cat but was cross-reactive to a Fel d 1-like dog allergen; this finding may explain the previous conclusion that dog extract was contaminated with cat allergen as well as the positivity to both dog and cat in many patients.[214] When comparing AP and UF dog extracts, the concentration of the Fel d 1-like allergen is >5 times greater in UF (7.08 in mcg/mL) than in AP (1.34 mcg/mL) and >300 times greater than conventional (0.023 mcg/mL) dog extracts.[214] Therefore, SPT with UF dog extract compared to other dog extracts could potentially lead to a higher rate of false positive SPT to dog in cat-allergic patients.

All available dog extracts may produce false-negative SPT results. Only 32% of adults are monosensitized to Can f 1, suggesting that allergen extracts lacking enrichments of dog allergen

components other than Can f 1 may produce false-negative reactions on ST and that the use of these extracts in dog SCIT may be ineffective.[212] Can f 5, a prostatic kallikrein component present in male dog hair, is absent from all commercial dog extracts. However, it is a "major allergen" as up to 70% patients sensitized to dog make sIgE to Can f 5.[215] In addition, up to 38% of Can f 5 positive patients lack IgE antibodies to Can f 1, 2, 3.[215]

A more ideal dog extract is needed. While Can f 5 is still absent, a tetrameric structure, produced as a soluble fusion protein and comprised of Can f 1, 2, 4, 6, is more efficient at binding sIgE to dog than existing commercial extracts and when administered to mice induced higher concentrations of dog-specific IgG4 antibodies; but there are no human clinical trials that have been completed.[216]

In a study comparing SPT and sIgE to dog in 90 patients, there was agreement (both positive or both negative) in 52.2%, but the scores have a weak correlation ($r=0.24$; $p<0.05$).[217] Skin testing is more sensitive than sIgE testing for dog allergy; however, based upon the cross-reactivity patterns with cat, cow, and horse, as shown in **Table 6**, there may be false positives on ST. All Can f 2 positive patients are also positive to Can f 1, but the reverse is not the case.[218] Can f 2 and Can f 4 have cross-reactivity with Fel d 4, all of which are lipocalins, further complicating the interpretation of ST to dog and cat. In 44 adult patients with symptoms of AR, AA, and/or AD attributed to dog and/or cat and dual sensitization to dog and cat, 61% had sIgE to the lipocalin Can f 6.[219] These cross-reactions may also help to explain the observed pattern of co-sensitization between dog, cat, and horse.[220]

Lent et al.[221] conducted a 5-week dog allergen dose-response study, evaluating three maintenance dose targets of Can f 1 (0.6 mcg, 3.0 mcg, and 15 mcg), delivered using a cluster build-up schedule, with seven patients per group. In this study, the highest dose (15 mcg Can f 1) was associated with greater suppression of titrated SPT, attenuation of late-phase cutaneous reactions, and increased sIgG4 compared with lower doses; however, no significant change in symptom scores following NAC was observed.[221]

Based in part on these immunologic and physiologic findings, the JTF 2011 AIT PP recommended a target maintenance dose not less than 15 mcg Can f 1 for dog allergen SCIT.[2] This target dose can be achieved with AP dog (1: 100 w/v) or UF dog (1:650 w/v) extracts, which contain mean Can f 1 concentrations of approximately 140-171 mcg/mL and 183 mcg/mL, respectively.[2, 191, 210] In contrast, achieving this target dose with other commercially available dog extracts would require administration of approximately 3 mL per maintenance injection of undiluted extract, and therefore these products are not recommended for routine use.[191] By using ultrafiltration and diafiltration (UF dog), the problem of precipitant formation during storage of AP dog was eliminated.[222, 223] In 2024, Hollister-Stier replaced AP dog with UF dog extract and indicated that 0.5 ml of a 5-fold dilution delivers a maintenance dose of 15 mcg Can f 1; however, the vial label does not list the Can f 1 mcg/mL content. In a retrospective analysis from a single US allergy clinic, UF dog extract showed a comparable number of positive SPTs to AP dog and a greater number of positive SPTs when compared to conventional dog extract.[224] Furthermore, SPTs using UF dog produce a significantly larger average wheal and erythema size compared to AP and conventional dog extracts.[224] However, the study lacked the power to establish statistical superiority or non-inferiority between the extracts.[224]

There have been few, well-controlled studies on the efficacy of SCIT in dogs using aqueous extracts. The first RDBPC trial (n=15 active; 12 placebo) of dog SCIT was in children with asthma and dog allergy and the only significant change following one year of treatment was a reduction in conjunctival challenge and an increase in sIgG4.[225] While dog bronchoprovocation and symptoms improved, they were not significantly different from placebo.[225]

A second small RDBPC of dog allergic patients with AA (n=7 active; 15 placebo) found at 12 months that 4 of the 7 patients had non-significant symptom improvement and no significant increased tolerance on conjunctival challenge.[203] Following unblinding, these 7 patients and 4 placebo dog-allergic patients completed 3 subsequent years of dog SCIT. At the end of the 1st year, 4 of the 9 patients remaining in the study had improvement in symptoms and in dog-specific bronchoprovocation testing; these improvements persisted after 3 years of treatment, but there was no further improvement.[201] Five years later, after discontinuation of SCIT, 3 of the 4 patients with symptom improvement at the end of three years of SCIT maintained this improvement.[226] There was no correlation between any laboratory measurements, e.g., sIgE, sIgG4, and symptom scores or allergen-specific bronchoprovocation following the first blinded year of SCIT or at 5 years following discontinuation of SCIT.[203, 226] This study, the dose-response Lent et al.[221] study discussed above, eight earlier studies summarized by Smith et al.[227], and a 2013 study[228] indicate that the use of individual surrogate immune markers, e.g., sIgE and sIgG4, in isolation are likely not useful in predicting clinical efficacy for SCIT in dog-allergic patients.

A 6-month observational study (n=66) using an ultra-rush cat or dog SCIT (aluminum hydroxide adjuvant modified allergen) protocol demonstrated significant clinical improvement in rhinitis and asthma symptoms, QOL, medication usage, and VAS symptom score.[229] The clinical improvement occurred earlier and to a greater extent using the cat extract compared to the dog extract.[229]

Following an extensive review of the dog SCIT-controlled trials from 1984 to 2015, Smith et al.[227] concluded that there are several important dog allergens, but no single dominant allergen for all patients; the most critical allergen is the one to which the patient is sensitized. Furthermore, the authors concluded that studies have failed to show reproducible clinical evidence to confirm the efficacy of dog SCIT for patients with AR and asthma. Chan et al.,[212] completing their own review of dog SCIT trials, indicated that it is “possible” that dog SCIT is efficacious. A 2006 US nationwide survey revealed that most allergists believe that dog SCIT offers modest relief from AR (92%) and asthma (90%).[230] The specialist will need to discuss the limited available evidence regarding the efficacy, as well as the risks and benefits of dog SCIT, with each patient prior to initiating dog SCIT.

Table 5. Quantitative assessment of commercial dog extract allergen components. Modified based on Brown and Austin, 2022[210] and Hellu et al, 2024.[214]

Dog extract (Mfg.)	Labeled concentration	Can f 1 mcg/mL	Can f 3 mcg/mL	Total protein mcg/mL
AP dog hair and dander (HS)	1:100 w/v	24-171	49	246

UF dog hair and dander (HS)	1:650 w/v	43-183	70	412
Dog hair and dander (HS)	1:10 w/v	1.6-10	2	23
Dog epithelia (SG)	1:20 w/v	<1	300	186
Dog epithelia (ALK)	1:20 w/v	2	5-10	47

ALK, ALK-Abello; AP, acetone precipitated; HS, HollisterStier; SG, Stallergenes Greer; UF, ultrafiltered.

Table 6. Dog allergen components. Modified from Smith et al, 2016[227] and Chan et al, 2018.[212]

Dog allergen	Biologic activity	Sensitization rate in dog-allergic patients (%)	Major cross-reactivity (animal)	Production/source	Commercial recombinant protein	Commercial antibody
Can f 1[a]	Lipocalin	49-70	Fel d 7[231]	Tongue epithelium/saliva & dander	X	X
Can f 2	Lipocalin	22-30	Fel d 4 (cat)	Parotid gland/saliva & dander	X	X
Can f 3	Albumin	16	Fel d 2 (cat)	Albumin	X	X
Can f 4	Lipocalin	35	Bos d 2 (cow)	Dander & saliva		
Can f 5[a] (only male dogs)	Prostatic kallikrein	70	Human prostate-specific antigen	Prostate/urine	X	X
Can f 6	Lipocalin	38	Fel d 4 (cat) Equ c 1 (horse)	Saliva		
Can f 7	Epididymal secretory protein CE1	14-17	Cat-NPC2[232]			
Can f 8	Cystatin	13%				

Cat-NPC2: Cat-Niemann pick type C2

[a]Considered “major” allergen

Efficacy of SCIT for laboratory animals and horse allergy

18. Recommendation: We suggest laboratory animal or horse SCIT for patients with AR and/or AA and occupational or recreational exposure.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

A large cross-sectional survey of over 5000 laboratory animal workers found that >25% reported allergic symptoms when exposed to mice, rats, rabbits, and/or hamsters.[233] Furthermore, most patients allergic to laboratory animals are sensitized to several different laboratory animals.[233, 234] Yet, there have been very few published studies on the efficacy of SCIT for reducing allergic symptoms when workers are exposed to laboratory animals. In Wahn and Siraganian's observational study with SCIT treatment of lab animal allergic patients (n=11 active; 12 controls), all actively treated workers had AR and 8 had asthma symptoms upon exposure to mouse (n=5), rat (n=5), and rabbit (n=1).[234] In this study, 78% were sensitized to mice and rats, and 65% were sensitized to mice, rats, and guinea pigs. Workers had been exposed for a mean of 8.1 years, with symptom onset a mean of 2.9 years after initial exposure. Of those receiving animal SCIT matched to their specific allergic animal to which they were exposed, 9/11 experienced a reduction in symptoms. The actively treated group developed significantly higher levels of blocking antibody compared to the placebo (a 12-fold increase), which correlated with the maintenance (2000-10,000 PNU) and cumulative allergen SCIT dose. In polysensitized patients, the blocking antibody was specific to the allergen used for SCIT, e.g., patients allergic to mouse and rat who were treated with mouse developed blocking antibodies only to mouse. However, one patient sensitized to both mouse and guinea pig, treated with mouse SCIT, developed blocking antibodies to both, raising the question of cross-reactivity. After the patient stopped working with lab animals and discontinued SCIT, the blocking antibodies returned to baseline when tested, 16-36 months after SCIT was discontinued.[234]

In a retrospective 4-case study of work-exacerbated asthma, polysensitized laboratory workers and veterinarians were treated with multi-allergen SCIT, which included 3-5 animal allergens, e.g., mouse, rat, rabbit, cat, dog, and/or horse allergens, pollen, mold, and/or HDM for 14 months to 5 years.[235] Following SCIT, asthma symptoms were reduced, and all workers were able to perform their required duties.[235] One case study reported elimination of rat allergen inhalant-induced rhinitis and asthma symptoms and undetectable sIgE to rat following 18 months of rat SCIT.[236]

In a 2002 prospective clinical observational study of 24 patients with horse-induced respiratory and cutaneous symptoms, maintenance doses of standardized (Alutard SQ- Spain) horse allergen SCIT were administered for up to 5 years (median 7.4 months, range 5-63 months).[237] Horse SCIT reduced symptoms of conjunctivitis, rhinitis, asthma, and skin itch/rash in 100%, 93%, 90%, and 87% of patients, respectively, with only one SR.[237] Standardized horse extract is not available in the US, and there have been no recent horse SCIT studies on efficacy using either aqueous (US allergens) or modified allergens for horse.

SCIT for prevention of allergic sensitization, AR, and asthma

19. Recommendation: We recommend against SCIT for the prevention of AR and/or AA in asymptomatic patients.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

20. Recommendation: We suggest SCIT for patients with AR and/or AA to prevent the development of additional sensitizations.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

A 2017 systematic review and meta-analysis, including 17 RCTs and 16 nonrandomized studies found that SCIT and SLIT in PST negative patients did not reduce the risk of developing a first allergic disease in the short term, and no studies examined long-term effects.[88] The same systematic review and meta-analysis found that the use of SCIT for AR reduces the risk of developing asthma for both the short-term (RR 0.40) and long-term (RR 0.62).[88] However, in a sensitivity analysis, a reduced risk of new sensitizations over the short-term was not confirmed, and there was no evidence for a long-term asthma prevention effect.[88]

A 2022 systematic review and meta-analysis looked at the effect of SCIT and SLIT on asthma prevention and included 12 RCT and 12 nonrandomized studies of interventions (NRSI), including cross-sectional, retrospective, and prospective studies published before 4/6/21.[238] Twelve studies were conducted in children or adolescents, one in adults, and 11 in mixed-age populations. Most of the patients had AR prior to entering the trial; 11 studies included participants with AA upon study entry, but most evaluated the results separately for those with and without asthma at study entry. Of the 24 trials included in this systematic review, 11 were SCIT-only patients: 6 RCTs, all published prior to 2007, and 5 NRSI, 2 of which were published after 2012. In the 3 mixed SCIT/SLIT trials, all of which were NRSI and published after 2011, 2 separated the outcomes by SCIT and SLIT. Only 17 out of 24 trials were included in the random-effects meta-analysis on the effectiveness of SLIT or SCIT in preventing asthma. For the random-effect analysis, there was a significant decrease in the risk of developing asthma (RR 0.75 [95% CI: 0.64, 0.88]). However, this finding was not significant in the sensitivity analysis. The method of AIT administration (SLIT or SCIT) did not influence these results. Subset analyses for the combined SCIT/SLIT patients showed a significant preventive effect in children (RR 0.71 [95% CI: 0.47, 0.88]), in monosensitized patients (RR 0.48 [95% CI: 0.39, 0.61]), and in patients completing 3 years of therapy (RR 0.64 [95% CI: 0.47-0.88]). Subset analysis by SCIT or SLIT was limited due to the small number of trials and the fact that most studies did not have asthma prevention as their primary outcome. The NRSI trials were predominantly large database studies. Most articles had a high risk of bias, and there was overall heterogeneity and possible publication bias.[238]

In a 2024 retrospective real-world evidence study from a large German claims database, Jutel et al.[239] evaluated native depot HDM SCIT in 892 patients aged 5–70 years and compared them

with 2676 matched non-AIT controls followed for up to 6 years. After at least 2 years of treatment, the SCIT group had fewer prescriptions for AR medication (−62.8%; p<0.0001) and asthma medication (−42.4%; p=0.0003), and among patients without asthma at baseline, the odds of new-onset asthma were reduced by 27.0% versus controls (OR, 0.73 [95% CI: 0.56, 0.95]; p=0.0212). The preventive effects of SCIT on asthma were observed after 15 months.[239] This product-specific real-world study is supportive but not definitive, and its relevance to US practice is limited because it evaluated a depot aluminum hydroxide–adsorbed HDM extract rather than an aqueous extract.

In a 2010 systematic review of SCIT for the prevention of new sensitizations, 10 of the 18 studies provided uncertain evidence that SCIT might prevent the onset of new sensitization.[90] Two[240, 241] of the 10 studies were published after 2009 and were not included in the JTF 2011 AIT PP.[2] One of these two studies showed no significant reduction in new sensitization after 4 years of HDM SCIT.[240] The second study reported that at a 3-year follow-up after completing 3 years of pre-seasonal 6-grass SCIT, new sensitizations developed in 77% of the placebo group compared to 23% of the SCIT patients.[241] In an RCT comparing 3 years of *D. pteronyssinus* SCIT (n=46) to pharmacotherapy (n=46) for AR, there was a significant reduction in SS and MS (p<0.05) and fewer SCIT patients developed asthma or new sensitizations (p<0.05).[242]

In summary, the studies supporting the preventive effect of SCIT on asthma and the development of new sensitivities since the JTF 2011 AIT PP[2] are few, are limited primarily to large database nonrandomized studies and real-world evidence, and overall provide uncertain evidence for the preventative effects of SCIT on asthma development. Well-controlled, high-quality RCTs are needed to establish the long-term preventive effects of SCIT in both children and adults.

SCIT length of treatment and long-term efficacy of single-allergen SCIT

21. Recommendation: We suggest single-allergen SCIT (at doses that achieve short-term efficacy) for a minimum of three years to achieve long-term efficacy lasting at least two years after SCIT discontinuation.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Since the JTF 2011 AIT PP,[2] substantial research has focused on the long-term efficacy of SCIT in treating AR and AA. These studies have explored seasonal and perennial allergens, different patient demographics, and varying durations of treatment to establish effective treatment protocols that can achieve efficacy following discontinuation of SCIT.

The JTF 2011 AIT PP did not make a specific recommendation for the length of treatment but stated that, upon discontinuation following 3-5 years of treatment, some patients might sustain clinical remission, while others might relapse.[2] Based upon the studies reviewed in 2010 (primarily published prior to 2010), a minimum of three years of SCIT is required for long-term efficacy, but any added benefit of SCIT beyond 3 years is uncertain.[243, 244] Furthermore, the

decision to stop or continue depends upon disease severity, treatment benefits, treatment convenience, and patient choice following a discussion of the risks and benefits.[2, 245]

Studies since 2010 have also shown that a minimum of 3-5 years of SCIT is required to maintain clinical benefits following discontinuation of SCIT. In a multicenter, RDBPC, phase III study conducted in 6 European countries, 649 monosensitized and polysensitized AR patients (n=434 active, 215 placebo) were treated with polymerized birch pollen for 3 years and followed for an additional 2 years.[246] Upon the recommendation of the EAACI, a post hoc primary efficacy endpoint was implemented. The new EAACI CSMS ($CSMS_{EAACI}$) included four nasal symptoms and two ocular symptoms. The daily SS and the daily MS were each given a value of 0-3 for a total $CSMS_{EAACI}$ of 0-6. For the intent-to-treat population, there was no significant improvement in $CSMS_{EAACI}$ at the end of years 1,2,3, and 5 compared to placebo. However, in a subgroup of monosensitized patients (n=200), there was a statistically significant improvement in $CSMS_{EAACI}$ compared to placebo at 2, 3, and 5 years. At 5 years, patients completing 3 years of birch SCIT had significantly reduced median [IRQ] $CSMS_{EAACI}$ compared with the placebo group (SCIT 1.10 [95% CI: 0.60, 1.90]) versus 1.60 (95% CI: 0.80, 2.40), respectively; p=0.013].[246] A RDBPC trial with 154 adult patients found significant improvements in SS, SMS, and RQLQ scores (p<0.001 for all) three years following the completion of 3 years of 6-grass, pre-seasonal SCIT for AR.[241]

In a phase IV, 5-year, prospective, controlled trial, double-blind for cluster or conventional schedule SCIT until the end of the first year, a mixture of mono- and polysensitized pediatric and adult patients were subsequently randomized to 3 or 5 years of standardized *D. pteronyssinus* extract containing Der p 1 and 2 (Pangramin Depot UM, ALK-Abello, Madrid, Spain) SCIT for AR and/or AA.[247] The monthly maintenance injection volume was 0.8 mL and contained 3.6 mcg of Der p 1. A later component-resolved post hoc analysis of this study cohort reported that the extract contained 2 mcg/mL of Der p 2;[248] therefore, the estimated maintenance dose was 1.6 mcg of Der p 2 per monthly injection (0.8 mL × 2 mcg/mL).[247] Following 3 years of SCIT, there was significant improvement in global rhinitis and asthma severity scores, a patient subjective severity VAS for respiratory allergies (1-10), AQLQ, and RQLQ (p<0.001 for all) in both the 3-year and the 5-year SCIT treatment groups. Two years later (5 years following randomization), the 3-year treatment group (n=41) maintained improvement in global rhinitis and asthma severity but did not show further improvement. The 5-year treatment group (n = 52), who had remained on SCIT, experienced an additional 19% relative reduction in global rhinitis severity scores but showed no further improvement in global asthma severity scores.[247] In a subpopulation of children (n=81; 5-15 years of age), both the 3- and 5-year groups showed significant improvement in global rhinitis and asthma severity scores following 3 years of SCIT.[99] At the end of 5 years following randomization, there was an additional 30% reduction in global rhinitis severity scores in the 5-year treatment group compared to no change in the 3-year treatment group; however, the difference in global rhinitis scores were not statistically significant when comparing the 3-year and 5-year treatment groups. While both the 3-year and the 5-year treatment groups showed significant improvement in asthma severity (p=0.001) following 3 years of SCIT, neither those who stopped or those who continued SCIT showed further improvement 2 years later.[99]

An observational study found that 5 years following the completion of 3 years of Alutard HDM SCIT (n=106) for persistent AR in mono-sensitized and polysensitized children, there was significant improvement in MS, VAS, and RQLQ compared to baseline ($p<0.05$) and compared to the pharmacotherapy control group (n=87; $p<0.001$).[249] Additionally, in a study of 31 adult HDM allergic patients who were followed for 10 years after discontinuation of treatment with a depigmented, polymerized HDM (dpg-pol HDM) SCIT, nasal ($p=0.0117$), conjunctival ($p<0.0001$), and bronchial ($p=0.0005$) symptoms were significantly improved compared to baseline, but only in patients who completed ≥3 years of SCIT.[250]

An observational, long-term clinical follow-up study of children (n=58) and adults (n=103) with perennial AR treated with HDM SCIT found that children could achieve sustainable post-treatment efficacy for over 3 years (up to 13 years) following 3 years of SCIT.[72] A small observational study followed 20 AR patients who completed 3 years of HDM SCIT and then monitored their symptoms for 10 years following cessation of SCIT, reported reduced symptoms compared to baseline.[251]

Discontinuation of SCIT prior to 3 years may not result in long-term improvement. The Gauging Response in Allergic Rhinitis to Sublingual and Subcutaneous Immunotherapy (GRASS) trial was a RDBPC 3-parallel group study that evaluated 106 patients with moderate to severe AR.[252] This study treated 36 patients with daily timothy grass pollen SLIT-T (containing 15 mcg of Phl p 5), 36 patients with monthly timothy grass pollen SCIT (20 mcg of Phl p 5), and 34 patients with a placebo for two years. At 3 years (1 year after ending active treatment), NAC was not significantly different when comparing the 2-year SCIT and SLIT groups to placebo. The GRASS trial likewise demonstrated that the desirable immunological changes, e.g., suppression of CD4 T-cell properties including ex vivo HLA class II tetramer staining for CD4+ peripheral blood lymphocytes, expression of CRTH2, CD161, and CCR4, surface markers along with an increase in CD27+ cells. There was also suppression of local mucosal cytokine responses (IL-4, IL5, IL-13) in nasal fluids, no effect on IFN-γ or IL-10 responses, an overall reduction in circulating allergen-specific TH2 cells, and reduced IgE-facilitated allergen binding (IgE-FAB) as determined by the IgE-FAB assay.[252] These were noted at the end of 2 years of SCIT; however they returned to baseline by year 3, one year post-treatment.[253] Similarly, a short-term, 5-month preseasonal recombinant grass pollen SCIT trial showed initial benefits, but these benefits disappeared by the five-year mark.[254] Based on these studies, it is not advised to discontinue SCIT prior to completing 3 years of treatment.

Many long-term efficacy studies conducted since 2010 have involved real-world effectiveness, often with retrospective designs, varying treatment durations, and heterogeneous observation periods after discontinuation of SCIT. In a retrospective, real-life study of 7142 patients treated with birch SCIT (90%) or SLIT (10%) for ≥ 2 seasonal treatment cycles (with >85% having ≤3 seasonal treatment cycles) and monitored for up to 6 years (average of 4.4 years) following the completing of SCIT, the active treatment groups were significantly more likely to have discontinued AR and asthma medications compared to matched controls.[255] In another retrospective study of 90 HDM monosensitized children with asthma, of whom 60 received HDM SCIT for either 3 or 5 years, 3 years following the discontinuation of SCIT (at year 6 for the 3-year treatment group and at year 8 for the 5-year treatment group), there was no difference in

the dosage of ICS, FEV_1, or asthma remission in those receiving either 3 or 5 years of SCIT.[256] The authors of this HDM study concluded that three years of SCIT is adequate for the treatment of childhood asthma.[256]

In a large retrospective, real-life study, there was a significant reduction in prescriptions for AR ($p<0.001$) and AA ($p=0.015$) in 2350 HDM allergoid SCIT-treated patients compared to 64,740 controls at follow-up, which was up to 6 years (mean 3.43; SD 0.83 years) following the first dose of SCIT.[257] In patients without asthma at baseline, the SCIT-treated group had a reduced onset of asthma (OR 0.81 [95% CI: 0.70, 0.95]; $p=0.008$). While all SCIT-treated patients received a minimum of one prescription of SCIT in two successive HDM seasons, only 64% and 37% completed 2 and 3 years, respectively, of SCIT.[257]

Three real-world retrospective studies have shown that patients receiving SCIT for AR have a significantly lower risk of incident asthma for up to 9 years following the termination of SCIT.[89, 257, 258] In one of these studies, SCIT administered for ≥3 years in AR patients had a stronger preventive effect on the development of asthma than the use of SCIT for less than 3 years.[89] Another real-world study used AIT (82% SCIT; 12% SLIT) for a mean duration of 1.5 years in 46,000 AR patients, of which 14,600 also had pre-existing AA.[258] All actively treated patients were matched 1:1 with controls who received only pharmacotherapy for their AR and AA. At 9 years of follow-up, the total AIT-treated AR cohort had 1846 subjects, and the pre-existing AA cohort had 517 subjects. Compared to the pre-index year, the AIT-treated cohort had a consistent and progressively greater reduction in AR and asthma medication prescriptions across the 9 years of follow-up. However, when compared to controls, the medication reduction achieved with AIT, although significant at 5 years ($p<0.0001$), lost significance after 9 years of follow-up. At 5 years of follow-up, when compared to matched controls, the pre-existing AA cohort that received AIT had a reduction in the number of severe asthma exacerbations ($p<0.0001$) and in the number ($p=0.01$), as well as in the severity, of pneumonia episodes, as measured by antibiotic prescriptions ($p=0.0068$), hospitalizations ($p=0.059$), and duration of in-patient stays ($p=0.0007$); however, there was no significant difference in any of these outcomes at 9 years of follow-up.[258]

Another large observational study has shown a reduction in asthma exacerbations and lower respiratory tract infections with SCIT.[259] A Danish prospective nationwide study (1995-2014) of adults with seasonal SAA or perennial AA treated with SCIT for a minimum of 3 years showed a significant average reduction in asthma exacerbations in seasonal AA and perennial AA of 57% and 74%, respectively, over the three years following discontinuation of SCIT.[259] In addition, there was a significant reduction in lower respiratory tract infections in seasonal AA and perennial AA of 17% and 20%, respectively, over the three years following SCIT compared to the year pre-SCIT.[259]

However, not all trials have shown long-term efficacy following 3 years of SCIT. In one RCT, following 3 years of pre-seasonal grass SCIT in 38 older adult (>65 years of age) AR patients, there was a significant short-term improvement of CSMS ($p=0.03$) and QOL ($p<0.05$) compared to placebo.[62] However, 3 years following discontinuation of SCIT, there was no significant difference in CSMS and QOL, compared to placebo.[62]

When assessing the published evidence for long-term efficacy of SCIT, both before and after 2010, the balance of evidence supports long-term efficacy of single-allergen SCIT, i.e., continued clinical benefit following discontinuation of SCIT. There is inconclusive evidence as to whether the long-term efficacy achieved with single allergen SCIT in polysensitized patients is as effective as single-allergen SCIT in monosensitized patients. While SCIT for less than 3 years may provide long-term efficacy, this is more likely with 3 years, and 5 years may provide an even greater likelihood of persistent effects. US specialists report that they continue SCIT beyond 5 years in approximately 20% of patients.[260] The sustainability of clinical benefits beyond five years after discontinuation varies, and additional research is warranted to confirm long-term outcomes.

Efficacy of multi-allergen SCIT

Multi-allergen SCIT refers to the administration of more than one, non-cross—reacting allergen concurrently during a course of treatment. Mixtures of homogeneous allergens, such as mixed Northern grasses, are typically considered a single allergen. Each heterogeneous allergen, e.g., a grass pollen, tree pollen, or animal dander, may be formulated in a separate vial or combined with other allergens in the same vial. Multiple allergens may be administered as a single injection or multiple injections. While all allergens are typically administered during the same injection visit, they may occasionally be administered on separate injection visits, such as on different days.

In unselected populations in the US and Europe, aged 6-59 years, literature sources report that 54% and 42% are SPT positive, respectively; of these, 71% and 63% are polysensitized, respectively.[261, 262] Not all polysensitized patients are polyallergic; up to 73% of positive SPT to common allergens may be clinically relevant.[263] In a US survey, 45% of specialists reported AIT with more than 10 allergen extracts.[264] These were likely formulated in multiple vials, as the responding specialists reported administering an average of 2.3 injections per SCIT visit.[264] Similarly, in Latin America, 22% of specialists surveyed mixed ≥ 6 allergens in one vial.[265]

22. Recommendation: We suggest the use of multi-allergen SCIT when there is evidence that symptoms are caused by more than one allergen.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

23. Recommendation: We suggest that multi-allergen SCIT contain the smallest number of relevant allergens, each at a maintenance dose sufficient to achieve clinical efficacy as established in single-allergen SCIT studies.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

24. Recommendation: We suggest administering maintenance multi-allergen SCIT for a minimum of three years, ensuring that each allergen component is delivered at a maintenance dose comparable to that shown to achieve clinical efficacy in single-allergen SCIT, to enhance the likelihood of long-term efficacy (≥2 years after discontinuation).

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

25. Recommendation: We suggest that AIT may be extended beyond five years in patients who place a high value on avoiding anti-allergy medications, provided a shared decision-making discussion documents the absence of evidence of additional benefits beyond five years of AIT.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Since 2010, there have been very few controlled clinical trials on multi-allergen SCIT. A 2-year DBPC trial conducted in Denmark in polyallergic AR patients (n=285) found a significant ($p<0.0385$) but modest (19%) reduction of CSMS vs. placebo.[266] The study utilized a combined birch and grass depigmented, glutaraldehyde-polymerized allergen extract, which is available in Europe, but not in the US, for year-round treatment. However, the authors considered that the limited efficacy may have been due to the 50% dose reduction for each pollen in the mixture, compared to the dose used for therapy of the monosensitized patients.[266]

In China, a 1-year RCT in HDM allergic, polysensitized children (n=78) compared *D. farinae* HDM SLIT to multi-allergen SCIT for the treatment of AR.[267] All children had positive SPT to both Der f and Der p, and to at least one additional relevant aeroallergen. The SCIT extract contained HDM and between one to three additional clinically relevant antigens, which were selected based upon each patient's SPT, sIgE, and clinical allergy symptoms. Compared to baseline, the TNSS and total medication score improved in both groups ($p<0.001$), and there was no significant difference in any outcome measure between groups.[267]

In a 3-year randomized, but unblinded, trial conducted in Korea, children 6-15 years of age with AR and AA, were treated with multi-allergen SCIT (n=53) using up to 4 standardized allergens plus pharmacotherapy or pharmacotherapy only (n=19).[268] The SCIT group had greater improvements than the drug-only group in asthma symptom scores ($p<0.001$), AR symptom scores ($p=0.001$), FEV_1 percent predicted ($p=0.011$), FEV_1/FVC ratio expressed as a percentage ($p<0.001$), and bronchial hyperresponsiveness assessed by methacholine challenge ($p=0.020$).[268]

There have been additional observational trials looking at multi-allergen SCIT. In the 2024 ARES prospective multicenter observational study, 115 polyallergic patients aged 5–60 years with allergic respiratory disease received 1 year of SCIT with mixtures of 2 polymerized pollen or mite extracts.[269] Mean global symptom and medication score improved from 3.5 to 1.6, and RQLQ improved by an absolute 1.6 points (both $p<0.001$); most patients also reported subjective clinical improvement and high treatment satisfaction. Safety was favorable, with no serious treatment-emergent AEs and only 1 SR (grade 1) (0.9%).[269] For US allergists, this study

is relevant because it addresses the practical problem of treating polyallergic patients with multi-allergen SCIT; however, extrapolation to US practice should be done with caution, as the preparation studied was a polymerized allergoid mixture, whereas US allergists generally use aqueous/liquid extract mixtures.

A retrospective, multicenter Swiss study was conducted in AR patients (n=97), with or without AA, who were allergic to multiple pollens.[270] All patients received SCIT to two pollens, the selection based upon the patient's individual allergic history and sensitization pattern. Following the rush build-up, all patients received 0.5 mL maintenance injections from a single vial of undiluted, depigmented, and polymerized allergen extract containing two pollens (Depigoid ® DUO pollen mixture (DPP) at 2000 DPP/ml). Following treatment for a median of 1.8 years, there was a significant patient reported improvement in the VAS for rhinoconjunctivitis (median increase of 3.6 points) and AA (median increase of 1.9 points) and in the mini RQLQ (median decrease of 1.1 points; IQR 2.1, 0.2) with all measurement differences being significant ($p<0.0001$). Clinically significant improvements were similarly observed in the individual dimensions of the mini RQLQ, including nasal and ocular symptoms, activities, and practical problems. The percentages of patients experiencing complete resolution of nasal, ocular, and lower respiratory symptoms (cough, wheeze, and dyspnea) were 5%, 22%, and 15%, respectively.[270]

In a 1-year, observational study conducted in China, HDM monosensitized (n=12), weed monosensitized (n=21), and HDM and weed polysensitized (n=11) AR patients received SCIT containing their respective allergens.[271] Significant improvement was noted in the author-defined symptom score and medication score and in the RQLQ, irrespective of the allergen(s) used. During the weed season, the RQOL was not significantly different in the weed pollen treatment group compared to the mixed HDM/weed pollen group. Similarly, in nonpollen seasons, there was no significant difference in the RQOL in the HDM-treated group and the mixed HDM/weed pollen-treated group.[271] This study showed that SCIT for a specific allergen group, e.g., weed pollen or mixed HDM, was equally effective whether administered as monotherapy or combined with another allergen group.

An observational study from Spain reported AR patients (n=250), with or without AA, treated with a glutaraldehyde-modified mixture of *D. pteronyssinus, D. farinae*, and *B. tropicalis* in a cluster up-dosing schedule with a maintenance dose of 5000 Therapeutic Units (TU) per month for 12 months.[151] One TU contains the same protein content as one Biological Unit (BU) of native allergen. Recognizing that sensitization to *B. tropicalis* is specific, without significant cross-reactivity with *D. pteronyssinus* and *D. farinae*, this would be considered a multi-allergen trial. Using the Federal Drug Administration (FDA) and European Medicines Agency (EMA) accepted symptom scoring system (0-3), and the EAACI consensus for CSMS,[272] the authors used the daily SS (0-3), daily MS (0-3), and the CSMS (0-6) to measure efficacy for AR, and the asthma control test (ACT)[5] and the Global Initiative for Asthma (GINA) score to demonstrate efficacy in AA. After 12 months of SCIT, there was a 40% reduction in the CSMS ($p<0.0001$) for AR.[151] AR patients with AA had a significant reduction in the ACT ($p<.0001$) and 58% had an improvement in their GINA medication score.[151] With a median increase in the ACT score from

20 at baseline to 25 following 12 months of treatment,[151] this exceeds the 3-point increase which defines a clinically meaningful difference.[273]

Another observational, retrospective, 3-year study from Korea demonstrated that participants with ICS-treated asthma achieved equal improvement in asthma control and ICS reduction with multi-allergen SCIT compared with those treated with HDM alone.[274]

In a 2022 review that critically evaluated the published evidence supporting the practice of multi-allergen SCIT, the authors concluded that there is no evidence from placebo-controlled trials that multi-allergen SCIT can reduce symptoms more than treatment with one clinically relevant allergen during the season of that particular allergen and that dose-finding trials for multi-allergen SCIT are inadequate, with none conducted since 1997.[275]

In 2016, a group of European SCIT experts from France, Italy, Germany, and Spain reviewed the published literature (including both clinical trial and real-world observational studies) and guidelines developed by regulatory bodies and professional societies and added their own clinical experience to develop a practice-based approach to the treatment of the polyallergic patient in Europe.[276] They concluded that single allergen SCIT should be used for polyallergic patients in whom one relevant allergen was responsible for the most intense and/or bothersome symptoms. Furthermore, they suggested that multi-allergen SCIT, using 2 relevant allergens, either in separate vials or mixed in one vial, could be considered for SCIT when treatment with both allergens would likely make a marked impact on clinical symptoms and QOL. They emphasized the use of high-quality, standardized allergen extracts. These experts discussed the option of reducing the dose of each single allergen when using multi-allergen SCIT and/or in administering each allergen with a delay between injections, but they provided no evidence to support this suggestion.[276] Their suggestions, coming from a European background where single allergen immunotherapy is common practice and single allergen immunotherapy is sold as end-product, are in sharp contrast with the previous and current recommendations by the JTFPP.

There are no published, well-controlled trials that address the long-term benefits of multi-allergen SCIT. Based upon longstanding clinical observations and studies showing that immunological changes occur with SCIT, there is expert clinical evidence for both the short-term efficacy and long-term efficacy of multi-allergen SCIT following 3-5 years of treatment, with the potential for remission in some patients. There are multiple factors that may contribute to differences between clinical experience and the available clinical trial data regarding the long-term efficacy of multi-allergen SCIT, particularly given the absence of adequately powered, long-term randomized studies. Both the duration of SCIT to achieve long-term efficacy and the duration of long-term efficacy following discontinuation of SCIT likely depend upon the number and type (e.g., pollen vs. fungi) of clinically relevant allergens, the level of allergen exposure, the quality and potency of the individual allergen extracts, the maintenance and accumulated doses of the allergen extracts administered over the course of the treatment, and the adherence to treatment, including both the persistence and consistency of SCIT. Unfortunately, even for long-term efficacy of single allergen SCIT, most studies account for very few of these factors, and no studies incorporate all of them. For the long-term benefit of multi-allergen SCIT, we can only make recommendations based upon very low certainty of evidence. Well-controlled studies on the long-term efficacy of multi-allergen SCIT are needed before we can provide specific

recommendations with a high degree of certainty. There are very few studies comparing treatment for three versus five years. However, one study noted an improvement in rhinitis scores only in the group that was treated for five years compared to three.[247]

In summary, since the publication of the JTF 2011 AIT PP,[2] there have been very few well controlled clinical trials on the short-term efficacy of multi-allergen SCIT and none on the long-term efficacy. Most of these trials have studied only 2 unrelated allergens, far below the average number of allergens that US specialists include in SCIT treatment sets. When considering pre- and post-2010 clinical trials on multi-allergen SCIT, we find considerable heterogeneity, many studies with small sample size, frequently poor study design, and incomplete reporting of efficacy for each allergen. Recommendations for multi-allergen SCIT continue to rely predominantly on evidence from hundreds of thousands of patients treated in clinical practice over the past 100 years and on indirect evidence from SCIT monotherapy. This is one reason real-world evidence from observational trials is gaining importance, as that is a practical, cost-effective means of showing multi-allergen AIT effectiveness. Establishing SCIT registries that collect data using standardized protocols may be the best strategy for capturing this valuable real-world evidence.[277] This concept is further discussed in the "Future of AIT" section.

SCIT and EoE

26. Recommendation: SCIT may be considered as an adjunct treatment option for clinically relevant aeroallergens in select patients with EoE poorly responsive to standard treatments and co-morbid AR.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Multiple older and current studies, including a systematic review of literature from 1950 to 2015, showed that environmental exposures can play a large role in the etiology of EoE.[278] In addition, case reports of SCIT to HDM and pollen have been described to produce remission of EoE that has been poorly responsive to standard therapies including elimination diets.[279-282] An abstract with a case series of 39 atopic EoE patients treated with both aeroallergen SCIT and an elimination diet based upon the results of CRD showed a 68% full histological and clinical response to treatment.[283] A larger study included 129 patients with EoE were treated with CRD-directed (using 112 recombinant and native allergens) AIT (SCIT and SLIT) and/or CRD-directed dietary elimination.[284] The predominant allergens were from the grass group 1 (55%), lipid transfer proteins (LTP) of peach and mugwort, hazelnuts, and walnuts and the most common AIT was for grass pollen. After AIT or diet elimination treatment, 78.3% had improvement in clinical symptoms ($p<0.017$) and 75.2% had complete histological and clinical remission. The AIT treated group had better outcomes (OR 177.3 [95% CI: 16.2, 1939.0]).[284]

A retrospective study compared 667 patients with EoE who were not treated with SCIT to 10 patients with EoE who were treated with aeroallergen SCIT.[285] Among the SCIT-treated patients, topical corticosteroid use was lower and dietary elimination was more common at follow-up than at the initial endoscopy. The authors were unable to draw definitive conclusions about the efficacy of SCIT treatment in patients with EoE; however, they did not observe worse

outcomes in the SCIT-treated group.[285] Notably, there is a single case report, with significant methodological limitations, of a patient with underlying EoE since a younger age, who developed EoE during grass pollen SLIT twice and experienced recurrence after subsequent treatment with grass SCIT.[286] Clear cause and effect association cannot be established in this single case, but this highlights the importance of ongoing clinical vigilance when initiating AIT in patients with EoE.

Overall, evidence for treating patients with refractory EoE and co-morbid AR with aeroallergen SCIT is very weak. There may be benefit as an individualized adjunct option, but AIT should not be used routinely.

Repeating SPT during or after a course of SCIT

27. Recommendation: We recommend against routine repeat skin testing and/or sIgE testing during or after successful SCIT solely to guide treatment continuation or discontinuation decisions.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

28. Recommendation: We suggest repeat skin testing or sIgE testing as part of a comprehensive assessment during or following 3-5 years of partially successful SCIT when new allergen sensitization is suspected.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

When there has been significant clinical improvement and the patient has completed 3-5 years of SCIT, the specialist must decide whether to continue or discontinue SCIT. Most studies show SPT size decreases after 1-5 years of SCIT and the decrease correlates with symptom scores and/or immunological parameters such as sIgG4.[287-290] However, the change in allergen sIgE is not universal. Although most studies show decrease in SPT size, a study in older adult patients, aged 65-75 years, did not find a change in sIgE levels pre- and post-3 years of SCIT, although sIgG4 levels did increase.[59] In a study of 81 children, SPT sizes decreased after three years of successful SCIT.[291] Another study of 181 patients showed that the pre-HDM SCIT SPT "intensity", measured as ++ to ++++, did not accurately predict AIT response.[292] Neither study addressed skin testing to predict post-treatment clinical effects. Studies examining skin testing to predict response after discontinuation of SCIT are lacking; therefore, the positive and negative predictive values of SPT to determine long-term efficacy after discontinuation are unknown. Therefore, shared decision-making with the patient is typically employed to determine whether SCIT should be stopped or continued, with a primary focus on the clinical response. Skin testing or sIgE may be considered a tool for a complete picture of the patient's current sensitization, including the development of new sensitization to allergens. However, it should not be used routinely as the sole reason to continue or to discontinue SCIT.

Efficacy of SLIT-tablets (SLIT-T) and liquid (SLIT-L)

Efficacy of HDM SLIT-T for AR and asthma

29. Recommendation: We recommend HDM SLIT-T for HDM allergic adults and children with AR to reduce symptoms and medication use.

Strength of Recommendation: Strong for adults and children aged 5 years and older

Certainty of Evidence: High

30. Recommendation: We suggest the patient be informed that treatment with the HDM SLIT-T initially becomes effective following 8-14 weeks of treatment.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Twenty-two RDBPC trials (12 HDM SLIT-T, 10 HDM SLIT-L) between 2009 and 2023 demonstrate benefit for HDM SLIT in the treatment of AR symptoms.[58, 75, 293-312] Most studies did include children, and many also included patients with mild to moderate asthma. One study focused on an elderly cohort of subjects.[58] The majority of studies measured decreases in total combined rhinitis scores (TCRS) and medication scores. Most studies utilized either 300 index of reactivity (IR; Stallergenes/Greer) tablets or 6-12 SQ-HDM tablets (ALK).

The FDA-approved 12 SQ-HDM dose for the ALK HDM SLIT-T contains roughly 15 mcg of group 1 mite allergens (Der f 1 and Der p 1 combined) and 15 mcg of group 2 mite allergens (Der f 2 and Der p 2 combined).[312] The 300 IR formulation for the Stallergenes-Greer HDM SLIT-T varies from 14-17 mcg Der p 1 to 53-68 mcg Der f 1.[300] The relative effects above placebo were 17-33%.[294, 297, 300, 303, 312] Duration was typically at least 12 months. The onset of benefit from HDM SLIT is as early as 8 weeks (time of first environmental chamber challenge) when measured in an allergen chamber[299] and 12 weeks[294] to 14 weeks[295, 298] when measured in natural exposure in AR trials.

Several SLIT-L trials demonstrated peripheral blood humoral and cellular immunologic changes including increased sIgG4,[293, 295, 305] increased IL10 and TGF-beta,[304, 310] decreased TH2A, CD38+ TH2A cells,[302] and decreased osteopontin.[304] High responders in one study showed an increase in IgG2, IgG4, and IgE[305] and in another lower ST2+CD45RO+CD4+ lymphocytes (IL-33 receptor positive memory Th2 cells).[307]

RDBPC trials using an environmental chamber show the onset of a clinically significant decrease in TNSS of 20.4% relative to placebo following allergen challenge is as early as 8 weeks (first challenge after starting SLIT) with the SQ-HDM SLIT-T (12 SQ-HDM daily dose) and 48% TNSS reduction after 24 weeks relative to placebo.[299] The Stallergenes-Greer HDM SLIT-T demonstrated reduction in the rhinitis total symptom score of 33%, 29% and 20% in the 500 IR-, 300 IR- and 100 IR-treated groups, respectively, after 6 months of treatment.[300]

RDBPC trials required for US HDM SLIT-T approval included Demoly et al.[298] who studied 992 adults (46% with asthma, 67% polysensitized) in 12 European countries for one year. In the 12

SQ-HDM group, the authors demonstrated decreased TCRS and medication scores and improved QOL with the onset of benefit at 14 weeks. After one year of treatment, absolute reductions in TCRS were 1.18 (p=0.002) and 1.22 (p=0.001) greater than placebo for 6 SQ-HDM and 12 SQ-HDM; differences relative to placebo ranged from 18-22% using adjusted means and medians.[298]

Nolte et al.[312] performed a RDBPC trial in the US and Canada for 12 months comparing 12 SQ-HDM SLIT-T (n=741) to placebo (n=741). In this study, 31% of subjects had asthma (controlled with FEV_1 ≥80%), and 76% were polysensitized. Compared with placebo tablets, treatment with 12 SQ-HDM improved the TCRS by 17% (95% CI: 10, 25), rhinitis daily SS by 16% (95% CI: 7, 24), total combined score by 17% (95% CI: 4, 25), and AR/C VAS score by 16% (95% CI: 8, 23) (all p<0.001).

On the basis of these aforementioned trials, the SQ-HDM SLIT-T is FDA approved for treatment of HDM-induced AR, with or without conjunctivitis, in persons aged 5 years to 70 years.[313] The panel cannot identify any reason the treatment would not be effective for children younger than 5 years or adults greater than 70 years of age.

31. Recommendation: We recommend HDM SLIT-T as a therapeutic option for HDM allergic adults and children with mild to moderate AA to reduce symptoms and to allow ICS dose reduction.

Strength of Recommendation: Strong for adults; Conditional for children

Certainty of Evidence: High for adults; Moderate for children

32. Recommendation: We suggest HDM SLIT-T for HDM allergic adults and children with mild to moderate AA to reduce exacerbations.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Ten RDBPC trials (6 SLIT-T, 4 SLIT-L) between 2009 and 2023 have examined the effect of HDM SLIT in patients with AR plus concomitant AA (**Table 7**).[314-323] These studies measured the effect of SLIT therapy on various aspects of the subjects' AA, including reduction of exacerbations and ICS dose, improvement of asthma control/symptoms and airway function, and desirable modification of immunologic parameters, as outlined below. Most studies included mild-moderate, persistent AA that was stable on ICS.

Asthma exacerbations

Virchow et al.[321] investigated the effects of HDM SLIT-T on asthma exacerbations and studied 834 partially controlled moderate-to-severe patients with AA, 18 years or older with concomitant HDM AR. The 6 SQ-HDM (n=275) and 12 SQ-HDM (n=282) doses decreased the risk of moderate to severe asthma exacerbations (HR 0.72 for the 6 SQ-HDM group and 0.64 for the 12 SQ-HDM group) during a 6-month ICS stepdown phase.[321] However, Tanaka et al.[320] performed another RDBPC trial in 826 Japanese patients with AA not well controlled by ICS

(equivalent to fluticasone propionate, 200-400 ug/day), as judged by the ACQ score of 1-1.5. They studied the time to first asthma exacerbation in adults with HDM allergy and AA and compared SQ-HDM doses of 10,000 JAU (6 SQ-HDM), 20,000 JAU (12 SQ-HDM) and placebo over a 19-month period. They found no significant difference in asthma outcomes, including time to first asthma exacerbation.[320]

ICS dose and asthma control

Several RDBPC trials (2 HDM SLIT-T, 2 HDM SLIT-L) demonstrate decreased ICS doses in the SLIT group.[314, 317, 318, 322] Mosbech et al.[318] demonstrated in subjects with mild-moderate AA that those receiving the 6 SQ-HDM dose had an average decrease in their ICS dose of 81 mcg, with 42% (mean) of subjects having at least a 50% decrease in their ICS dose after 12 months. Baba et al.[314] demonstrated that 3 years of SLIT-T therapy permitted a decrease in the ICS dose, improved ACT scores and TNSSs, and decreased new sensitizations. In a post hoc analysis, de Blay et al.[324] found that 6 SQ-HDM significantly reduced baseline daily ICS use by 327 mcg in a group of patients with mild to moderate, persistent AA with pre-trial daily ICS use of 400-800 mcg and ACQ scores of 1-1.5.

Wang et al.[322] demonstrated improvements in subjects with moderate persistent (401-800 mcg budesonide/day) AA, but not mild persistent AA, compared to placebo in a 12-month study using 300 IR SLIT-L. They demonstrated significant improvements in well-controlled and totally controlled AA with a higher percentage of ACQ scores <0.75 and greater mean reduction in ICS dose (218.5 mcg vs 126.2 mcg).[322] Queiros et al.[319] in a pediatric study of HDM SLIT-L showed decreased symptoms and medication scores as well as increased serum IgG4, IgG1, and salivary IgA.[319]

Airway function and inflammation

In a unique study looking at different aspects of SLIT-T on both airway function and inflammation, Hoshino et al.[316] demonstrated in a RDBPC trial of 102 asthmatic patients with rhinitis that 6 SQ-HDM daily for 48 weeks resulted in a significant reduction of clinical symptom scores, fractional exhaled nitric oxide (FeNO), airway wall area/body surface area, bronchial wall thickness, and percentage bronchial wall area with a concomitant increase in bronchial luminal area and airflow. The change in FEV_1 correlated with changes in FeNO and airway dimensions. The decrease in FeNO independently predicted the improvement in FEV_1.[316]

Another randomized, case-control study (non-blinded or open trial) did not show improvement in FEV_1 with 3 years of HDM SLIT-T.[314]

Woehlk et al.[323] published a study demonstrating a novel modification of the innate antiviral immune defense by HDM SLIT-T. They performed a RDBPC trial, abbreviated the VITAL study (Effect of Allergen Immunotherapy on Anti-viral Immunity in patients with Allergic Asthma), in which adult subjects with HDM AA received HDM SLIT-T 12 SQ-HDM (n=20) or placebo (n=19) for 24 weeks. Bronchoscopy at baseline and at 24 weeks showed increased viral mimic polyinosinic:polylcytidylic acid-induced expression of IFN-beta (type I IFN) and IFN-lambda (type III IFN) at both the protein and gene expression level. The alarmin IL-33 trended lower without changes in thymic stromal lymphopoietin (TSLP). They concluded that HDM SLIT-T

improves bronchial epithelial resistance to viral infection via a novel modification of the innate antiviral immune defense in the bronchial epithelium.[323]

Wongsa et al.[325] performed a meta-analysis of HDM SLIT in subjects with asthma and found 7 RCTs. They concluded that HDM SLIT-T therapy at 6 and 12 SQ-HDM tends to consistently allow reduction of ICS maintenance dose in adults and adolescents with well to partly controlled, mild-to-moderate AA.[325] It is also notable that the updated GINA guidelines from 2021 include HDM SLIT as an "add-on" treatment for step 2 through 4 mild to moderate, persistent AA in patients sensitized to HDM, provided the FEV_1 is ≥70%.[326] Furthermore, in 2025 the indication for HDM SLIT was broadened from step 1 onward, also leaving it as optional add-on medication in severe AA, once controlled.[327]

Table 7. Selected studies of HDM SLIT-T or SLIT-L in patients with asthma.

Study author, year	Site	Type/duration	Size/# pts	Age +/- SD, y	Intervention (n)	Asthma severity	Baseline ICS (mcg/d)	FEV_1 % predicted	Significant changes	Nonsignificant/ negative findings
Virchow et al, 2016[321]	Europe	RDBPC/13-18 mo	834	33.6 +/- 11.3	6 SQ-HDM (275) vs. 12 SQ-HDM (282) vs placebo (277)	Moderate -severe	582 +/- 246 BUD	92.3 +/- 12.66	Exacerbations decreased ICS dose increased IgG4 (both 6 SQ and 12 SQ)	ACQ, AQLQ
Tanaka et al, 2020[320]	Japan	RDBPC/ multicenter/13-19 mo	826	38.3 +/- 10.3	6 SQ-HDM (10,000 JAU) (274) vs. 12 SQ-HDM (20,000 JAU (276) vs. placebo (274)	Moderate - severe	78.8% vs. 75% vs 73.4% received >400 mcg/d Fluticasone propionate	79.9% (6 SQ), 81.2% (12 SQ), 78.1% (P)	↓sIgE ↑sIgG4	Time to first exacerbation, asthma symptoms, AQLQ, ACQ, ICS used, FEV_1
Hoshino et al, 2019[316]	Japan	Open RCT/48 wk	102	42 +/- 11	6 SQ-HDM (10,000 JAU) (50) vs no intervention (52)	Mild-moderate	487.5 +/- 169.7 BUD	94 +/- 24.8	↓FeNO, total IgE, airway wall thickness ↑FEV1, FVC Improved AQLQ,	None
Mosbech et al, 2015[328]	Europe	RDBPC/multicenter/52 wk	604	31 +/- 14	6 SQ-HDM (156) vs 3 SQ-HDM (159) vs 1 SQ-HDM (146) vs placebo (143	Mild-moderate	443 +/- 416.8 BUD	93.3 +/- 12.65	↓ICS used 6 SQ HDM vs placebo	FEV_1, ACQ, AQLQ, exacerbations
Wang et al, 2014[322]	China	RDBPC/12 mo	484	Adults	LIQUID 300 IR HDM (308) vs. placebo (157)	Mild-moderate			In moderate asthma, ↑well controlled	No change in mild asthma vs placebo

									subjects, ↑ACQ score, ↓ICS dose	
Bush et al, 2009[329]	US	RDBPC allergen challenge/12-18 mo	31	29.4	LIQUID 70 mcg Der f 1 (11) vs. 10 mcg Der f 1 (10) vs. placebo (11)	Intermittent	n/a	>80%	↑bronchial threshold to allergen challenge and *D. farinae*-specific IgG4	None
Nolte et al, 2016[312]	US Canada	RDBPC/multicenter/52 wk	1,482	35 +/- 14	12 SQ-HDM (741) Placebo (741)	Mild-moderate		98.6 +/- 16.7	Improved asthma daily SS	None
Woehlk et al, 2023[323]	Denmark	RDBPC/24 wk	39	28 +/- 8	12 SQ-HDM (20) Placebo (19)	Mild-moderate	862 mcg avg BUD	93 +/- 12	Increased polyinosinic: polycytidylic acid-induced expression of Type 1 (IFN-β) and Type 3(IFN-λ) at both gene and protein levels	None

ACQ, asthma control questionnaire; AQLQ; asthma quality of life questionnaire; BUD, budesonide; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IFN, interferon; JAU, Japanese allergy units; RDBPC, randomized, double-blind, placebo-controlled; SS, symptom score.

Efficacy of SLIT for AD

33. Recommendation: We suggest considering HDM SLIT-T as an adjunct to standard topical treatment for patients with moderate-to-severe AD that remains uncontrolled with standard topical treatment and who have clinically relevant HDM sensitization.

Strength of Recommendation: Conditional

Certainty of Evidence: Very low

Note: In the absence of SLIT-T studies, the certainty of the evidence must be extrapolated from SLIT-L, which has moderate certainty.

Multiple studies in the last decade have demonstrated the benefit of HDM SLIT-L in improving AD but the dosing has been variable among the studies (See SLIT for AD evidence table in **Appendix 2**). The AD evidence for SLIT-L is derived predominantly from HDM SLIT-L administered in addition to standard skin-directed therapy. Since no studies have utilized SQ-HDM tablets, which are currently approved in the US, the recommendation to use SLIT-T for AD must be extrapolated from the SLIT-L studies, thereby reducing the certainty of the evidence to very low.

In the 2023 systematic review and meta-analysis, SLIT and SCIT had similar relative estimates of benefit for AD severity, with no evidence of effect modification by route (P for interaction = .63).[34] This result is based on indirect subgroup comparisons; there are no direct randomized comparisons of SCIT and SLIT for AD. All SLIT randomized trials included in that review used SLIT-L rather than US SLIT-T products.[34]

An HDM-restricted meta-analysis found SLIT-L numerically outperformed SCIT on SCORAD (mean difference −7.22 vs −5.93) and worked best in children.[176] However, some SLIT-L trials had methodological weaknesses; the pooled SCORAD benefit fell below the MCID, and local reactions were more frequent in children. This analysis found no significant overall increase in systemic (RR 0.98 [95% CI: 0.52, 1.84]) or local (RR 1.49 [95% CI: 0.85, 2.62]) AEs, but a clear age signal that children (RR 6.19) and mild-to-moderate patients (RR 4.11) had significantly more local reactions.[176]

The most rigorous recent SLIT-L trial was RDBPC study of *D. pteronyssinus* SLIT-L in 91 patients aged 3 years or older with HDM sensitization and SCORAD scores of 15 or greater.[330] Background AD therapy was continued. The maintenance dose was a liquid formulation containing 0.3 mcg of Der p 1 + Der p 2 allergens, three times a week, using a Brazilian ASAC Pharma product. At 18 months, 66 participants completed treatment (35 SLIT and 31 placebo). The primary outcome, a decrease in SCORAD of 15 points or more, occurred in 74.2% of SLIT-L-treated participants and 58.0% of placebo-treated participants (RR 1.28 [95% CI: 0.89, 1.83]), and the difference was not statistically significant. Prespecified secondary outcomes favored SLIT-L: mean SCORAD reduction was 55.6% with SLIT-L and 34.5% with placebo (between-group mean difference, 20.4; 95% credible interval, 3.89-37.3), objective SCORAD also improved more with SLIT-L, and investigator global assessment of clear or almost clear skin was more frequent (14 of 35 versus 5 of 31; RR 2.63 [95% CI: 1.09, 6.39]). Eczema Area and Severity Index, Dermatology Life Quality Index, symptom VAS, and pruritus scores did not differ

significantly. The complete-case analysis and attrition of 25 of 91 enrolled participants limit certainty.[330]

In a multicenter, RDBPC phase II trial, Liu et al.[331] randomized 239 adults aged 18 to 60 years with mild-to-moderate HDM-sensitized AD to high-, medium-, or low-dose *D. farinae* SLIT-L (*D. farinae* drops, Zhejiango Bio) or placebo for 36 weeks. High- (2 drops of 1,000 mcg/mL q day) and medium-dose (1 drop of 1,000 mcg/mL q day), but not low-dose, SLIT-L produced significantly greater decreases in SCORAD and medication use than placebo. The reported clinical efficacy rates were 56.0% and 58.7% in the high- and medium-dose groups, respectively, compared with 38.0% with placebo. Forty-eight participants withdrew before study completion. Most reported adverse drug reactions were mild, although the study reported five serious adverse reactions; no life-threatening reactions were reported.[331]

Additional supportive evidence is provided by several smaller randomized studies of HDM SLIT-L. In a small 6-month randomized study of 14 patients with mild-to-moderate HDM-sensitized AD and concomitant AR, adjunct HDM SLIT-L with Staloral 300 (300 IR/ml) in 8 patients was associated with improvement in SCORAD, objective SCORAD, rhinoconjunctivitis-related QoL, and transepidermal water loss; however, the sample size was very small and the study was not designed to provide definitive efficacy evidence.[332] In a 24-month RCT of 96 patients aged 4 to 60 years with mild-to-moderate HDM-sensitized AD, Yu et al.[333] compared 2 years of SLIT-L (Chanllergen Wolwo Bio-Pharmaceutical Co, top concentration 1000 mcg/mL; 2 drops/day maintenance) to placebo. They reported greater reductions in SCORAD, symptom VAS, and rescue-medication use with SLIT-L than with control treatment beginning at 12 months; 77 participants completed follow-up, and no severe AEs were reported.[333] In a 12-month randomized study of 107 patients, Qin et al.[334] found that *D. farinae* SLIT-L plus pharmacotherapy was associated with lower daily medication and VAS and higher IgG4 levels at 6 and 12 months than pharmacotherapy alone; 23 participants withdrew. In an open-label, 12-month RCT of 60 children aged 5 to 17 years, Kim et al.[335] observed a reduction in mean SCORAD by 3 months that persisted through 12 months in the SLIT-L group, together with an exploratory reduction in new sensitizations. These studies provide supportive evidence but are limited by small sample sizes, open-label or non-placebo control designs, attrition, and variable outcome definitions.

An open-label controlled study extends the improvement in pediatric AD with HDM, with longer follow-up. Huang et al.[336] treated children aged 4 to 13 years with *D. farinae* SLIT-L (0.04 to 40 mcg protein maintenance) plus conventional therapy versus conventional therapy alone (309 SLIT-L, 131 controls), stratified into 1-, 2-, and 3-year treatment-duration subgroups. Effective rates and clinical response were significantly greater with SLIT-L after 2 and 3 years, and post-treatment SCORAD scores were significantly lower than controls across all duration subgroups, with longer treatment yielding greater benefit. Improvement was maintained one year after treatment cessation (SCORAD below both baseline and control values), and no significant safety concerns were reported. Attrition was substantial, with an overall loss to follow-up of 30.7%; therefore, the apparent duration-response relationship and post-treatment findings should be interpreted cautiously.[336] The open-label, non-randomized design reduces certainty, but the dose- and duration-dependent response is consistent with the broader HDM SLIT-L literature.

The lower acute reaction burden is an advantage of SLIT-L, but it should not be characterized as risk-free. In the 2023 evidence synthesis, which supplemented AD trial safety data with evidence from AR and asthma, AEs occurred in approximately 13% of SLIT-L recipients and 8% of control participants; events were mainly transient oral or oropharyngeal symptoms.[34] Systemic allergic reactions were uncommon (approximately 0.14% with SLIT-L versus 0.1% with control), and AEs causing discontinuation were uncommon (1.2% versus 0.9%).[34]

No clinical studies were identified that evaluated pollen SLIT-L specifically for the treatment of AD. Studies of pollen SLIT-L conducted for AR or asthma have not reported AD-specific clinical outcomes; therefore, evidence is insufficient to infer that pollen SLIT-L improves AD.

SLIT-T may be an appropriate add-on option for patients with clinically relevant HDM allergy who prefer home administration and can reliably adhere to daily treatment. The evidence supporting SLIT for AD is derived almost exclusively from trials of liquid HDM extracts, with substantial variation in extract composition, allergen dose, dosing schedule, and background AD treatment. The evidence cannot be directly extrapolated from the liquid HDM products studied in AD to other liquid formulations, to SLIT-T, or to allergens other than HDM.[34, 330, 331, 336]

Duration of treatment with HDM SLIT-T

34. Recommendation: We suggest a minimum of three years of HDM SLIT-T for long-term clinical efficacy (1-3 years of efficacy after discontinuation of SLIT).
Strength of Recommendation: Conditional
Certainty of Evidence: Low

Multiple studies have demonstrated long-term efficacy extending at least 1 year after SLIT is discontinued, including two studies demonstrating 3 years of long-term efficacy after 3 years of SLIT.[101, 337] Bergmann et al.[338] demonstrated in a study of 509 adults with AR that after one year of SLIT-T (500 IR or 300 IR dosing), when compared with placebo, AR symptoms were decreased 20.2% and 17.9%, respectively, with onset of benefit at 4 months. The effect was maintained for at least 1 year after SLIT was discontinued.[338] Tahamiler et al.[339] studied 67 patients and compared the effect of 2 years of SLIT (67 patients) to 3 years of SLIT (70 patients). They compared efficacy at year 6 after starting SLIT. The 3-year treatment showed greater efficacy in terms of symptom scores and nasal allergen challenge scores than the 2-year treatment group.[339]

For AD, Huang et al.[336] reported that variable durations of SLIT (1, 2, or 3 years) all result in persistent improvement in numerous measures one year after SLIT discontinuation.

Efficacy and length of treatment using SLIT-T in patients with grass allergy

35. Recommendation: We recommend pre-seasonal combined with co-seasonal or perennial grass SLIT-T for AR in adults and children who are Northern grass pollen allergic.

Strength of Recommendation: Strong

Certainty of Evidence: High

36. Recommendation: We recommend 3 years of Northern grass SLIT-T to reduce AR symptoms for at least 2 years following discontinuation (long-term efficacy).

Strength of Recommendation: Strong

Certainty of Evidence: High

There are currently 2 FDA approved sublingual dissolving Northern grass pollen SLIT-Ts available in the US which are marketed as Grastek (called Grazax in Europe) and Oralair. Each Grastek tablet contains 2800 BAU of timothy grass pollen which is approximately 15 mcg of Phl p 5. Oralair is comprised of 5 grass pollens: sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass. Oralair is supplied in 100 and 300 IR Units. 300 IR is equivalent to approximately 25 mcg of group 5 major grass pollen allergens. "An allergen extract is said to have a titer of 100 IR/ml if a prick-test performed using a Stallerpoint® in 30 subjects sensitized to that allergen produces a wheal of 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate 9% or 10 mg/ml histamine dihydrochloride. The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers."[340] 18.6 mcg of Phl p 5 is an optimal maintenance dose for SCIT established in studies by Varney in the 1990s and cited in the textbook, 6th Edition of Allergens and Allergen Immunotherapy.[341] Grass pollen SLIT-L are available in Europe. A product called Staloral is available in France and contains 300 IR/ml or approximately 21 mcg /ml Phl p 5.[342]

Onset of action is an important consideration when counseling patients and managing expectations for Northern grass pollen SLIT. The two FDA approved grass pollen SLIT-Ts have definitive prescribing recommendations delineated in the package insert. For Oralair, treatment should be started 4 months prior to the expected onset of the grass pollen season and continued through the season. For Grastek, treatment should begin 12 weeks prior to the onset of the grass pollen season and continued daily for the duration of the season, or it can be administered daily and continuously (perennial therapy) for 3 consecutive years.

In 2009, the efficacy, safety and tolerability of co-seasonal ultra-rush SLIT (ECRIT) study evaluated co-seasonal administration of 300 IR 5-Northern grass pollen SLIT-L.[342] In this RDBPC trial (n=209 patients) conducted in France, a mixture of pollen extracts of five Northern grasses (cocksfoot or orchard, meadow, perennial rye, sweet vernal and timothy grasses) called Staloral developed by Stallergenes was administered at a concentration of 300 IR/ml (equivalent to 21 mcg/ml of Phl p 5).[342] The ultra-rush protocol in this study was as follows: on day 1, patients took four increasing doses of SLIT, corresponding to 30, 90, 150 and 300 IR, at

20-min intervals followed by a daily intake of 300 IR for the duration of the pollen season. This is a sublingual drop/liquid unlike Grastek or Oralair. Treatment commenced when pollen counts were greater than or equal to 100 pollen grains per m^3 and discontinued when pollen counts were less than 50 grains per m^3 plus an additional 7 days. The average duration of treatment was 81-92 days during each of the 3 consecutive pollen seasons. Patients were treated for 3 pollen seasons and followed for 2 subsequent years. Results indicate an improvement in symptom scores from baseline in the SLIT-L treatment group compared to the placebo, as well as an increase in sIgG4 after season 1 and subsequently in seasons 2 and 3 and in the 2- year follow up period.[342] This may indicate that for those patients who are not able to begin immunotherapy in the recommended pre-seasonal time frame, they could still achieve symptom reduction if SLIT is commenced during the pollen season (co-seasonal).

Horak et al.[343] performed a RDBPC trial in 2007-2008 outside of grass pollen season utilizing an environmental exposure chamber. The aim of this study was to demonstrate the placebo-controlled efficacy of a 5-grass pollen 300 IR SLIT-T and provide the first determination of the onset of action of SLIT-T under the controlled, stable conditions present within an allergen control chamber. They demonstrated symptom score reduction as early as 1 month after initiation of 300 IR 5-grass pollen SLIT-T (n=45) compared with placebo (n=44). The mean reduction in challenge symptom scores at 4 months in the treatment group was 29.3% compared with placebo.[343]

Panizo et al.,[344] in a RDBPC trial, demonstrated a statistically significant increase in Phl p sIgG4 from baseline after one month of treatment with Grazax (Grastek in the US). There was no change in placebo compared to baseline.[344]

In a randomized study, Pajno et al.[345] compared pre-seasonal and co-seasonal administration of a 5-grass pollen liquid mixture, Staloral, in children ages 8-16 years old. The outcomes noted a statistically significant greater improvement in symptom scores in the pre-seasonal treatment group in the first year, but at years 2 and 3 there were no statistical differences between the pre- or co-seasonal groups.[345] This illustrates that co-seasonal administration can achieve optimal results and speaks to potential cost-effectiveness and decreased allergen use.

In summarizing available RDBPC trials for Northern grass pollen SLIT, optimal symptom control is achieved when therapy is started prior to the onset of the pollen season; however, there is evidence that it can be effective to utilize a co-seasonal schedule.

Durham et al.[346] were the first to report a sustained reduction in nasal symptom scores 1 year after completion of 3 years of timothy grass pollen SLIT-T in a RDBPC trial. Participants received continuous treatment with grass pollen SLIT-T for 3 years in this study. The initiation of treatment was 4 to 8 months prior to the onset of the grass pollen season. The product administered was Grazax and the age of the study participants was 18 to 65 years. Subsequently, Durham et al.[347] published a follow-up study evaluating the same cohort 2 years after 3 consecutive years of treatment with Grazax. They demonstrated a statistically significant reduction in symptom scores through the 2nd season without additional treatment. A combined rhino-conjunctivitis symptom and medication use score showed a statistically significant 27% reduction at follow-up during season 2 compared to the placebo group. There was a lack of

statistical significance in the medication use in both groups during season 2, postulated to be due to an unusually low pollen count and thus lower symptoms during season 2.[347]

Didier et al.[348] studied pre- and co-seasonal treatment with Oralair in a RDBPC trial. Participants aged 18-65 years received pre- (2 or 4 months prior to onset of grass pollen season) and co-seasonal 5-grass pollen SLIT-T for 3 consecutive years. At year 4, one year after discontinuation of SLIT-T, the treatment group demonstrated sustained reduction in symptom scores as well as an increase in timothy grass sIgG4 compared to the placebo group.[348]

REACT (real world effectiveness in allergen immunotherapy) was a retrospective cohort study using claims data from 2007-2017 in Germany.[258, 349] This study noted that for grass pollen SLIT-T compared with control patients, there was a reduction in AR prescriptions at years 3, 5, and the available 7 years of follow-up. This subgroup analysis did not specify if treatment was pre- and co-seasonal or continuous.[258, 349]

Scadding et al.[252] demonstrated that 2 years of continuous Northern grass pollen AIT was not better than placebo in nasal response challenge scores 1 year post discontinuation of treatment. In this RDBPC, 3-parallel group designed study, 36 participants received 2 years of Grazax and monthly placebo injections, 36 received monthly SCIT containing 20 mcg of Phl p 5 and daily placebo tablets, and 34 received matched double-placebo injections and tablets. Nasal allergen challenge was performed before treatment, at 1 and 2 years of treatment, and at 3 years (1-year post-discontinuation of treatment). The study was not powered to compare SLIT and SCIT.[252]

In open studies, both Pajno et al.[345] and Stelmach et al.[350] compared pre- and co-seasonal with continuous Northern grass pollen SLIT in children. There was no difference in symptom scores, sIgG4, or peripheral blood Foxp 3 regulatory T cells over 3 years of treatment between the 2 types of treatment strategies. However, the investigators did note that at year 1 the pre-seasonal group fared better, but this difference was not evident after 3 years of treatment.[345, 350]

In the study by Stelmach et al.[350], children ages 6-18 years sensitized to Northern grass pollen were administered Staloral either continuously or pre- and co-seasonally for 2 years. Active therapy was 10 mcg of the major allergen. Nasal symptoms scores were better compared to placebo in the pre-seasonal group. Staloral was administered for 6 months followed by 6 months of placebo. They did not observe significant differences in medication, ocular, and asthma scores between the regimens. They did not observe changes in morning PEF, FEV_1, and PD20 in any of the three groups compared to baseline nor between the groups throughout the study. They showed a significant comparable decrease in FeNO level from baseline in both active groups. There were no differences between groups in the induction of CD4+CD25+Foxp3- cells in peripheral blood during the study.[141]

These studies add to the discussion regarding cumulative dose of allergen administered over several years and attempt to answer questions pertaining to timing of treatment vs cumulative dose of allergen required to induce clinical benefits. There is less cumulative allergen administered with pre/ co-seasonal regimens than with continuous treatment.

An observational study in France called the Diagram Study, concluded that while pre- and co-seasonal grass pollen SLIT was prescribed more often, perennial treatment was preferred in those with the most severe symptoms.[351, 352]

37. Recommendation: We suggest three years of Northern grass SLIT-T in adults and children to reduce AA symptoms for at least two years following SLIT discontinuation.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Marogna et al.[353] performed an open, parallel group, RCT including patients ages 18-65 years with AR and mild AA solely due to Northern grass pollen allergy. Patients with an incomplete response to inhaled budesonide, 200 mcg twice daily in previous grass pollen seasons, were randomized to receive either budesonide 400 mcg twice daily (26 patients) or SLIT-L in addition to rescue medications (25 patients). Incomplete response to budesonide 200 mcg was defined by rescue medication use and symptoms during the grass pollen season. Treatment was continuous for 5 years. In this Italian study, treatment was with glycerinated timothy grass pollen extract and the estimated, annual cumulative dose of the major allergen Phl p 1 was 70 mcg. At year 5, those in the SLIT-L group vs those in the budesonide group had improved upper and lower airway symptom scores as well as decreased rescue inhaler use. In the SLIT-L group, nasal eosinophils were reduced, and bronchial hyperresponsiveness as measured by methacholine challenge was reduced at year 5.[353]

Stelmach et al.[141] evaluated the safety and efficacy 300 IR 5-Northern grass pollen SLIT-L in pediatric patients ages 6-17 years with asthma in a 2-year, prospective RCT. There were 15 in the SLIT-L group and 15 in the placebo group. Likely due to the small size of the study, statistical significance was not achieved for symptom scores, FEV_1, or specific and total IgE and total IgG4 at the 2-year comparison between groups.[141]

In a real world retrospective study assessing prescription data in France, the number of prescriptions for AR medications, as well as asthma medications, increased in a placebo group of patients receiving only symptomatic medications versus those receiving 2 consecutive years of Grazax or Oralair.[354] The relative risk of medication dispensing for new onset asthma was lower in the SLIT-T group. SLIT-T was also associated with slower progression of asthma medication dispensing during the 1 year follow-up period compared to the control group.[354]

Efficacy of ragweed SLIT-T in patients with ragweed allergy

38. Recommendation: We recommend pre-and co-seasonal or perennial ragweed SLIT-T for adults and children (> 5 years of age) with ragweed-induced AR.

Strength of Recommendation: Strong

Certainty of Evidence: High

FDA-approved ragweed SLIT-T are highly likely to improve ragweed-induced AR/C symptoms based upon the findings of multiple RDBPC trials.[79, 355-357] Most studies involving ragweed SLIT-T for AR have administered the tablets with 12 mcg Amb a 1 for 12-20 weeks prior to the expected start of the ragweed season (pre-seasonal).[79, 355-357] Two pivotal trials included patients with pre-seasonal (before and during the pollen season) treatment and met clinical endpoints for total combined symptom scores (sum of AR/C daily SS and daily MS averaged during peak ragweed season).[355, 357] Significant improvement in RQLQ scores has also been shown (-0.36 [95% CI: -0.55, -0.17]; p<0.001).[358] The current prescribing label recommendation is for ragweed SLIT-T to be started at least 12 weeks prior to the onset of the expected ragweed season and continued until the end of the ragweed season, for both children and adults.[359]

39. Recommendation: We suggest ragweed SLIT-T for adults and children (> 5 years of age) with mild-moderate ragweed-induced AA.

Strength of Recommendation: Conditional

Certainty of Evidence: Low in adults; Moderate in children

Ragweed SLIT-T are not approved in the US for the treatment of AA.[359] A few studies have shown statistically significant improvements in asthma outcomes in patients treated with ragweed SLIT-T, but the clinical relevance of these findings is unclear. For example, a RDBPC trial of 1,022 ragweed-sensitized children with AR, ages 5-17 years, included 43% children with AA who were considered well controlled with FEV_1 >80% and requiring no more than moderate-dose ICS.[79] Among individuals with AA receiving ragweed SLIT-T starting 12-20 weeks before the season, statistically significant improvements were seen throughout the ragweed season and at peak pollen levels for asthma daily SS, SABA use, and nocturnal awakenings (all nominal p≤0.02). However, the patients were already well controlled on standard asthma medications, and the study did not use validated measures of asthma symptom assessment.[79] A multicenter, 3-year, prospective, observational study of SLIT-L that only included 9 ragweed sensitized patients with AA, reported improvements in asthma symptom scores among patients on SLIT-L for 2 consecutive years.[360] Well-designed RCTs specifically evaluating the impact of ragweed SLIT-T on validated ragweed-related asthma outcome measures are needed.

There are no studies regarding ragweed SLIT-T that have included subjects with severe or uncontrolled AA. Uncontrolled AA is considered an absolute contraindication for ragweed SLIT-T, given safety concerns for all forms of immunotherapy in such patients, as discussed elsewhere in this parameter.

40. Recommendation: We suggest 3-5 years of pre-and co-seasonal or perennial ragweed SLIT-T.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Insufficient data are available regarding how long one needs to continue ragweed SLIT-T or liquid formulations in order to maintain long-term efficacy for any indication. Data regarding long-term efficacy for grass pollen SLIT-T are summarized elsewhere in this parameter (see Recommendation 31). It may be reasonable to extrapolate data from grass pollen SLIT-T to ragweed SLIT-T until additional studies specifically focused on the long-term efficacy of ragweed SLIT are performed.

Efficacy of Tree SLIT-T

41. Recommendation: We recommend birch pollen and Japanese cedar pollen SLIT-T, where available, for patients with birch or Japanese cedar tree pollen-related AR with or without conjunctivitis for ages 5 years and older.

Strength of Recommendation: Strong

Certainty of Evidence: High

SLIT-T for tree pollens are not currently available in the US but have been utilized elsewhere.[361-365] In a phase III RDBPC trial for the 12 SQ-Bet tree pollen SLIT-T (for the birch-homologous group including birch, alder, hazel, and oak) conducted at 57 sites in Europe, including Russia, 634 subjects ages 12-65 years were treated.[366] Clinically relevant changes were seen for AR/C related daily MS, daily SS, and TCS during the tree-pollen season. For the birch pollen season, absolute (relative) differences from placebo were 3.02 (40%) for the average daily AR/C TCS, 1.32 (37%) for daily SS and 1.58 (49%) for daily MS (all $p<0.0001$). For the tree pollen season, absolute (relative) differences from placebo were 2.27 (37%) for the average daily AR/C TCS, 0.99 (33%) for daily SS, and 1.20 (47%) for daily MS (all $p<0.0001$). Subjects received the SLIT-T for at least 16 weeks prior to the tree pollen season. A post hoc analysis of the same study, specifically evaluating effects of the 12 SQ-Bet SLIT-T, showed clinically relevant effects during the oak pollen season, although participants were not monosensitized to oak.[367] There was no analysis of symptom-medication scores outside the oak pollen season for the polysensitized patients.[366, 367] A phase III RDBPC trial has also verified the efficacy and safety of the 12 SQ-Bet SLIT-T in tree pollen-induced AR/C in children ages 5-17 years.[368] Efficacy data for tablets derived from recombinant Bet v 1 are similar to those seen for tablets developed from natural extracts.[363] A multicenter RDBPC trial for birch pollen SLIT-L (40,000 Allergy Units Native/ml, 100 mcg Bet v 1 per dose of 5 drops daily) in Europe that included 406 patients ages 18-65 years showed clinically relevant changes in AR/C SS, MS, and QoL scores.[369] Primary efficacy results demonstrated a significant ($p<0.0001$) and clinically relevant (32%) reduction in the CSMS compared with placebo after 3 to 6 months of SLIT. Significantly better rhinoconjunctivitis QoL scores ($p<0.0001$) and the patient's own overall assessment of his or her health status, including the VAS score (Euro Quality of Life Visual Analogue Scale; $p=0.0025$) were also demonstrated. Subjects received the SLIT-L for 3-6 months prior to the pollen season.[369]

Because cross-reactivity between birch homologous allergens is only partial (approximately 85%), some patients who are sensitized to birch pollen homologues (such as alder or hazel) may not respond to birch pollen SLIT alone. Using data from a prescription database in Germany, the impact on AR and AA outcomes of six products for birch or 3-tree (birch/alder/hazel) pollen SLIT or SCIT was evaluated.[255] A sub analysis later compared outcomes for 493 3-tree SLIT-L (birch/alder/hazel;300 IR/ml) patients versus 311 birch-only SLIT-L (300 IR/ml) patients, as well as 44,835 matched controls who received symptomatic treatment with medications alone.[370] The study concluded that 3-tree SLIT-L or birch-only SLIT-L both slowed the progression of birch, alder, and hazel pollen-induced AR to clinical AA up to 6 years post-treatment cessation. Overall, 70.5 % of patients presented solely AR, 24.2 % solely AA, and 5.3 % both diseases. Compared with controls, patients treated with 3-tree SLIT-L had reduced risk of AR (OR 3.21 [95% CI: 2.54, 4.06]; p<0.001), asthma progression (OR 2.03 [95% CI: 1.43, 2.89]; p<0.0001), or asthma onset (OR 0.592 [95% CI: 0.408, 0.860]; p=0.006). Birch-only SLIT-L showed similar effectiveness in reducing AR and asthma medication dispensation but had no significant effect in reducing new-onset asthma; the sample size for birch-only SLIT-L was smaller.[370]

In a RDBPC trial with dose-ranging of SLIT-T for Japanese cedar pollen-induced rhinitis in 1,042 patients ages 5-64 years, the mean treatment period before the pollen season was 6 months.[362] Primary and secondary efficacy end-points were achieved for all doses, although 5,000 JAU daily (10,000 JAU contains 7.3–21 mcg of Cry j 1) was determined to be the optimal dose for efficacy and safety over a 3-year period.[362, 371] Similar findings have been reported after approximately 6 months of receiving SLIT-L for Japanese cedar at a dose of 2,000 JAU (1.5-4.2 mcg of Cry j 1) daily.[372] Based on a placebo-controlled study involving 128 patients, SLIT-T and SLIT-L for Japanese cedar pollen may improve sleep disturbance at peak pollen season.[373] In agreement with the dose-finding results from above, greater effects were documented for the tablets (5,000 JAU daily) after 1 year than for the drops/liquid (2,000 JAU daily) after 2 years.[373] As the drop-dose was 2.5 times less than the tablet dose, no conclusions about drops/liquid versus tablets can be drawn from this trial.[373] Another study between 2014-2018 involving 95 patients receiving SLIT-L containing 2000 JAU daily found clinical improvements in AR in the first year of treatment, but changes in airway inflammation took longer;[374] 5 years of treatment was associated with significant decreases in type 2 airway inflammation as measured by FeNO. This finding should be interpreted with caution given that the study did not include subjects who dropped out prior to 5 years of therapy.[374]

At this time, more data are needed regarding asthma outcomes to inform asthma-specific recommendations for tree pollen SLIT.

42. Recommendation: We suggest at least three years of either pre- and co-seasonal tree pollen SLIT or year-round tree pollen SLIT.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

For Japanese cedar pollen SLIT-T, data from a RDBPC trial that included 1,042 subjects ages 5-64 years showed that after 3 years of treatment, efficacy was maintained for AR/C SS and MS for up to 15 months after stopping therapy with the 5000 JAU daily tablets.[362] In a post-marketing clinical trial that included 233 patients who received Japanese cedar pollen SLIT-L

(2000 JAU) for approximately 3 years, treatment duration-dependent effects persisted for 2 years after stopping SLIT-L.[372] Outcome measures included nasal and ocular symptom scores, daily use of rescue medication, and Japanese RQLQ scores during the cedar pollen season each year. Based on data from the same study population, there were significantly better improvements in nasal, ocular, and medication scores in the second and third seasons for those who received continuous Japanese cedar SLIT-T (5000 JAU) dosing for 30 months versus dosing that was alternated with placebo.[362, 364] The largest relative reduction in total nasal symptom and medication scores was seen in the group receiving active treatment both during the initial treatment period (third season, 46.3% vs placebo, $p<0.001$) and during the 2-year follow-up period (fourth and fifth seasons, 45.3% and 34.0% vs placebo, respectively; $p<0.001$). This has been interpreted to indicate that continuous dosing regimens may be superior to pre- and co-seasonal treatment.

Efficacy for multi-allergen SLIT-T in polysensitized patients

43. Recommendation: We suggest using either monotherapy with the most clinically relevant, dominant allergen or multiple SLIT-Ts for polyallergic adults and children with AR.

Strength of Recommendation: Conditional

Certainty of Evidence: Low for one tablet; Very Low for more than one tablet

Efficacy of single and multi-allergen SLIT-L formulations in monosensitized and polysensitized patients

44. Recommendation: We recommend FDA-approved SLIT-Ts for relevant allergens rather than off-label SLIT-L/extracts for AR and AA.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

We recommend the use of FDA-approved SLIT-Ts for the treatment of AR and AA over off-label SLIT-L or extract formulations due to their established safety, efficacy, and quality assurance. SLIT-Ts have undergone rigorous evaluation in large RDBPC trials demonstrating consistent clinical benefit, standardized dosing, and a well-characterized safety profile. In contrast, off-label SLIT-L/extract formulations lack regulatory approval, are not standardized in terms of allergen content or dosing, and have limited high-quality evidence supporting their efficacy and safety. Additionally, FDA-approved products ensure manufacturing consistency, clear prescribing guidelines, and patient information, which support safer and more reliable clinical use. Therefore, prioritizing SLIT-Ts aligns with evidence-based practice and regulatory standards, ultimately improving patient outcomes and minimizing variability in care.

45. Recommendation: We suggest single or pauci-allergen (3 or less) SLIT-L for patients with allergy to allergens without available SLIT-T options and whose values and preferences are to undergo AIT without frequent clinic visits or with less risk than SCIT. The patient should be informed of the limitations of extrapolated evidence for efficacy of multi-allergen SLIT-L with ≥3 allergens.

Strength of Recommendation: Conditional

Certainty of Evidence: Low.

46. Recommendation: We suggest that when SLIT-L is prescribed, the dose should be in the range of proven efficacy for other products (see Table 8).

Strength of Recommendation: Conditional

Certainty of Evidence: Low

SLIT-L for individual allergens

Historically, the best data for the use of SLIT-L in AR came from a Cochrane meta-analysis of SLIT-L from 2005.[375] In 2011, the same investigators published and updated Cochrane including 11 trials on SLIT-T and 35 on SLIT-L, concluding both were effective in reducing symptoms scores, but only for SLIT-T were medication scores reduced.[376] Dosing in the reviewed SLIT-L trials varied considerably.

Since then, studies on SLIT-L with more uniform dosing have been published. Thus, some of the more recent meta-analyses present a reduced heterogeneity among the studies, as only trials with similar products and trial designs were included. In 2017, the EAACI, supported by experts in meta-analysis methodology, conducted several meta-analyses on AIT, separated by disorder or disease treated.[86, 88, 121] Though both SCIT and SLIT were analyzed in each meta-analysis, separate results for SLIT were presented.

In **Table 8** several of the more recent trials are described, per allergen and per allergic disease.

Table 8. SLIT-L evidence from several studies per disease and per allergen after the 2011 Cochrane meta-analysis[376] or dose-finding.

Allergen and disease	Study details	Design, duration	Daily dose[a]	Ref.
HDM				
AR	Meta-analysis comparing results of 12 non-RCT and 8 RCT. SMD showed moderate-to-large improvement in both groups in symptom and medication scores, with higher impact in studies >12 month.	Meta-analysis, 6-36 mo	38-300 IR	DiBona et al, 2024[377]

AA	Moderate AA,↑well controlled subjects, ↑ACQ score,↓ICS dose. No change in mild asthma.	DBPC, 12 mo	300 IR	Wang et al, 2014[322]
	60 vs 4200 AU dose-finding safety study.	DBPC, 12-18 mo	4200 AU	Bush et al, 2009[329]
	4200 AU SLIT-L ↑bronchial threshold to allergen challenge and Der f sIgG4	DBPC allergen challenge, 12-18 mo	4200 AU	Bush 2011(8, 21333346)
	In asthma patients (34,595 SLIT vs 97,535 controls) analysis with propensity score weighing: reduction in frequency of GINA step-up. In no asthma patients (77,897 SLIT, vs 235,547 controls), 32.7% were HDM SLIT-L. Of those, less new onset asthma (HR [95% CI]: 0.63 [0.61–0.65]).	Cohort-based French	Staloral liquid (=300 IR)	Demoly et al, 2024[378]
AD	Positive outcome: probability to improve 50% in AD severity: RR 1.45 (1.25, 1.69). Improvement QoL: RR 1.44 (1.00, 2.08).	Meta-analysis, 11 trials, mean 12 mo (3-36)	SLITone (1.4 mcg Der gp 1-2) up to 300 IR (72 mcg Der p gp 1-2)	Yepes-Nunez et al, 2023[34]
Tree pollens				
AR	88 children (5-15y). Dose-finding. Low dose: symptom improvement. High-dose: symptom and medication improvement.	DBPC, 18 mo	5d/wk. Mean dose: LOW: 3,400 HIGH: 28,600 SQ-U/day	Valovirta et al, 2006[379]
	406 adult respiratory allergy patients, improved AR combined symptom-medication score after 3 and 6 mo and improved quality of life scores.	DBPC, pre-co season	10,000 allergy units native^3	Pfaar et al, 2019[369]
	German PDB: triple-tree SLIT-L and birch SLIT-L reduce AR medication.	Prescription data base	300 IR	Zielen et al, 2025[370]
	2 years of Japanese cedar pollen SLIT-L reduces nasal symptom score vs untreated group.	Retrospective, 2 y	2000 JAU^2	Fujii et al, 2022[373]

	86 children (≥5 years): 80% decrease in AR symptoms, and also a reduction in symptomatic medication.	Retrospective observational, 2 seasons	300 IR	Al-Asad et al, 2017[380]
AA	88 children (5-15y). Dose-finding. Low dose: asthma symptoms improvement. High-dose asthma symptom and medication improvement.	DBPC, 18 mo	5d/wk. Mean dose: LOW: 3,400 HIGH: 28,600 SQ-U/day	Valovirta et al, 2006[379]
	German PDB: triple-tree SLIT-L and birch SLIT-L reduce asthma medication in patients with previous medication. Triple-tree SLIT-L reduces new asthma medications.	Prescription data base	300 IR	Zielen et al, 2025[370]
	In asthma patients (34,595 SLIT vs 97,535 controls) analysis with propensity score weighing: reduction in frequency of GINA step-up. In no asthma patients (77,897 SLIT, vs 235,547 controls), 2.5% were birch SLIT-L. Of those less new onset asthma (HR [95% CI] = 0.45 [0.41–0.50])	Cohort-based French	Staloral liquid (=300 IR)	Demoly et al, 2024[378]
AD	No data			
Grass pollens				
AR	Meta-analysis of 8 RCT, showing benefit of 5-grass pollen SLIT-L over placebo for both symptoms and medication use.	8 trials	100 IR alternate day – 300 IR daily	Di Bona et al, 2025[381]
	50 children (6-17y) 5-grass SLIT-L improved nasal symptoms.	DBPC, 2 y	300 IR	Stelmach et al, 2009[141]
AA	Pediatric trial. 40% reduction in asthma symptoms score, 10% medication score and improved FEV_1. 2nd year: also improved bronchial hyperresponsiveness	DBPC, 2 y	300 IR	Stelmach et al, 2009[141]
	Reduced new onset of asthma in pediatric AR patients.	Open, RCT, 3 y	0.5 mcg Gp 5	Novembre et al, 2004[382]

			grasses, 5 days/wk	
	In asthma patients (34,595 SLIT vs 97,535 controls) analysis with propensity score weighing: reduction in frequency of GINA step-up. In no asthma patients (77,897 SLIT, vs 235,547 controls), 14% were grass SLIT-L. Of those less new onset asthma (HR [95% CI] = 0.56 [0.53–0.58])	Cohort-based French	Staloral liquid (=300 IR)	Demoly et al, 2024[378]
AD	No data			
Weed pollens				
AR	115 adults, when correcting for pre-seasonal symptoms: high-dose improved symptoms and medication scores. No improvement in eye symptoms.	DBPC, 1 season	LOW: 4.8 mcg HIGH: 48 mcg Amb a 1	Skoner et al, 2010[383]
	SLIT-L for non-grass pollens (53% Pellitory, 14% Ragweed), in 162 patients with AR with/without mild-to-moderate allergic asthma. Global score (symptoms+medication) reduced each year.	Prospective, multicenter, observational, 2 y	SLITone ALK	Milani and Pecora, 2011[360]
AA	See row directly here above.			
AD	No data			
Alternaria				
AR	26 patients, 14–42 years. Significant reduction in symptoms and medication intake vs placebo, reduction in SPT reactivity and rise in spIgE.	DBPC, 10 mo	0.4 mcg Alt a 1 alternate days	Cortellini et al, 2010[384]
AA	The above study included mild asthmatics, but no subgroup analysis.			
AD	No data			
Other (Cockroach, mold, etc.)				
N = 54, adults, 6 months. Only biomarker data, with rise in sIgE and IgG4, but no functional blocking antibody response.		Pilot, 6 mo	Bla g 2: 4.2 mcg Bla g 1: 50 mcg	Wood et al, 2013[385]

N = 89, 2-dose study. Children, there was a biomarker response, but no difference between SLIT dosing groups.	Pilot, 3 mo	Low dose Bla g 2: 4.2 mcg Bla g 1: 50 mcg High dose: 4-times	Wood et al, 2013[385]

AA, allergic asthma; AD, atopic dermatitis; AR, allergic rhinitis; IR, index of reactivity (Stallergenes®); PDB, prescription database; RR, relative risk; SMD, standard mean difference.
[a]300 IR Staloral corresponds roughly to ~20–25 mcg Phl p 5 for grass, ~25.4 mcg Bet v 1 for birch, and for HDM includes about 60 mcg Der p 1, 12 µg Der p 2, and 150 mcg Der f 1(23, 19601728); 2000 JAU = 90–150 mcg of the major allergens (Cry j 1 + Cry j 2); the Bet v 1 content of the product is 0.4 mg/mL; 0.25 ml is administered daily = 100 mcg.

A major limitation of the evidence for SLIT-L has historically been the heterogeneity and lack of standardization across RCTs. Across older studies of SLIT-L there was a wide variation in the allergen extracts used, the dosing schedules, the treatment duration, and the outcome measures. This led to high heterogeneity, making pooled estimates less reliable in the 2005 meta-analysis.[375] Since then, we have learned that SLIT has to be given daily and high-dose in order to be effective, which is now done by most, as can been observed in **Table 8**.

Further, the evidence suggesting benefit comes from a meta-analysis from 2014 of 16 randomized, double-blind trials (n=794) which found: reduced asthma symptoms (SMD −0.74, p=0.006), reduced medication use (SMD −0.78, p=0.02), but no consistent improvement in lung function (FEV_1). This report did not document evidence for individual allergens nor individual allergic disorders.[386]

Earlier systematic reviews (from 2006 including ~25 RCTs, many using drops, and from 2008 including 9 DPBC trials in children 3-18 years with AA) found small overall benefit in asthma severity, but effects were modest and inconsistent depending on outcome measures.[387, 388]

Thus, there is a signal for efficacy (symptoms, medication reduction), but it is inconsistent and outcome-dependent for SLIT-L regimens.

Multi-allergen SLIT-L

The JTF 2011 AIT PP emphasized that few studies had investigated the efficacy of multi-allergen AIT commonly practiced in the United States.[2] This was based on conflicting results for both multi-allergen SCIT and SLIT and a preference for investigators to undertake studies that treat single allergens, including SLIT. The JTF 2017 SLIT-focused PP described the absence of studies addressing the efficacy of multiple allergens administered as a mixture and the need for future studies.[3]

Polysensitization to aeroallergens is more common than monosensitization in the US and internationally, although mono-allergy has been reported in some patients with AA.[389-404] Nonetheless, poly-allergy or clinical sensitivity to multiple, likely relevant, aeroallergens occurs

frequently in patients with both AR and AA. Strategies for selection of SLIT allergen extract(s) for treatment of poly-allergy can vary by country and prescribing specialist. To identify the dominant allergens responsible for symptoms, in Europe and in limited US clinics, patients undergo a NAC; however, more commonly, US physicians base their selection on clinical history and SPT results. Strategies for treating poly-allergic patients include 1) selecting only the (seemingly) dominant allergen causing symptoms, 2) treating with a combination of the suspected top symptom producing allergens and 3) treating all allergen sensitizations identified.[267, 276, 405-412] No studies have conclusively defined the best strategy. A 2009 study comparing single allergen versus 10-allergen SLIT showed no superiority of either active group in the primary endpoint, in the medication score, or in the reduction of SPT response.[413] However, compared to the 10-allergen group, the mono-allergen group reached a statistically significant greater improvement in NAC score and increased timothy grass sIgG4 compared with placebo.[413]

Whereas there is strong evidence for use of FDA-approved single allergen SLIT-Ts in monosensitized patients, not unlike multi-allergen SCIT, there is a paucity of evidence supporting the use of multi-allergen SLIT in polysensitized patients.[262, 389] The most convincing evidence for mono-allergen SLIT-L efficacy with US extracts comes from two separate dose-finding studies conducted with US extracts of ragweed pollen[414] and HDM.[315] Efficacy of dual allergen SLIT-L with US extracts (*Dermatophagoides* and timothy grass pollen) was demonstrated by Swamy et al.[415] in a single-center, RDBPC trial, albeit with extracts given from separate vials. Investigators moreover evaluated both immunologic and epigenetic changes. After 12 months, nasal symptom and medication scores, titrated SPT, and NAC all showed a statistically significant reduction in favor of dual SLIT-L, as well as greater peripheral blood immunologic changes (increase in both sIgG4, and Foxp3 positive T-cells).[415] The efficacy of dual SLIT-L is supported by a randomized trial of four groups: grass-pollen SLIT-L, birch pollen SLIT-L, dual SLIT-L, and open controls.[416] Symptoms improved in all active groups as opposed to the controls during the actively treated pollen seasons, with a numerically greater improvement during both active pollen seasons for the dual SLIT-L patients.[416]

However, no study has rigorously addressed the use of off-label, multi-allergen SLIT in polyallergic patients. In a 2016 pilot study of SLIT-L, 16 participants sensitized to at least 6 allergens, were randomized to SLIT-L with one, three, or all potentially relevant allergens.[411] In all groups, rhinoconjunctivitis symptoms were significantly reduced and mini RQLQ improved. Inter-group differences were not identified, but the study was not powered to detect these differences.[411] Moreover, individual allergen doses in this study were variable and generally low, based on American Academy of Otolaryngologic Allergy treatment guidelines.[412]

In vivo allergen extract potency is maintained after six months in a pauci-allergen SLIT-L maintenance vial containing a US allergen extract of *Dermatophagoides spp* and two unrelated pollens.[417]

A 2009 RDBPC trial compared treatment with SLIT-L placebo, SLIT-L monotherapy with 19 mcg Phl p 5 timothy grass extract, and SLIT-L with the same dose of timothy grass pollen plus nine additional pollen extracts.[413] Likely due to the low grass pollen counts during the season, there were no significant differences in symptom and medication scores between treatment groups and placebo. Biomarker and nasal challenges favored both active groups; mono-allergen SLIT-L was statistically superior to placebo in all these parameters, while 10-allergen SLIT-L only in

titrated SPT. Medication score reduction was greater in the multi-allergen SLIT-L group, but this did not reach statistical significance.[413]

Notably, some emerging evidence and the availability of a limited number of FDA approved allergen SLIT-Ts in the US has prompted interest for treating poly-allergic patients with mono- or dual-allergen SLIT-Ts,[418, 419] taking into account that AIT is allergen-specific and the improvement in symptoms is usually only documented during the season of the allergen used for treatment (see section on SLIT-T).

There is evidence that single allergen SLIT-T is effective in polysensitized patients. Post-hoc analyses of pivotal phase III RDBPC trials in 1,163 monosensitized and 4,116 polysensitized adult AR patients treated with mono-allergen grass, ragweed, tree, or HDM SLIT-T demonstrated efficacy in reducing TCMS scores during the relevant allergen season regardless of whether patients were mono- or polysensitized.[420] Treatment effect size comparisons were challenged by overlapping pollen seasons and small sample sizes. However, the effect size was comparable for grass and HDM SLIT-T treatment.[420] Another example includes a 2020 published RCT in which 1,025 children age 5-17 years, 77% of whom were polysensitized, were treated with ragweed SLIT-T for up to 28 weeks.[79] The results showed a 38.3% reduction in total combined score ($p<0.001$) compared to placebo, as well as reductions in both symptom and medication scores individually.[79]

In another study, efficacy of a grass SLIT-T was also similar between 283 children and 1,218 adults with 85% of participants polysensitized to aeroallergens.[421]

The efficacy and safety of treatment with multiple SLIT-Ts has rarely been studied. An open label study of 102 patients with AR treated daily with timothy and ragweed SLIT-Ts demonstrated that combined treatment was well tolerated when administered initially several hours apart (morning and evening) for two weeks and subsequently within five minutes of each other.[418]

In summary, there is evidence to support the use of mono-allergen SLIT-L with high-dose US extracts of ragweed and HDM; there is some evidence for the use of dual to pauci (≤3 allergen extracts) SLIT-L showing both efficacy and immunologic changes. Allergen extracts in a maintenance, pauci-allergen SLIT-L vial maintain their potency at six months. Multi-allergen SLIT-L seems to be effective; however, additional studies are needed to clearly define the best approach to treat polyallergic patients with both AR and AA. We recommend using a shared decision-making approach with patients. We suggest using FDA-approved SLIT-Ts if possible and, if not, use the fewest number of relevant allergens with SLIT-L at doses that approximate the doses used in the pivotal mono-allergen studies: daily maintenance dosing of SLIT-L should be between 0.5-2 times the monthly SCIT dose (**Table 9**). This means 2 ml of the highest concentration of the commercially available extract in a 10 ml vial, with daily administration of 2 drops sublingually.

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Table 9. Clinically effective dose of SLIT in randomized dose-finding studies.

Allergen	SLIT					SCIT monthly dose	Daily SLIT/ monthly SCIT dose
	Manufacturer	Tablet or liquid	Daily dose (manufacturer units)	Daily dose (mcg major allergen)[a]	Daily dose (expressed in (B)AU)		
Grass pollens[422-424]							
Phleum pratense	ALK-Abelló	Tablet	75,000 SQ-U	15 mcg Phl p 5	6200 BAU	1000-4000 BAU[a]	1.5
5-grasses	Stallergènes	Tablet	300 IR	25 mcg Phl p 5	8200 BAU	1000-4000 BAU[a]	2
Tree pollens[379]							
3-tree[b]	ALK-Abelló	Liquid 0.4 ml	28.6 SQ-U	4.3 mcg Bet v 1/ Aln g 1/ Cor a 1 (850,000 SQ-U monthly)	No info	100,000 SQ-U	0.35
Weed pollens[355, 383, 414, 425]							
Ambrosía	Greer	Liquid	48 mcg Amb a 1[c]	48 mcg Amb a 1	No info	6-12 mcg Amb a 1[a]	5
Ambrosía	ALK-Abelló	Tablet	12 Amb a 1 units	12 Amb a 1 units	No info	6-12 mcg Amb a 1[a]	1-2
HDM for AR[338, 426] **or AA**[303, 321, 328, 427]							
Dpt+Df: 1:1:1:1	ALK-Abelló	Tablet	6 SQ-HDM=10,000 JAU; 12 SQ-HDM[d]	6 SQ-HDM = 7.5 mcg group 1 and 7.5 mcg group 2.	No info	500-2000 AU[a] 7 Der p 1[f] Using ALK-US analysis: 1-8 Der p 1, Der f 1;	1 (range 1-7)

						0.1-9 Der p 2, Der f 2	
Dpt+Df: 1:1	Stallergènes	Tablet	300 IR	16 mcg Der p 1 68 mcg Der f 1 (=84 grp 1)	(Some calculated: 15,000 AU)[e]	500-2000 AU[a] 7 Der p 1[f] Using Inbio analysis: 4-10 Der p 1, Der f 1; 0.65-7 Der p 2, Der f 2	8 (range 8-20)

AU, allergen units; Dpt = *Dermatophagoides pteronyssinus*; Df = *Dermatophagoides farinae*; 1:1:1:1 = equal amounts of Der p 1: Der p 2: Der f 1: Der p 2; 1:1 = equal amounts of Der p 1: Der f 1, group 2 is not mentioned; IR = index of reactivity; JAU = Japanese allergy units; SQ-U, standardized quality units.

[a]Source: publications in indexed journals or prescribing information (*Package insert*)

[b]3-Trees = Betula verrucosa, Corylus avellana and Alnus glutinosa

[c]94% received this dose. Those who did not tolerate were left with the lower dose of 18 mcg Amb at 1 daily.

[d]The dose chosen for marketing in Europe is 12 SQ-HDM (due to greater efficacy in secondary outcome parameters in the dose-finding study) and in Japan the marketed dose is 6 SQ-HDM/10,000 JAU.

[e]https://www.aaaai.org/ask-the-expert/allergen-immunotherapy-IR-units

[f]Haugaard et al, 1993[428](referenced in JTF 2011 AIT PP[2])

Safety of AIT

Local reactions to SCIT

47. Recommendation: We suggest treating symptomatic SCIT LRs/LLRs with topical corticosteroids, topical antihistamines, and/or oral antihistamines.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

Local reactions (LRs) or large local reactions (LLRs) manifest as erythema, swelling, pruritus and sometimes discomfort at the site of the SCIT injection and do not involve other organ systems. Varying size definitions for LLR have been proposed, ranging from >15 mm, to >25 mm of redness or swelling, to greater than the size of the patient's palm. The incidence of LLRs range from 0.4% using a definition of redness and swelling larger than size of the patient's palm, to 4-7% when using a 15 mm definition, and to 5-19% when using a 25 mm definition.[429-433] In a survey of 249 patients, 20.3% reported at least one LLR larger than the palm.[434] Ninety-six percent of patients in this survey chose not to stop SCIT secondary to LLRs.
The specialist should educate patients that LRs are common, and do not predict future LRs or LLRs.[435] Education should occur before initiating SCIT, when LRs occur, and at routine follow-up appointments. Patients should be encouraged to notify office staff and the specialist if LRs are bothersome so that pretreatment and symptomatic therapy may be utilized.

48. Recommendation: We suggest against using LLRs to routinely predict the risk of anaphylaxis following subsequent SCIT injections.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

LLRs do not predict subsequent LLRs or SRs, and routine dose adjustments for LLRs did not lower SR rates compared to a no-dose adjustment policy.[433, 436] However, a subset of patients with frequent LLRs may have an increased risk for future SRs at some point during their SCIT course.[432, 437] Despite this, routine LLR dosage adjustments did not affect this association.[432]

There are circumstances in which patients with repeated LLRs eventually experience SRs or anaphylaxis. In general, LLRs should not be the primary reason for a dose change or influence the decision to continue SCIT unless the discomfort is sufficiently bothersome to the patient. A shared decision-making discussion is very important concerning continuation of SCIT in the context of recurrent LLRs, particularly if associated with SRs.

49. Recommendation: We suggest against routine SCIT dose adjustments for most patients with LLRs.
Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

Routine dose adjustments for all patients with LLRs are not recommended; however, the specialist may decide to dose adjust for individual patients, such as when the LLRs are bothersome to the patient, patient preference, or for high-risk patients (usually defined as patients with co-morbidities such as cardiovascular disease, a history of uncontrolled asthma,

prior anaphylaxis to SCIT, or a high degree of allergic sensitivity). Routine dose adjustments did not decrease subsequent LLRs or SRs, and dose adjustments delay achieving maintenance dosing.[432, 433] Routine adjustments may hamper adherence by introducing additional visits, injections, and cost. It may also lead to dosing errors if only done with one vial in a patient receiving multiple injections per visit. A 'no routine dose adjustment' policy results in fewer patient visits to achieve maintenance and may lead to monetary savings and fewer dosing errors.

50. Good Practice Statement: We cannot recommend for or against routine premedication with oral AH and/or LTRA with conventional build-up schedules or with maintenance injections to prevent LLRs from SCIT.

Various premedication prevention strategies have been trialed by specialists to prevent the development of LLRs. Antihistamines (AH) and LTRA (montelukast) have been most studied. The specialist may use H1-AH in an attempt to reduce discomfort and decrease the frequency of bothersome LLRs. There are no controlled studies in conventional schedules, though expert opinion is that H1-AH do provide some comfort and relief from troublesome LRs. Antihistamine pretreatment decreases LLRs during accelerated build-up rush and cluster protocols.[438, 439] LTRA therapy has demonstrated benefit for rush protocols.[440]

Additional management strategies for bothersome LLRs include application of ice to the injection site during the 30-minute, post-injection wait period, and topical H1-AH/corticosteroid. There is no evidence for or against the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) to treat LLR. The specialist may also utilize a slower build-up schedule (e.g., advance by 0.05 mL instead of 0.1 mL per injection), "dry needle" technique (using different needle to inject than what was used to draw up allergen dose), and using split dosing in patients (half the dose in each arm or at 2 sites).

51. Recommendation: We suggest against the routine use of epinephrine or AH rinses of syringes to prevent LLRs from SCIT.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Epinephrine and diphenhydramine rinses have been studied in two small pilot trials.[441, 442] An epinephrine rinse is a procedure which involves aspirating 0.1-0.5 ml of 1:1000 w/v epinephrine and then expelling it from the syringe, thereby coating the syringe prior to allergen vaccine aspiration. One study investigating epinephrine rinses was a small RDBPC trial of 17 patients ≥6 years of age (76% with asthma) who were on maintenance SCIT complicated by LLRs with ≥20% of SCIT injections despite AH +/- LTRA premedication.[441] Interventions were performed during two SCIT visits scheduled 4 weeks apart. Subjects were randomly assigned to receive either an epinephrine or normal saline coated syringe; the 1 mL syringes were coated with 0.2 mL of epinephrine 1 mg/mL or normal saline. Patients were observed for 30 minutes and late reactions were recorded at 2, 4, and 6 hours at home. A LLR was defined as erythema or swelling >25 mm. The investigators found the epinephrine reduced the LR size compared with placebo at 30 minutes, 2, 4, and 6 hours by 100%, 61%, 55%, and 39.8%, respectively. Epinephrine reduced LRs by >25% in 64.5% of injections and by >50% in 35.5% of injections. No SRs were observed during these visits.[441]

The second study was a single-blind investigation in which participants 5 years of age and older (mean age 30.6 years) had experienced a LLR despite AH premedication; 34% of participants had asthma. They were randomized to receive either epinephrine rinses, diphenhydramine rinses, or placebo rinses for the next 3 SCIT injections.[442] The rinse technique involved aspirating 1 mL of diphenhydramine (12.5 mg/5 ml), epinephrine 1:1000 w/v, or sterile water into a 27-gauge, ½ inch syringe, and once the syringe was coated with the rinse, the rinse was discarded. The coated syringe was then used to aspirate the desired dose of the allergy extract. Seventy subjects completed all three visits. At visit 1, 91.4% (32/35) of subjects in the epinephrine group, 64% (16/25) in the diphenhydramine group, and 27.8% (5/18) in the placebo group reported a statically significant reduction in the LRs. In visits 2 and 3 there were no statistically significant improvements (Visit 2: 25/35 epinephrine, 17/25 diphenhydramine, 9/18 placebo; Visit 3: 21/35 epinephrine, 11/19 diphenhydramine, 7/15 placebo). Seventy-one percent (22/31) in the epinephrine group reported a consistent improvement in all 3 visits vs 60.9% in the diphenhydramine group vs 31.3% in the placebo group. No AEs or SRs were reported.[442]

In very select patients who are having bothersome LLR despite AH + LTRA pre-medication and having trouble advancing their dose, we suggest the specialist consider an epinephrine rinse to help lower the risk of LLRs. This should not be routine practice. Larger studies are needed to detect any safety issues with such an approach, such as an increase in delayed SRs from potentially delayed allergen absorption with using epinephrine rinses and an increase in the risk of contamination and infection from the extra step of adding the epinephrine rinse. Finally, adding steps to the process may increase errors in SCIT dosing due to staff distraction.

Systemic reactions to SCIT

52. Recommendation: We recommend written informed consent, including the risk of anaphylaxis, be obtained for all patients prior to initiating SCIT.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Given the risk of life-threatening anaphylaxis from SCIT, detailed below, a shared decision-making discussion that informs patients of potential risks, including strategies to mitigate risks, should be conducted (**Table 10**). Obtaining written informed consent to document this discussion is highly recommended, to verify that the patient acknowledges and understands these risks. The AAAAI and ACAAI have provided examples of written informed consents on their websites.[443, 444]

Most of the recent data regarding the risk of SRs and anaphylaxis comes from the NAISS, which was initiated in 2008.[445-447 448-452] Practicing allergists were recruited to voluntarily complete annual surveys regarding SRs in their respective practices. Response rates varied from 2008-2018 with a mean response rate of 33%. Thus, results may overestimate or underestimate true incidence rates. These pooled data are the most ever collected on SRs to SCIT, representing 64.5 million injection visits between 2008-2018, and 3.9 million patients between 2013-2018. Based on these data, the fatality rate from SRs to SCIT for 2008-2018 was estimated at 1 fatal SR per 7.2 million injection visits, or less than one reported fatality per year. Of note, available data summarized in this parameter are based on injection visits, which could

include more than one injection for a given patient on the same day. Based on these data, fatal anaphylaxis after SCIT injections is infrequent and may have decreased over the past 30 years, but fatalities still occur. Similarly, in a recent European Anaphylaxis Registry study, only 1.1% of 15,748 cases of anaphylaxis were attributable to AIT with only one reported fatal reaction associated with a SCIT injection.[453]

The reported incidence of near-fatal anaphylaxis from SCIT has not declined since 1990. Using the 2010 WAO system for grading severity of SRs, where the grade 4 severity category defines near-fatal SRs (i.e. near-fatal anaphylaxis), 6.25 near-fatal events were estimated for every one million injection visits from 2011-2018 (or 1 in 160,000 visits). Near-fatal SRs occurred in approximately 0.06% of patients surveyed between 2013-2018.[445, 446, 448-452] These figures are similar to data reported between 1990-2001.[454]

It is important to recognize and address SRs of lesser severity when they occur, to prevent progression to more serious reactions. Based on data from the NAISS collected between 2008-2018, SRs of any severity grade were reported by 76-85% of practices surveyed and at a mean incidence of 10 per 10,000 (0.1%) injection visits. [445, 446, 448-452] Between 2013-2018, SRs were reported in a mean of 0.8% of patients (range of 0.4%-1.5%). There were 4.9 WAO grade 1 SRs, 3.0 grade 2 SRs, and 0.36 grade 3 SRs per 10,000 injection visits between 2008-2018.[446, 447, 455]

Table 10. Suggestions to improve SCIT safety in all treated patients.

1. Modify doses or consider discontinuation of SCIT after grade 3 or 4 SRs
2. Adopt clinic protocols and routinely conduct training to prevent dosing errors
3. Administer SCIT injections only in clinics with adequate facilities, personnel trained to manage anaphylaxis, and space to adhere to a 30-minute observation period
4. Monitor patients directly or visually for 30 minutes
5. Consider reducing target doses for accelerated cluster build-up
6. Prescribe and train the patient on the correct use of self-administered epinephrine for individuals at heightened risk for SRs, including those patients with a prior history of SRs to SCIT injections (immediate or delayed); with a prior history of uncontrolled and/or severe asthma; with administration of injections at outside clinics; or with utilization of cluster SCIT
7. Educate patients and staff regarding risk factors for severe reactions, and incorporate screening procedures to prevent administration of SCIT injections when not appropriate (e.g., uncontrolled asthma)

SR, systemic reaction.

53. Recommendation: We recommend direct monitoring of patients for 30 minutes after SCIT injections, with a physician, nurse practitioner, or physician assistant present during the observation time.

Strength of Recommendation: Strong

Certainty of Evidence: Low

As discussed below, there are concerns about increased risk for fatal and severe SRs when patients leave the treating physician's office less than 30 minutes after an injection is given. The majority of SRs occur within 30 minutes of injection.[2, 455, 456] Although some studies previously reported that delayed onset SRs may occur in up to 50% of patients on conventional schedules (not cluster or rush) in either build-up or maintenance vials, more recent data indicate that this is likely an overestimate.[2, 448, 449, 457] Based on data collected in the NAISS from 2009-2010, 14% of SRs began more than 30 minutes after injections.[449] Based on survey data from 2014-2016 (n= 8692 SRs), 23% of SRs began at 10 minutes or less after injections, 31% between 11 and 20 minutes, 27% between 21 and 30 minutes, and 30% were reported to have begun after 30 minutes; however, when the analysis considered practices that directly observed patients for at least 30 minutes, only 15% of SRs were observed to have begun after 30 minutes.[448] Of SRs beginning after 30 minutes, 51% were grade 1, 44% were grade 2, 4.5% were grade 3, and 0.3% were grade 4 SRs.[448] There were no reported delayed-onset fatal SRs. This is consistent with previous studies indicating that the most severe, life-threatening SRs occur within 30 minutes.[2, 456, 457] Risk factors for delayed SRs have not been well defined. Based on NAISS data, practices that track the time after injections and require checking out with office personnel have lower rates of grade 3 and 4 SRs overall ($p<0.001$).[446] In addition, there is no evidence that prescription of self-administered epinephrine lowers the risk of severe SRs when patients leave the office less than 30 minutes after receiving an injection, possibly because of historically low rates of patient-self administration.[449, 458]

54. Recommendation: We recommend that all health care personnel working in a facility administering SCIT receive training on the recognition and treatment of anaphylaxis with epinephrine as well as other treatment measures.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

55. Recommendation: We recommend that epinephrine be immediately available in a healthcare facility administering SCIT.[459, 460]

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Epinephrine remains the first-line treatment for SRs to AIT of all severity grades.[459, 460] Delays in treatment with epinephrine are associated with a higher risk for fatal and severe anaphylaxis.[446, 448, 454, 459-462] When administered IM, the dose should be 0.01 mg/kg of a 1:1000 [1 mg/mL] solution to a maximum of 0.5 mg in adults and 0.3 mg in children into the anterolateral thigh.[460, 463] Data are evolving regarding other routes of delivery for treatment of SRs to AIT; of note at the time of this publication an intranasal epinephrine product is approved and indicated for the treatment of anaphylaxis. Detailed descriptions regarding signs and symptoms and anaphylaxis, as well as medications and equipment that should be available in the practitioner's office, were

provided in the JTF 2015 and 2020 Anaphylaxis PP.[459, 460] Based on expert opinion, training of office personnel, ideally including mock anaphylaxis drills, should be performed regularly.

56. Recommendation: We suggest prescribing self-administered epinephrine for patients who are at higher risk for severe or fatal SRs including those 1) with prior anaphylaxis, 2) with prior delayed-onset SRs, 3) with severe asthma, and 4) on accelerated build-ups.

Strength of Recommendation: Conditional
Certainty of Evidence: Low

There is much debate regarding whether prescription of self-administered epinephrine improves safety outcomes for patients on SCIT.[458] At this time, there is insufficient evidence to recommend prescribing self-administered epinephrine for every patient on SCIT. There is no contraindication to prescribing self-administered epinephrine based on patient or physician preference. Based on expert opinion, the potential benefit of prescribing self-administered epinephrine for patients at higher risk of anaphylaxis may outweigh other considerations. Data regarding risk factors for fatal anaphylaxis from SCIT are discussed below.

Based on available information for 34 patients who experienced fatal anaphylaxis from SCIT between 1985-2001, the number one risk factor was uncontrolled asthma (62% of patients).[2, 461, 462, 464] Other cited contributing factors based on all fatal SRs reported between 1945-2001 are listed in **Table 11**.[461, 462, 465] Details regarding 10 additional, recent cases of fatal anaphylaxis reported by allergists between 2008-2019 were identified via the NAISS.[445, 446, 448, 451] Among the eight fatalities for whom age was reported, two occurred in teenagers and six in adults. Among the seven fatalities for whom sex was reported, five occurred in males and two in females. At least two fatalities occurred in patients with severe asthma based on the European Respiratory Society(ERS)/American Thoracic Society (ATS) definition of severe asthma.[466] One fatality occurred in a patient who left the office before the prescribed waiting period. At least two fatal events occurred in settings where the supervising provider was not specifically trained in allergy/immunology and anaphylaxis was not recognized or treated promptly, or there was a question regarding provider supervision at the time of the injection. One fatality occurred in a severe asthma patient upon receiving the second dose from the maintenance (1:1) vial after having just completed cluster AIT build-up. Obesity was cited as a contributing factor in one fatal anaphylactic event, due to concerns that obesity made treatment of the SR more difficult, possibly due to inadequate needle length. This patient was also on an ACEi, highly allergic to weeds based on skin testing (based on physician self-report), and the reaction occurred during a peak weed pollen season.

Table 11. Risk factors for fatalities related to SCIT injections.

Years/number of fatalities reported	Uncontrolled or severe asthma	Prior SRs	Injections during peak pollen seasons	Suboptimal treatment of anaphylaxis	Dosing errors	Less than 30 minute post-injection observation	Injections in a suboptimal setting	SR beginning >30 minutes after injection	ACEi/ARB/Beta-blocker use	High degree of aeroallergen sensitization[a]	New vial	Accelerated build-up	Obesity
1945-1987[465] 24 pts	2 pts (known; information not available for most pts with asthma)	4 pts	9 pts	Unable to assess	3 pts	2 pts	12 pts (includes no physician present at time reaction began)	3 pts	2 pts	11 pts	6 pts	Unable to assess	Unable to assess
1985-2001[461, 462] 34 pts	21 pts	18 pts	16 pts	15 pts	12 pts	4 pts	3 pts	3 pts	1 pt for each	13 pts	4 pts	Unable to assess	2 pts
2008-2018[446, 448, 451] 10 pts	2 pts	None reported	1 pt	1 pt	None reported	1 pt	2 pts	None reported	1 pt	1 pt	None reported	1 pt	1 pt

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; pt, patient; pts, patients; SR, systemic reaction.

[a]As reported by the specialist based on skin test responses.

Asthma as risk factor for SCIT

57. Recommendation: We recommend against initiating and administering SCIT to patients with uncontrolled asthma.

Strength of Recommendation: Strong

Certainty of Evidence: High

Recent studies reporting on grade 3 (severe) and 4 (very severe) SRs based on the 2010 WAO grading system have reinforced the importance of optimal asthma control while receiving SCIT.[446, 448, 451, 467] Based on NAISS data from 2016-2017, practices with a higher percentage of individuals with asthma on SCIT had significantly higher rates of grade 3 SRs ($p<0.02$); there was a trend towards more grade 4 SRs among such practices as well.[446] This is consistent with older literature emphasizing a higher risk for adverse outcomes among patients with asthma receiving SCIT.[245] Since the JTF 2011 AIT PP,[2] newer data have emphasized the importance of having well-controlled asthma, based on validated measures, when SCIT is prescribed.[446, 451]

The importance of optimal asthma control in patients treated with SCIT has been known for decades.[2] Older literature emphasized a FEV_1 cut-off of 70% or 80% of predicted, depending on the study, to determine whether administration of SCIT was safe in a person with asthma.[454, 468] While this remains an important consideration, recent surveys have not found avoiding SCIT in patients with FEV_1 less than 70% or checking peak flows or spirometry prior to SCIT injections to be independent predictors of grade 3 or 4 SRs. This is possibly because the large majority of patients with reduced lung function have been excluded from receiving SCIT, at least for the past 10 years.[446, 451] Having symptomatic asthma or injections administered during periods of asthma exacerbations are well-known risk factors for severe and fatal SCIT reactions, as described in the JTF 2011 AIT PP.[2] Preinjection screening of all patients with asthma should include an assessment for increased asthma symptoms (preferably with a standardized asthma control survey). Preinjection screening with peak flow or lung function can also be performed at the discretion of the physician.

Since at least 2008, studies have emphasized the importance of not prescribing SCIT in patients with uncontrolled asthma. Utilizing standardized measures to assess asthma control at the time SCIT is originally prescribed significantly lowers the risk of severe SRs. Between 2012-2013, 429 practices routinely administered the ACT in patients with asthma before prescribing SCIT.[451] Of these, 25% of practices always avoided prescribing SCIT in asthma patients with an ACT score less than 20 (uncontrolled asthma), whereas 18% often, 28% sometimes, and 28% prescribe SCIT for those with uncontrolled asthma. Practices that never administered SCIT to patients with uncontrolled asthma based on the ACT had significantly fewer grade 3 and grade 4 SRs ($p<0.05$).[451] This finding was replicated in 217 practices utilizing the ACT to identify patients with uncontrolled asthma prior to prescribing SCIT from 2016-2017 ($p<0.05$).[446]

58. Recommendation: We suggest using a validated measure to determine the degree of asthma control prior to prescribing and administering SCIT to patients with asthma.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

59. Recommendation: We suggest that SCIT can be cautiously used in patients with severe asthma who remain well controlled while receiving SCIT.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

60. Recommendation: We suggest in patients with severe asthma that preferred asthma treatments, including biologic drugs with better safety profiles, be considered to achieve asthma control before initiation of SCIT.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

There is an increased risk for adverse events from SCIT in patients with severe asthma. For example, from 2016 to 2017, practices in the NAISS were asked to report the percentages of patients with severe asthma receiving SCIT,[446] using the definition of severe asthma adopted by the ERS/ATS Task Force (2014).[466] Practices reporting that greater than 20% of their patients receiving SCIT had severe asthma had significantly higher rates of total, grade 1, and grade 2 SRs ($p<0.001$).[446] This finding was not seen for grade 3 and 4 SRs, likely because of the rarity of such events. From 2017 to 2018, participating physicians were directly asked the following question: “Of those patients who had WAO grade 3 or 4 SRs in the past year, how many had severe asthma?” Respondents indicated that 50% (105/209) of grade 3 or 4 SRs occurred in patients with severe asthma.[446] As previously mentioned, at least two fatalities from SCIT since 2008 have occurred in patients with severe asthma.[446] Of note, a retrospective chart review from 2015-2019 that included 65,855 patients, including 1072 patients with severe asthma, did not find an increased risk of severe SR among patients with severe asthma; however, asthma severity was defined by ICD-10 codes rather than the ERS/ATS definition, and standardized measures of asthma control were not included in the definition of severe asthma or in the analysis.[467]

The risk/benefit ratio of SCIT in patients with severe asthma is debated.[467, 469] SCIT improves asthma outcomes, especially for HDM allergic patients.[121, 467, 470-472] Data regarding SCIT in patients with severe asthma are very limited, although some studies show benefit in asthma outcomes.[163, 466, 473-475] These benefits must be balanced with the increased risk of severe adverse events in such patients, particularly given that asthma biologics can improve outcomes in severe, allergic asthma, with minimal risk of SRs (link to section on asthma biologics). Further guidance regarding treatment of severe asthma is beyond the scope of this parameter, but multiple recent systematic reviews and meta-analyses have addressed this issue.[476-479]

Due to the increased risk of severe SRs, specialists should avoid prescribing SCIT in patients with uncontrolled asthma, regardless of severity. Close monitoring of asthma symptom control, lung function, and compliance with controller therapies is required in all patients with asthma treated with SCIT, especially those with severe disease. Injections should be withheld when asthma is not well controlled (i.e. ACT < 20). Accelerated build-up regimens further increase the risk in patients with severe asthma. Coadministration of biologic agents to lower the risk of adverse events from SCIT is discussed (Recommendation 73).

61. Recommendation: We recommend discontinuation of SCIT after near-fatal anaphylaxis.
Strength of Recommendation: Strong
Certainty of Evidence: Low

Although there is an increased risk of further SRs, including near-fatal and fatal SRs, among patients who have previously experienced such reactions, data are lacking regarding when specialists should stop SCIT after a SR (or multiple SRs).[480] Nevertheless, the decision to stop SCIT is recommended when the perceived harms of future severe SRs far outweigh potential therapeutic benefit. Recommendations are based on expert opinion, and there is an unmet need for additional data. There are rare circumstances where the specialist may consider resuming SCIT after a WAO 2010 grade 4 SR; these circumstances include dosing errors. While lower target maintenance doses in patients with multiple SRs can be considered based on expert opinion, the specialist should also consider whether lower maintenance doses will provide significant benefit. Prescription of a self-administered epinephrine for patients with prior SRs is recommended, although there is no evidence that this will prevent near-fatal or fatal events in such patients, in part due to poor patient adherence with the use of self-injectable devices.[448, 449] Avoidance of accelerated build-ups in patients with prior SRs should be considered.

Cofactors as risk factors for SCIT

As stated in the JTF 2023 Anaphylaxis PP, “Anaphylaxis severity is a continuum that results from a combination of risk factors, including those related to the allergen (e. g., allergen dose and route of exposure) as well as the patient (e.g., immune response, behaviors, concomitant medications, and other patient specific factors and comorbidities)”.[39]

62. Recommendation: We suggest withholding SCIT during an acute URI in individuals at higher risk, such as those with asthma or a severe infection.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

The decision to withhold SCIT in the setting of an upper respiratory viral infection (URI) is at the discretion of the specialist. It may be difficult to distinguish whether symptoms are due to a SR from a SCIT injection versus the URI. In addition, URIs may trigger asthma exacerbations, which are a contraindication to SCIT injection. Very few studies have evaluated the impact of URIs on SCIT safety. A web-based retrospective European survey study published in 2021 evaluated the safety of administering AIT during the COVID-19 pandemic.[481] In this survey, the majority of participants followed the EAACI recommendation to avoid administration of AIT during an active COVID infection. There were 16/305 physicians who continued AIT (SLIT or SCIT), despite (early) symptoms of COVID-19 and/or a positive viral test result. One significant adverse event was reported in the build-up phase and one in the maintenance phase for COVID-19 infected patients receiving SCIT; adverse event rates for non-infected patients were not provided. Another study found that acute influenza infection in patients with asthma receiving SCIT did not impact markers of allergic inflammation, but no clinical parameters were reported.[482] Despite the lack of evidence specifically related to the influence of viral infections on SRs to SCIT, respiratory viral infections are a known trigger for asthma exacerbations in allergic patients.[483, 484] Based on this, there is a theoretical increased risk for adverse outcomes from SCIT in patients with asthma and comorbid viral infection.

63. Recommendation: We suggest that patients avoid vigorous exercise within two hours after the administration of SCIT.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

Exercise has been identified as a non-trigger related concomitant factor (co-factor), increasing the risk of anaphylaxis.[39, 485, 486] The proposed mechanisms of this association include altered sensitivity of basophils and mast cells; a hyperosmotic state due to vascular volume loss; a hypermetabolic state with redistribution of blood flow; and increased gut permeability to allergens.[487] Although there is a paucity of data of exercise as a co-factor for an increased risk of anaphylaxis specifically in aeroallergen SCIT, data are available for food associated exercise induced anaphylaxis as well as exercise during food OIT.[488-490] The package insert for the only FDA approved treatment for peanut OIT also includes exercise avoidance as a recommendation.[491] For strenuous exercise immediately prior to SCIT, it would be appropriate for the clinician to assess clinical status prior to administration of SCIT.

Other potential cofactors for SRs and anaphylaxis

Alcohol is a well-known cofactor for anaphylaxis, with multiple mechanisms proposed.[488, 492-494] Although there are no studies specifically related to SCIT, there are theoretical risks associated with alcohol consumption prior to or immediately after SCIT. In addition, alcohol may inhibit a patient's ability to identify early symptoms of a SR, leading to a delay in treatment.

Stress may exacerbate symptoms of AR,[495] and acute stress may impact the immediate response to SCIT, including the risk of SRs.[496] The mechanism is not clear but may be associated with the release of corticotropin releasing hormone, as has been suggested in ingested food anaphylaxis.[497] Other non-IgE mediated acute stress responses, such as manifestations of anxiety, may be confused with symptoms of an acute allergic reaction. Stress has been noted as a risk factor for anaphylaxis in several prior publications.[39, 485] Furthermore, when formally studied in association with response to COVID-19 vaccines, efficacy was lower and reported side effects were higher in patients with higher stress.[498] In one study of 40 children with asthma, the efficacy of HDM SLIT was higher in children with less chronic stress.[499] There is very little direct data giving evidence specifically for SCIT during times of stress and mechanistic studies are also lacking.

Sleep deprivation has been noted as a cofactor for increasing the severity of allergic reactions or decreasing the threshold of reaction in food-related anaphylaxis.[486, 500-502] Although there are no specific studies related to sleep deprivation and SCIT, patients should be informed of the theoretically increased risk of SRs when sleep deprived.

As with other cofactors discussed, there is insufficient evidence in patients receiving SCIT for most other potential cofactors for anaphylaxis, such as menstruation and non-steroidal anti-inflammatory drug (NSAID) use. At this time, no change in guidance related to these cofactors can be recommended for patients receiving SCIT.[39]

SCIT dosing and schedules

64. Recommendation: We suggest that routine dose adjustment during peak pollen season is not necessary for most patients.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

65. Recommendation: We suggest against increasing the dose of SCIT during peak pollen season in highly sensitized patients.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

As discussed in the JTF 2011 AIT PP,[2] it is controversial whether SRs are more likely to occur during peak allergen seasons, or if lowering or not increasing doses during peak allergen seasons should be considered.[503] Fatal SRs have been associated with administration of SCIT during peak allergen seasons, but it is not clear that SRs occur more frequently during particular seasons, or if dose adjustment during pollen seasons is needed for most patients.[503] Based on NIASS data from 272 practices in 2010-2011, practices that did not increase doses during peak pollen seasons were less likely to report moderate or severe SRs based on a previous grading system for SRs ($p=0.04$).[450] This finding was replicated for WAO grade 3 and 4 SRs in data from 2011-2012 ($p<0.001$).[445] The previous JTF AIT PPs suggested that dose adjustment during peak allergen seasons may be reasonable to minimize risk in patients who are highly sensitized to relevant allergens. Subsequent findings from the NAISS support this approach. Based on data from 443 practices from 2012-2013, significantly lower rates of SRs of all severity grades occurred in practices in which specialists "reduce doses during pollen seasons for patients with highly positive skin test results (e.g., pseudopods or positive tests to >50% of aeroallergens tested) to relevant allergens," ($p<0.05$, Mantel-Haenszel χ^2 test).[451] Survey data do not demonstrate a lower risk of severe SRs when doses are adjusted specifically for patients with previous SRs during particular pollen seasons, possibly due to the rarity of such events. Based on expert opinion, it is reasonable to consider dose adjustment in peak pollen seasons for patients with previous SRs during specific pollen seasons.

66. Recommendation: We suggest modifying subsequent doses based on the length of the delay and treatment phase when scheduled SCIT doses are missed.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Prior recommendations for dose adjustments during SCIT build-up were due to concerns for an increased risk of SRs after prolonged interruptions in treatment.[2, 504] These risks may be mitigated by decreasing doses after a gap in therapy.[505] Several suggested dose adjustment recommendations have been published including Table e5 in the JTF 2011 AIT PP,[2] but these should be individualized for a specific patient.[506-508] Specific adjustment schedules were based on expert consensus in the JTF 2011 AIT PP,[2] and these continue to be largely consensus based, with limited data from newer studies described below.

NAISS study data from March 2020 to July 31, 2020 (n=203 practices) showed a large divergence in responses regarding whether practices decrease, repeat, or advance doses after gaps in therapy.[509] There appears to be reduced risk for SRs with more aggressive dose adjustments after gaps in therapy. For example, practices reducing to one vial lower in concentration in patients who were >7 weeks late for maintenance vial injections had fewer grade 4 SRs ($p=0.02$). Practices decreasing to the next lower concentration vial in patients who were >28 days late during build-up had fewer grade 3 and 4 SRs ($p=0.03$).[509] Nevertheless, there are insufficient data comparing the outcomes of various dose adjustment strategies for gaps in treatment.

Table 12 is based on consensus of the workgroup and has not been rigorously evaluated in comparison with other potential strategies.

Table 12. Recommended dose adjustments for interval gaps in conventional SCIT.

Build-up phase: Dose adjustments when conventional build-up is planned weekly	
Time from Last Administered Dose	**Recommended Adjustment**
<14 days	Increase as planned
>14 days but <21 days	Repeat last dose
>21 days but < 28 days	Decrease dose by one step of escalation protocol
>28 days but <35 days	Decrease dose by two steps of escalation protocol
>35 days	Variable- Decrease dose proportional to gap, and consider restarting build up
Maintenance phase: Dose adjustments when conventional maintenance doses are being given every four weeks	
Time from Last Administered Dose	**Recommended Adjustment**
<35 days	Repeat last dose as planned
>35 days but < 42 days	Repeat last dose
>42 days but < 49 days	Decrease dose by one step of escalation protocol
>49 days but <56 days	Decrease dose by two steps of escalation protocol
>56 days	Variable- Decrease dose proportional to gap

Beta-blockers, ACEi, and SCIT

67. Recommendation: We suggest that initiation or continuation of SCIT is an option in patients receiving a BB, ACEi, or ARB, following a documented shared decision-making discussion about potential risks.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

The perception of risk with BB is based primarily on data from older studies with non-selective BBs, with many reports not considering the confounder effects of cardiac comorbidities in BB-treated subjects that could independently increase the risk of severe anaphylaxis. Given the increased use of more cardio-selective BB agents (e.g., metoprolol) and the favorable risk/benefit ratio for BB therapy, the PP work group recommends a shared decision-making model and discussion between patient and specialist. While most of the original studies investigating the risk of BBs and increased risk of anaphylaxis were with radiocontrast media (RCM) administration in patients treated with non-selective BBs,[510] subsequent SCIT studies, including two retrospective and one prospective study of 3,178 patients treated with venom or inhalant SCIT, found no increased frequency of SRs with BB therapy.[511-513] Furthermore, a seven-year retrospective, observational study of patients with anaphylaxis due to all causes in the emergency department assessed the association between BB use and the requirement for more than 1 dose of epinephrine for anaphylaxis management.[514] Similar epinephrine requirements were reported regardless of BB use (OR 1.26; 95% CI, 0.58-2.75). The authors concluded that BB therapy may not be clinically significant regarding the need for epinephrine

dosing among ED patients with anaphylaxis, and these patients may not require more intensive anaphylaxis treatment.[514]

Similarly, there were initial case reports of anaphylaxis in patients on VIT receiving ACEi that did not occur when the ACEi therapy was discontinued and recurred with reinitiation of ACEi.[515, 516] However, two retrospective cohort studies did not find an association between ACEi and SRs to SCIT.[513, 517] Another study investigated the risk of anaphylaxis during build-up of honey bee or vespid VIT and found that severe SRs were associated with the use of any antihypertensive medication, not ACEi specifically.[518] Subsequent studies had conflicting conclusions. One study demonstrated an increased risk of a SR during rush VIT build-up in patients using an ACEi.[519] However, a study of maintenance VIT found no association with either BB or ACEi therapy and SRs.[520] This study also noted that SRs were actually less frequent in patients taking any kind of cardiovascular medication, including ACEi.[520]

A 2018 systematic review and meta-analysis of observational studies investigated the relationship between the use of BB or ACEi and the severity and incidence of anaphylaxis.[521] BBs and ACEi increased the severity of anaphylaxis (BBs, OR 2.19, 95% CI 1.25-3.84; ACEi, OR 1.56, 95% CI 1.12-2.16), but not the occurrence of anaphylaxis (BBs, OR 1.4, 95% CI 0.91-2.14; ACEi, OR 1.38, 95% CI 0.39-4.86). It was not possible to perform an analysis adjusted for cardiovascular disease, and the authors concluded that the quality level of evidence was low owing to differences in the control of these confounders. The authors concluded that while there may be a slight increased risk of severity of a SR should one occur with BB or ACEi, the underlying cardiovascular disease may also make a SR more severe, confounding the analysis.[521]

Most studies suggest that BB or ACEi do not increase the frequency of SRs or anaphylaxis. It is also important to understand that, although the relative risk may be increased, the absolute risk remains very small. For example, recent North American AIT safety surveillance studies report that the risk of a SR is about 0.1% per patient from 2008-2018, and the risk of a grade 4 SR is 1 in 160,000 injection visits for 2011-18, and in approximately 0.06% of patients between 2013-2018.[445, 446, 448-452] Even if the relative risk of a severe reaction is 2-fold higher as has been reported in patients taking BB or ACEi, the absolute risk would still be very low (<0.2%). For VIT, the JTF 2016 Stinging Insect Allergy PP summarizes the shared decision-making process for VIT and BB or ACEi.[522]

Given the available evidence, initiation or continuation of SCIT in patients treated with a BB or ACEi may be considered with shared decision-making. It would be preferable to replace the BB or ACEi, if there is a safe, effective alternative, such as for migraine prophylaxis, tremor therapy, or hypertension in patients without associated coronary artery disease. However, the available evidence suggests that patients have a minimal increased absolute risk of severe anaphylaxis when treated with a BB/ACEi medication and may consider continuing SCIT and the BB/ACEi medications based on shared decision-making. The framework for the evaluation should include evaluation of the potential benefit of SCIT, the potential benefit of the ACEi or BB, and the potential risk/harm of withholding treatment with either the SCIT or the cardiovascular medication. The JTF 2023 Anaphylaxis PP has a table summarizing this analysis.[39]

SCIT and other anti-hypertensives, including ARBs

A retrospective SCIT study found that among SRs in patients receiving either ACEi or ARBs (n=20), 15% were grade 3 or 4 vs 3.2% in the patients not treated with these drugs (n=246); however, there were no differences in number of epinephrine doses or time to symptom resolution.[523] The authors utilized the WAO SR grading system (2010) and only included SRs requiring epinephrine treatment in their analysis. A subsequent study by the same group performed over 7 years analyzed 266 SRs, 29 of which involved patients on anti-hypertensives (13 ACEi, 2 ARB, 10 diuretics, 12 calcium channel blockers, none on BBs).[524] Grade 4 SRs were associated with use of anti-hypertensive therapy (50%) vs grade 2 (9.09%; $p<0.001$) and grade 1 SRs (10.74%; $p=0.002$). A higher percentage of grade 4 SR patients were on diuretics (25%) vs grade 1 (3.3%) and grade 2 (3.3%) SR patients. There was no association of severity of SRs with calcium channel blocker therapy.[524]

It should not be assumed the risk of taking ARBs carries the same potential risk of ACEi, but there is also not enough evidence to sufficiently recommend avoidance or to verify an increased risk for ARBs in patients receiving SCIT.

Premedication for SCIT

68. Recommendation: We recommend against using H1-AH to reduce the risk of anaphylaxis during SCIT with conventional (non-accelerated) build-up schedules.
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

While AH given prior to conventional AIT injections may improve tolerance and comfort, there is very limited data to suggest they either increase or reduce the risk of SRs. There was originally a theoretical concern that AH may mask the early signs or symptoms of a SR if taken before an AIT injection. However, in a post hoc analysis of the effect of omalizumab on the tolerability of cluster SCIT in patients with moderate-severe asthma, there was a similar incidence of SRs in those who received AH premedication and those who did not; however, AH use was at physician discretion and not randomized.[525]

Regarding potential benefit of AH use, there was one RCT showing that premedication with AH reduced the frequency of severe SRs (0% fexofenadine group vs 9% control group) resulting from conventional SCIT, and pretreatment was associated with an increased proportion of patients who achieved the maintenance dose in the cedar pollen group (97% vs 83%).[526] The effect of AH on LLRs was not reported. However, this is a single study, and no other study has reported the effect, if any, of AH on LLRs or SRs during conventional build-up or maintenance inhalant AIT.

While a recent meta-analysis investigated the use of AH in AIT found that AH were beneficial, it only included one conventional inhalant allergen trial (11 studies total; 7 with venom and 2 with cluster/rush inhalant or peanut).[527] While AH premedication is not necessary for the majority of patients, it may be utilized to help patient comfort from LLRs or may prevent milder SRs, such as pruritus.

Accelerated schedules for SCIT

69. Recommendation: We suggest that cluster SCIT build-up is an option in patients with AR and/or co-morbid asthma, only if their asthma is not severe and is controlled.
Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

70. Recommendation: We recommend oral AH and LTRA pretreatment during cluster or rush SCIT build-up schedules.
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

71. Recommendation: We suggest oral AH, LTRA, and oral corticosteroids to reduce the risk of SRs in one-day rush or modified rush build-up schedules.
Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

72. Recommendation: We suggest stopping cluster immunotherapy protocols in the 1:10 v/v vial and converting to conventional build-up dosing.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

Examples of conventional and accelerated AIT build-up schedules are shown in Appendix 3. Cluster SCIT studies utilizing premedication have been performed with either AH alone or a combination of premedications (**Table 13**).[195, 196, 528, 529] A controlled study demonstrated that loratadine premedication reduced the SR frequency during cluster SCIT with grass or birch pollen extract when taken 2 hours before the first injection (33% SR in the loratadine group, 79% SR in the placebo group).[528] A cat cluster SCIT study using loratadine for all 28 subjects (no placebo premedication) demonstrated no SRs.[195] A 4-week grass cluster study using loratadine for all subjects reported no immediate LLRs or SRs, but delayed SRs occurred in 18% of the active treatment group and 22% of the placebo injection group.[529]

Since the JTF 2011 AIT PP,[2] four cluster studies were performed that utilize multi-allergen SCIT. One US inhalant mixture study by a large, multicenter, private allergy practice utilized an 8-week cluster schedule to reach maintenance.[530] Premedication was at the discretion of the physician; 92.3% routinely premedicated (55.8% premedicated with oral AH alone, 3.4% with montelukast alone, and 40.8% with a combination of AH and montelukast). Overall, 10.9% of patients had SRs, with most SRs being grade 1 or 2 (87.2%), though 10.6% were grade 3 and one grade 4 SR; 87.5% of SRs were in the 1:10 or 1:1 v/v vials, and 55% of SRs were delayed (>30 min after the last cluster dose). SR rates were not compared between premedication and no-premedication groups.[530]

A second prospective study compared cluster SCIT to the 1:1 v/v vial to standard SCIT; 70% of patients in both groups were taking continual oral AH.[531] Patients selected their build-up group, and premedication was not standardized or placebo-controlled. On average, 33 days were required to achieve the first maintenance dose in the cluster group. Overall, on a per patient basis, 37% of the cluster patients vs. 21% of the standard patients had a nonsignificant SR (grade 1 or 2). However, the SR rate per injection was significantly higher in the cluster group (2.29%/injection vs 0.69%/injection, incident rate ratio 3.3; 95% CI, 1.5-7.3; p=0.003). In the

cluster group, 31% were grade 1, 63% grade 2, and there was 1 grade 4 SR (no grade 3 SR). All SRs were in the second half of cluster.[531] Lee et al.[532] retrospectively compared standard, cluster, and rush protocols. In their cluster subgroup (n=122), their protocol was 9 weeks, but patients took an average of 19 weeks to complete it due to variable adherence to the protocol. They found a SR rate of 9.84% SR/patient; premedication was not studied. Finally, Winslow et al.[533] also retrospectively compared standard, cluster, and rush protocols. Their cluster protocol was 9 visits and took patients into the 1:1 v/v vial. They premedicated 90 minutes prior to SCIT with prednisone 20 mg, H1-AH, and 10 mg of montelukast, and only 2.52% of patients had a SR.

None of these studies compared the SR rates in the premedication group to the no premedication group, and future studies are needed in this area. Additionally, future studies are needed to see if cluster protocols with lower final target allergen concentrations (e.g., 1:10 v/v vial) have lower SR rates than cluster protocols with higher target doses (e.g., 1:1 maintenance vial).

Table 13. Cluster studies with premedication.

Study	Allergen	Protocol[a]	Target dose	Premedication	Safety (SR, % patients)[b]
Walker et al, 2001[529]	Grass	7 visits over 4 wks	20 mcg Phl p 5 vs. placebo	Loratadine 10 mg (>15 min prior) for all subjects	All delayed SRs 18% loratadine 22% placebo
Ewbank et al, 2003[195]	Cat	8 visits over 4 wks	0.6, 3, 15 mcg Fel d 1 vs. placebo IT	Loratadine10 mg 2 hr prior for all subjects	No SRs
Nielsen et al, 1996[528]	Timothy, birch	7 weekly visits	23 mcg Bet v 1 25 mcg Phl p 5	Loratadine 1 mg 2 hr prior vs placebo premedication	33% loratadine 79.2% placebo
Nanda et al, 2004[196]	Cat	8 visits over 4 wks	0.6, 3, 15 mcg Fel d 1	Zafirlukast 20 mg + Loratadine 10 mg 2 hr prior; no placebo	3.8%
Copenhaver et al, 2011[530]	Inhalant mixtures	8 visits over 5-8 wks	Per JTF 2011 AIT PP[2]	92% premedicated 55.8% AH 40.8% combo 3.4% LTRA alone	10.9% (87.5% occurred in 1:10 or 1:1 v/v vials) grade 1-4: 38/48/10/2% 55% delayed
Chen et al, 2023[531]	Inhalant mixtures	5 visits once weekly vs. 26 weekly injections	Standardized per JTF 2011 AIT PP[2]	70% taking AH No placebo premedication group	37% cluster (per injection 3x higher than standard) vs. 21% standard SR all in 2nd half of cluster grade 1-4: 31/63/0/6%
Lee et al, 2023[532]	Inhalant mixtures	9 wks (but on avg took 19 wks)	Not mentioned	Not described	9.84% grade 1-4: 8/25/67/0%
Winslow et al, 2016[533]	Inhalant mixtures	9 visits into 1:1 v/v vial	Lower end of dosing range of JTF 2011 AIT PP[2]	90 min before montelukast 10 mg prednisone 20 mg H1-AH	2.52% grade 1-4: 51/37/11/1%

AH, antihistamines; avg, average; LTRA, leukotriene receptor antagonist; SR, systemic reaction; wks, weeks.
[a]All studies took the cluster protocol to the final maintenance dose.
[b]If severity grade is not stated, then it was not specified in the report.

One- or two-day rush immunotherapy (RIT) schedules into 1:1 v/v

Initial RIT studies were 1 to 3 days and ended in the 1:1 v/v vial and are summarized in **Table 14**. Two separate 3-day RIT studies of either HDM or pollen AIT demonstrated that premedication with a regimen of ketotifen, methylprednisolone, and theophylline decreased the SR frequency.[439, 534] First, a study of 1152 HDM-allergic subjects 3-63 years old examined the effects of 4 different RIT regimens.[534] The investigators found a significant reduction in the SR rate with preventive measures including premedication, modifying the schedule for LLR >10 cm occurring during RIT, and excluding patients with FEV_1<70%. Premedication with methylprednisolone (0.5 mg/kg QD), ketotifen (1 mg BID), and long-acting theophylline (5 mg/kg BID) alone reduced the SR rate from 36% to 16% of patients ($p<0.015$), while premedication plus the preventive measures (i.e., modifying RIT for LLR, excluding patients with low FEV_1) reduced the rate to 7.3% ($p<0.005$).[534] The same group found similar results in a study of 454 pollen-allergic subjects (olive, parietaria, orchard grass, plane tree), with premedication reducing SR rates from 31.3% to 14.7%.[439]

After an initial RIT study without premedication resulted in a 55% SR rate (6/11), a university-based pediatric group investigated the effect of premedication on RIT with allergen mixtures.[535] In the first study of 22 children (5-18 years old) undergoing a 9 injection 2-day RIT study, the SR rate was 27% in the premedication group (complicated schedule of astemizole, ranitidine, and prednisone started one day prior to rush), compared to 73% in the placebo premedication group.[536] A subsequent study of an 8-injection, 1-day RIT with similar active premedication resulted in a 23% SR rate (5/22); there was no placebo group in this study.[537] All SRs occurred at doses of 0.3 mL of 1:10 v/v or higher.[537] Finally, a retrospective review of 65 patients undergoing RIT reported that 38% (25/65) had a SR.[538] They underwent a 7 injection 4-hour protocol, reaching 0.05 mL 1:1 v/v. All patients were premedicated one day prior to and the day of the rush with prednisone 40 mg QD, cetirizine 10 mg QD, ranitidine 150 mg BID, and zafirlukast 20 mg BID or montelukast 10 mg QD. Most SRs (72%) occurred after the final dose of the protocol. Overall, these 1–3-day RIT protocols reaching the 1:1 v/v concentration resulted in SR rates of >50% without and 7.5-38% with premedication.

One two-day RIT study by Winslow et al.[533] ending at the 0.5 mL 1:1 v/v vial on Day 2 using dosing on the lower end of the effective dosing range reported an 11.9% SR rate/patient (grade 1 through 4: 62/29/4/4%). Premedication 90 minutes prior to RIT included prednisone 40 mg, the daily adult dose of H1-AH, H2-AH, and montelukast 20 mg. The starting dose was in the 1:100,000 v/v vial, dosing was done at 30-minute intervals, and stopping dose on Day 1 was 1:10 0.5 mL. Three doses were repeated on Day 2, and they had a 2-hour post-RIT observation period.[533] This was the lowest reported SR rate in a 1-2 day RIT study.

Table 14. One or two-day rush studies.

Study	Allergen	Protocol	Target dose	Premedication regimen	Results (SR, % patients)
Hejjaoui et al, 1990[534]	HDM	1-day	3,000 BU	Methylprednisolone 0.5 mg/kg QD, ketotifen 1 mg BID, theophylline 5 mg/kg BID vs. historical control	36% no premedication 16% premedication 7.3% if exclude FEV_1<70% and LLR dose adjust
Heijaoui et al, 1992[439]	Pollens	1-day	2,000 BU in patients ≥10	Same as above	31.3% no premedication

			years old; 1,000 BU if <10 years old		14.7% premedication 7.5% premedication plus exclude FEV_1<70% and LLR dose adjust
Portnoy et al, 1994[536]	Inhalant mixtures	9 injections over 2 days	0.1 mL 1:1 v/v (1:100-1:400 wt/vol)	3 days, all BID astemizole 15 mg, ranitidine 150 mg, prednisone 30 mg	73% placebo 27% premedication (all SRs at ≥0.05 mL 1:10 v/v)
Sharkey et al, 1996[537]	Inhalant mixtures	8 injections in 1 day	0.2 mL 1:1 v/v cumulative	Same as Portnoy et al, 1994[536]	No placebo group 23% SR (all ≥0.3 mL 1:10 v/v)
Harvey et al, 2004[538]	Inhalant mixtures	7 injections over 4 hours	0.05 mL 1:1 v/v	cetirizine 10 mg ranitidine 150 mg BID zafirlukast or montelukast prednisone 40 mg	No placebo group 38% SR 72% of SRs after final dose
Winslow et al, 2016[533]	Inhalant mixtures	2-day Intervals: 30 minutes	0.5 mL 1:1 v/v AIT dosing lower end of JTF 2011 AIT PP range[2]	90 min prior prednisone 40 mg H1-AH H2-AH montelukast 20 mg	No placebo group 11.9% Grades 1-4 (%) 62/29/4/4% 2-hour post-RIT observation

AH, antihistamine; LLR, large local reaction; RIT, rush immunotherapy; SR, systemic reactions.

Modified rush schedules (mRIT) into the 1:100 or 1:10 v/v

In recent years, modifications to the RIT schedules have resulted in many protocols stopping on the first day in the 1:100 v/v or 1:10 v/v. The patients then continue a conventional schedule to their maintenance dose, which is typically 1:1 v/v 0.5 mL. Multiple studies are summarized in **Table 15**,[539-544] and SR severities are per WAO SR SCIT grading system from 2010.[455] All studies utilized combination premedication with prednisone, H1-AH, H2-AH, and most utilized montelukast. The timing of premedication varied from the day of, to 1-2 days prior to the mRIT, and the dose of prednisone ranged from 40-60 mg. SR rates were <10% in the mRIT studies stopping in the 1:100 v/v vial and ranged from 10.4-28% in the studies stopping in the 1:10 v/v vial. However, patient selection and premedication were not controlled in these trials. Additionally, a recent study reported grade 2/3 WAO SR rates (2010 WAO system) appear lower when stopping mRIT at 1% (0.05 1:10 v/v) or 4% (0.2 1:10 v/v) of the final maintenance dose, compared to 10% of the final maintenance (0.5 mL 1:10 v/v) dose;[542] this finding has not been reproduced. Nearly all mRIT studies have lower SR rates than initial 1-day RIT studies ending in the 1:1 v/v vial, which were generally higher than 20%,[536-538] except for the two studies by Hejjaoui et al.[439, 534]

Unanswered questions and future areas of interest

There are multiple important unanswered questions surrounding accelerated SCIT schedules and optimizing safety. These include the optimal dosing intervals (15 vs. 30 vs. 60 minutes), rate of build-up (0.05 vs 0.1 vs 0.2 mL per increase), and the length of the post-RIT or mRIT observation period to monitor for delayed or biphasic SR. It would seem logical that longer dosing intervals, slower rates of build-up, and longer post-RIT or mRIT observation periods would all optimize safety, but this has not been evaluated in a controlled manner. Repeating

doses post-RIT or mRIT may also improve safety, as Cook et al.[540] found a peak in SRs in the first several weekly build-up injections immediately following the mRIT. There is no evidence regarding the safety of cluster SCIT during peak pollen season; however, there is evidence of increased risk for SRs using conventional therapy during peak pollen seasons among high-risk patients. In summary, premedication prior to accelerated schedules seems preferable to no premedication, as the risk of premedicating is minimal and there appears to be benefit. Cluster studies generally show low SR rates with H1-AH premedication. While the addition of oral corticosteroids and LTRA may lower SR rates further in cluster visits, the risk of using oral corticosteroids prior to 8 or 9 cluster visits may lead to corticosteroid-related side effects. Controlled cluster AIT trials utilizing inhalant mixtures comparing the safety of premedication to no premedication are limited.

RIT studies into the 1:1 v/v maintenance vial have lower SR rates with combination premedication compared to placebo or no premedication, and mRIT studies into the 1:100 v/v and 1:10 v/v overall have lower SR rates compared to the initial RIT trials. The ideal premedication regimen is unknown, as controlled trials looking at different premedication regimens have not been performed. In RIT and mRIT schedules, it seems logical to utilize a combination premedication regimen compared to oral AH alone. Though the ideal starting time of the premedication regimen has not been studied in a controlled fashion, it seems preferable to start premedication the day before the RIT or mRIT compared to immediately or hours before the RIT; mRIT studies starting 1 or 2 days before[539, 541-543] had generally lower SR rates than those starting 1-2 hours before.[540, 544] Furthermore, continuing the premedication for 2-3 doses post-RIT or post-mRIT may lower the SR risk.[540]

Table 15. Modified rush studies.

Study (# of pts)	Time/stop dose	Premedication; time before start of mRIT	SR[a] rate, % pt; severity when known	Time to maintenance	Post mRIT SR (% pt)
Temino et al, 2013[544] (138 pts)	1-day/5 hr 0.2 mL 1:10 v/v	prednisone 60 mg; 2 hrs cetirizine; 30 min famotidine 40 mg; 30 min	28%; Most grade 1/2 82% after last dose	11 weeks (repeat dose x 3 after mRIT; then 8 wks)	0.45% SR/injection
Cook et al, 2017[540] (72 pts)	1-day 0.1 mL 1:10 v/v	prednisone 50 mg H1/H2/LTRA; All >1 hr before	26%	Not specified	Peak in SR at 2nd post-mRIT injection (0.3 mL 1:10 v/v)
Teachout et al, 2019[543] (231 pts)	1-day 0.2 mL 1:10 v/v	prednisone[b]/H1/H2/ LTRA; 2 days before and day of	10.4%; All grade 1/2	Not specified	Not specified
Fajt et al, 2017[541] (362 pts)	1-day/8 hr 0.4 mL 1:100 v/v	prednisone 40 mg H1/H2/ LTRA; day before and day of	4.7% day of mRIT; 13.6% at any time to maint	16 doses to maintenance	10.2% 73% delayed SR
Chu et al, 2022[539] (peds 34; adults 43)	Same as Fajt et al, 2017[541]	Same as Fajt et al, 2017[541]	Peds 5.8% Adult 9.3% (at any time)	16 doses after mRIT	Not specified
Hajirawala et al,	3 groups: 1%/4%/10 % of	prednisone 20 mg PO BID/H1/H2/LTRA;	1% 0.05 1:10 (n=20;0%)	Not specified	Not specified but 75% of SR were

2023[542] (103 pts)	maintenance (0.05 mL vs 0.2 mL vs 0.5 mL of 1:10 v/v)	2 days before and day of	4% 0.2 1:10 (n=31;12.9%) 10% 0.5 1:10 (n=52;17.3%)		biphasic during mRIT
Lee et al, 2023[532] (74 pts)	1-day; 0.1 mL 1:10 v/v	prednisone 50 mg/H1/H2/LTRA; 60 min	14.86%	14 weeks	Not specified

H1= H1 antihistamine; H2=H2 antihistamine; LTRA=leukotriene receptor antagonist; mRIT, modified rush immunotherapy; Pt, patient; SR, systemic reaction; wks, weeks.
[a]SR grades are based on the WAO SR grading system 2010.[455]
[b]Dose not specified.

Biologics combined with SCIT

73. Recommendation: We suggest the clinician consider using omalizumab, and perhaps other asthma biologics, to improve the safety and tolerability of SCIT, especially in patients at high risk of SRs.

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

The JTF 2011 AIT PP highlighted the evidence to support that pretreatment with omalizumab improves the safety and tolerability of rush SCIT for environmental allergens.[2] Since 2010, there have been three RCTs evaluating the role of omalizumab in SCIT for those with asthma.[525, 545, 546] Two of the trials assessed the benefit of adding omalizumab to HDM SCIT in HDM-driven AR and controlled AA while the third trial evaluated the role of omalizumab combined with SCIT in those with moderate-persistent, uncontrolled AA while on ICS.[525, 545, 546]

Bozek et al.[545] conducted a 3-armed RCT in 52 patients aged 18 years and older with HDM allergy and controlled mild to moderate AA. The study compared three treatment groups: omalizumab alone, SCIT-HDM plus omalizumab, and SCIT-HDM alone. All patients were randomly assigned to the following groups: Group A: omalizumab with placebo; Group B: SCIT-HDM and omalizumab; and Group C: SCIT-HDM with placebo. Omalizumab was administered 4 weeks before SCIT 150 mg (one vial) and a continued dose of 150 mg every 4 weeks for 12 months of SCIT. The main outcomes were evaluating ACQ score, number of asthma exacerbations, and reduction in the daily dose of ICS during 12 months of observation. All 3 treatment groups had improvement in ACQ scores and reduction in asthma exacerbations after 12 months of treatment. There was a statistically significant reduction in daily doses of ICS in both the omalizumab alone group as well as the SCIT-HDM alone group with a greater significant reduction in the SCIT-HDM + omalizumab group. In the omalizumab alone group, ICS dose was decreased from 650 mcg +/- 150 mcg to 500 +/- 50 mcg. In the SCIT-HDM plus omalizumab group, ICS dose was decreased from 550 mcg +/-275 mcg to 375 mcg +/- 75 mcg.[545]

Bozek et al.[546] also conducted a 4-armed RCT study with 82 patients aged 16 years and older with a 24-month observation period. All participants were HDM allergic and had controlled, mild to moderate AA. The study compared the following therapies during 24 months of observation: Group A was omalizumab plus placebo, Group B was SCIT-HDM plus omalizumab, Group C was SCIT-HDM plus placebo, and Group D was placebo plus placebo. Omalizumab 150 mg was administered 4 weeks before SCIT HDM and every 4 weeks for the 24-month study period. The primary outcome was the change in ICS use at 24 months and the number of asthma exacerbations. After 12 and 24 months there was a statistically significant reduction in

ICS dose in Groups A and B with a more robust response in Group B. At 12 months, comparing Group A (omalizumab alone) vs placebo, the reduction in inhaled budesonide was more than 50 mcg at 12 months (p=0.042) and remained significant at 24 months with continued reduction of approximately 50 mcg dose of budesonide (p=0.027). Group B (SCIT-HDM plus omalizumab) compared to placebo demonstrated a reduction of inhaled budesonide of more than 100 mcg at 12 months (p=0.023) and a sustained or increased ICS reduction at 24 months (p=0.008). At 24 months, there was also a significant reduction in asthma exacerbations in Groups A and B compared to Group C and the placebo group (0.42 patient per year vs. 0.39 vs. 0.84 vs. 0.91, respectively; p=0.023).[546]

Massanari et al.[525] designed a 26-week placebo-controlled trial to assess if pretreatment with omalizumab in those with uncontrolled AA would improve tolerance to SCIT. This was a multicenter, parallel-group RDBPC trial which randomized patients to treatment with omalizumab or placebo, after which they received specific SCIT to at least 1 of 3 perennial aeroallergens (cat, dog, and HDM) according to a 4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance therapy. The primary efficacy variable was a SR after SCIT. A total of 248 randomized patients (126 omalizumab, 122 placebo) received at least 1 dose of SCIT and were evaluated for efficacy. Patients receiving omalizumab experienced significantly fewer SRs to SCIT than those receiving placebo and also had fewer respiratory-related (grade 3) SRs (6 vs 24, respectively). Grade 4 reactions were reported in 2 patients in each group. More omalizumab patients were able to reach the target maintenance SCIT dose (110 [87.3%] vs 88 [72.1%], respectively; p=0.004).[525]

In a letter to the editor, 6 pediatric patients with severe asthma were started on rush HDM SCIT after 8 months of omalizumab therapy and control of asthma.[547] These patients achieved maintenance dose of 10 mcg of Der p 1. One patient stopped due to lack of asthma control. After 1 to 4 years, omalizumab was stopped and HDM SCIT was continued with persistent asthma control. The duration of follow up was not specified by the authors.[547]

In a small retrospective study, Valdesioro-Navarrete et al.[548] noted that in those with severe AA and AR, treatment with omalizumab for 1 year prior to starting RIT resulted in better tolerance of treatment along with improvement of AA and AR.

In a retrospective review, Har and Lee[549] noted that 19 SRs occurred in 30 children ages 6 to 18 years with AA receiving SCIT alone (1550 injections), but only 3 SRs occurred in the 29 children who received SCIT plus omalizumab (954 injections).

In 2023, Corren et al.[124] conducted a parallel group, RDBPC trial in patients with cat-induced AR; 121 patients were randomized to receive either intravenous tezepelumab plus cat SCIT, cat SCIT alone, tezepelumab alone, or placebo for 52 weeks, followed by 52 weeks of observation. Maintenance dose of cat AIT was 4000 BAU or maximum tolerated dose. Tezepelumab, 700 mg intravenously, or matched placebo was administered 1 to 3 days before the SCIT to placebo and cat once every 4 weeks through week 24, and then before or on the same day as the SCIT or placebo injection through week 48 (end of dosing). The primary response variable was the TNSS area under the curve (0-1 h) after NAC. Consistent with results from prior trials, this study "demonstrated that SCIT monotherapy was superior to placebo after 1 year of treatment, but this effect was no longer present 1 year after stopping therapy. In contrast, patients receiving the combination of SCIT and tezepelumab demonstrated a significant reduction in peak nasal symptoms 1 year after stopping therapy, indicating partial persistence of tolerance."[124]

Corren et al.[123] also assessed the role of dupilumab in patients with AR to timothy grass pollen. This RDBPC trial consisted of four treatment arms: SCIT to timothy grass plus placebo dupilumab, dupilumab plus SCIT placebo, SCIT plus dupilumab, or placebo for both SCIT and dupilumab. The authors used an NAC as part of the inclusion criteria and identified peak TNSS score after the challenge. Dupilumab 300 mg or placebo was administered subcutaneously (SC) every 2 weeks for a total of 16 weeks, after a 600 mg dupilumab loading dose or placebo on Day 1. Timothy grass-specific SCIT or placebo was administered using a rapidly escalating cluster protocol over 8 weeks, followed by a maintenance regimen for the following 8 weeks. The recommended SCIT target maintenance dose was 4000 BAU, equivalent to approximately 20 mcg Phl p 5. The SCIT treatment protocol consisted of escalating doses of 1 to 3 SCIT injections per weekly study visits for the first 8 weeks and then maintenance SCIT for the next 8 weeks. Another NAC was performed at week 17. The primary endpoint was the percent change from pretreatment baseline in the area under the curve at week 17 for TNSS (0-1 h post peak TNSS), after NAC. Sixteen weeks of SCIT plus dupilumab did not improve TNSS; however, more patients in the SCIT plus dupilumab group reached maintenance therapy and fewer patients required epinephrine treatment.[123] These data indicate that SCIT plus dupilumab is not superior to SCIT alone when utilizing TNSS scores and NAC; however, there may be a benefit to tolerability to SCIT with dupilumab.

Details of AIT, in combination with biologics, and additional mechanistic data were recently reviewed.[550]

Risk of Infections with SCIT

The risk of infections from SCIT prepared following standard guidelines (see Vial preparation section) is extremely low. Based on reporting from the NAISS, between 2018-2023, a physician identified two consecutive local SCIT injection-site infections in a single patient.[509] The reporting physician described both events as cellulitis, and both were treated successfully with oral antibiotics. The prescribing physician suspected bacterial contamination of the vial, prepared with diluent containing phenol. After preparing a new allergen vial, the patient experienced no additional infections. This is the first and only local infection captured by the survey from 2014-2023, representing 55 million SCIT injection visits and almost 5 million SCIT-treated patients. There are no reported systemic infections.[509]

Safety of SLIT

74. Recommendation: We recommend that if the initial dose is tolerated in the office, remaining SLIT doses can safely be self-administered at home.

Strength of Recommendation: Strong

Certainty of Evidence: High

In a review of 66 SLIT studies conducted outside of the US, including 4,378 patients, SRs occurred in 0.056% of doses.[551] These studies reported 14 probable treatment-related serious adverse events, including 7 asthma exacerbations, abdominal pain, vomiting, severe uvular edema and urticaria.[551]

Most US SLIT studies have reported no SRs, although two have reported SRs.[357, 383, 413, 414, 425, 552-555] In a recent summary of 29 SLIT-T trials, epinephrine was administered in 35 subjects; 25 were receiving active treatment with SLIT (vs placebo), and 16 administrations were for SLIT treatment-related events.[556] These authors calculated that 0.2% of subjects (16/8,152) received

epinephrine for SLIT-related events, and that none of the events were considered serious or compromised the airway.[556] No fatalities or near-fatal reactions were reported.

A recent analysis using strict criteria were applied to a pooled data set of all subjects from 48 timothy grass, ragweed, HDM, and tree SLIT-T trials (SLIT-T, N = 8200; placebo, N = 7033).[557] Using these standardized criteria and subsequent medical review, 8 anaphylaxis cases were identified; 3 were considered treatment-related, resulting in a proportion of anaphylaxis cases/subject of 0.02% (2 of 8200) with SLIT-T and 0.01% (1 of 7033) with placebo.[557]

Surveillance data for off-label SLIT-L (non-standardized and generally multi-allergen) in the US identified 45 SRs in 3343 patients (1.4% of patients) between 2012 and 2013, including 9 grade 2 SRs (0.3% of patients) and 1 grade 3 SR (0.03% of patients).[451]

There are case reports from outside the US of at least 11 severe SRs from SLIT-L and SLIT-T.[558-566] Risk factors identified in these reports included newly started SLIT (first dose), overdose, multi-allergen SLIT, prior SR to SCIT, or asthma exacerbations with SCIT. Two studies specifically designed to compare the safety of multi-allergen to single allergen SLIT found no significant differences in severity or frequency of side effects.[567, 568]

It is worth noting that patients with uncontrolled asthma are likely at higher risk for severe adverse reactions from SLIT, as this has been a risk factor for severe reactions to SCIT.[454, 461, 462] Data on persistent or uncontrolled asthma using SLIT is limited. One study involving 43 patients on HDM SLIT-L involving 63% participants with asthma reported 7 SRs in 11.6% of patients, all of which were grade 2 or 3 SRs.[565] In contrast, a study of HDM SLIT-T in 834 adults with asthma that was not well controlled by ICS or ICS-LABA did not report any SRs and only one possible treatment-related, moderate asthma exacerbation.[321]

An action plan for severe LRs and SRs to SLIT has previously been published (see Appendix 4).[569]

75. Recommendation: We suggest the use of a standardized grading system for both local and systemic reactions to SLIT.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

There has been no change since the JTF 2017 SLIT PP update regarding grading for SLIT LARs.[3] There has been a change since the JTF 2017 SLIT PP regarding grading for SLIT SRs.[3] Prior to 2017, there was no formal grading system for SLIT SRs, which are rare (see above). 2024 updates to the WAO grading system for SRs now include reporting for SLIT.[570] Authors agree with the JTF 2017 SLIT PP[3] in that it remains challenging to clarify SRs versus LRs in SLIT, which necessitates utilizing the 2013 WAO grading system[571] for all SLIT AEs except those expressly identified as SRs.

Most patients tolerate SLIT. Adverse events can occur, with mild LARs near the site of administration reported in 7–95% of studied patients.[572, 573] There is a similar frequency of reported LARs comparing pollen and HDM studies. Reactions in the mouth, throat, ear, gastrointestinal (GI) system, or even mild respiratory symptoms, such as cough, are considered LARs of SLIT.[565, 572-576] Oral itching and throat irritation are the most common AEs reported in clinical trials and occurred in almost half of patients in whom investigators inquired about

specific AEs.[577] In the same study, less than 20% (placebo-subtracted frequency) of SLIT patients spontaneously complained about oral or throat discomfort.[577]

When considering the impact of undisclosed LRs to SLIT, there is a high risk of self-discontinuation and associated lost opportunity cost for the patient if AEs are not discussed with the treating specialist, categorized, and managed. On average, half of SLIT patients discontinue treatment before completing a full three-year treatment course (ranges from 7–97%).[578] If some of those discontinuations occur due to uncomfortable and undisclosed AEs, proactively addressing and preventing LARs may support patients in adhering to a full treatment course.

Characterizing LARs first requires localizing symptoms in body areas considered contiguous with the sublingual area (**Table 16**). For example, while diarrhea would be considered a SR with SCIT, it is considered a local symptom or AE with SLIT due to the lower GI tract being contiguous with the upper GI tract and mouth. Another example of a SLIT LAR that would be considered a SCIT SR is mild cough. After classifying a reaction as local, further documenting if symptoms were bothersome, if they required treatment, or if SLIT was subsequently discontinued are important factors for determining severity of the LR. Pre-2024 SR or anaphylaxis grading systems did not appropriately address SLIT LARs. For example, the WAO Systemic Reaction Grading System was designed for grading reactions a specialist determines to be systemic (Appendix 5).[455, 579] Since there is some overlap of certain symptoms being considered local for one form of AIT, yet being considered systemic for another, the SR grading system was felt to be inadequate for classifying LRs. Because of this, the WAO Grading System for SLIT Local AEs was developed as a specific grading system for SLIT AEs to focus on the unique AEs characterized as “local” that would in other cases be deemed systemic (**Table 16** and **Table 17**).[571] The scale is a comprehensive tool that takes into account symptom severity, if treatment was required, and if SLIT was discontinued as a result of the adverse reaction. Selecting the appropriate grading system for LARs versus SRs allows for more detailed tracking of SLIT reactions,[580] which can aid in identifying reasons for discontinuing SLIT and understanding how to achieve better adherence to treatment**.** For research purposes, there has been a lack of use of standardized grading scales for LARs, which makes comparing safety results across studies difficult.[575]

Table 16. Description of local side effects related to SLIT (MedDRA 14.1). Reproduced from Passalacqua et al, 2013.[571]

	Local side effect	MedDRA preferred term	MedDRA code	MedDRA low-level term
Mouth/ear	Altered taste perception	Dysgeusia	10013911	Taste alteration
	Itching of lips	Oral pruritus	10052894	Itching of mouth
	Swelling of lips	Swelling of lips	10024570	Swelling of lips
	Itching of oral mucosa	Oral pruritus	10052894	Itching of mouth
	Swelling of oral mucosa	Mucosal edema	10030111	Mucosal swelling
	Itching of ears	Ear pruritus	10052138	Ear pruritus
	Swelling of tongue	Swollen tongue	10042727	Swelling of tongue, nonspecific
	Glossodynia	Glossodynia	10018388	Glossodynia
	Mouth ulcer	Mouth ulceration	10028034	Mouth ulcer
	Tongue ulcer	Tongue ulceration	10043991	Tongue ulceration
	Throat irritation	Throat irritation	10043521	Throat irritation
	Uvular edema	Pharyngeal edema	10034829	Pharyngeal edema
Upper	Nausea	Nausea	10028813	Nausea
gastrointestinal	Stomach ache	Abdominal pain, upper	10000087	Stomach ache
	Vomiting	Vomiting	10047700	Vomiting
Lower	Abdominal pain	Abdominal pain	10000081	Abdominal pain
gastrointestinal	Diarrhea	Diarrhea	10012735	Diarrhea

Table 17. Grading system for SLIT local AEs. Reproduced from Passalacqua et al, 2013.[571]

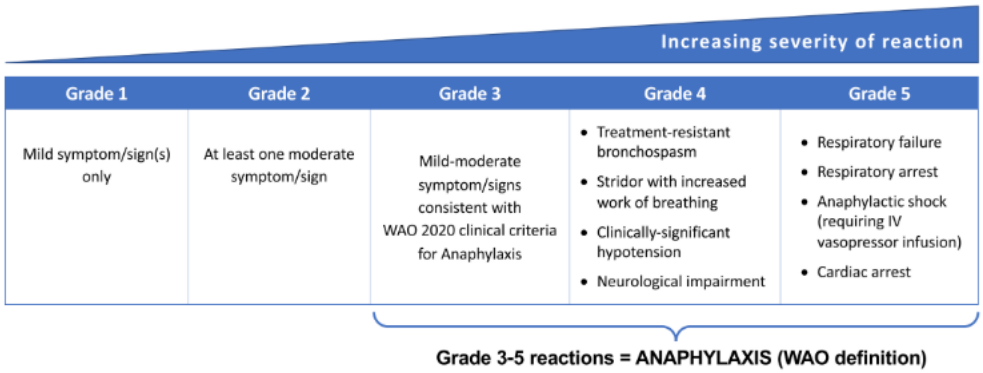
Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	• Not troublesome AND • No symptomatic treatment required AND • No discontinuation of SLIT because of local side effects	• Troublesome OR • Requires symptomatic treatment AND • No discontinuation of SLIT because of local side effects	• Grade 2 AND • SLIT discontinued because of local side effects	Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician.

Each local AE can be early (<30 minutes) or delayed.

Systemic reactions to SLIT are rare, reported in as few as 0.02% of 8,200 patients in an extensive study reviewing SLIT clinical trial anaphylaxis rates (0.01% reported in placebo groups).[557] These SRs are generally not life-threatening and usually do not require epinephrine for treatment.[565, 572, 574, 575] The review of clinical trial data identified an epinephrine administration rate of 0.2% of 8,200 clinical trial participants.[557]

Due to the paucity of SRs or anaphylaxis to SLIT, a SLIT-specific grading scale for SRs has not been developed. Historically it has been difficult to compare safety between AIT trials due to the lack of a common AE grading scale independent of route of administration or allergen treated (aeroallergen, venom, or food). Despite originally being designed for SCIT AEs, there was a trend in using the 2010 WAO SR grading scale for grading SLIT SRs, which prompted an update in 2017 to allow for more inclusive grading irrespective of the form of immunotherapy or trigger.[455, 579] These scales were not being used in food immunotherapy trials, as the Consortium for Food Allergy Research developed a separate adverse reaction to food immunotherapy scale, that was modified in 2022 in a similar format as the WAO scale.[581] In 2024, the WAO updated their SR grading scale to be inclusive of systemic AEs from SCIT, SLIT, and OIT (**Figure 1**).[570] The complexity of this scale may limit its use in clinical practice; however, the use of a common systemic AE/SR grading scale for SLIT, SCIT, and OIT, regardless of allergen treated, will aid in comparing AIT clinical trials and clinical practice across the board.

Figure 1. Concept underlying the WAO grading system. This grading scale is intended as a systemic reaction grading scale for AIT, including SCIT, SLIT, and OIT. Reproduced from Turner et al, 2024.[570]



Treating SLIT Reactions

76. Recommendation: We suggest that patients be given instructions using a symptom-based approach to recognize and treat SLIT reactions.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

The JTF 2017 SLIT PP update gave general advice regarding SLIT reactions.[3] The prescribing specialist was advised to provide patients with specific written instructions for managing AEs at home and for when to withhold doses. Specific instructions were left to the specialist's discretion. There is no SLIT-specific evidence related to treating SLIT AEs.

Most SLIT LRs are not bothersome enough to treat. Since most SLIT reactions are local to the mouth, throat, and GI system, treatment of those symptoms is symptom-based. Local mouth reactions to SLIT like itch, tingling, and swelling can be treated with oral AH and an ice cube held in the mouth. Systemic corticosteroid treatment is not generally indicated but is a consideration for persistent bothersome symptoms (*Expert opinion).* Rare SRs should be treated as with SRs to SCIT, including epinephrine with or without AH. The AAAAI's SLIT Local Reaction and Systemic Reaction Emergency Plan template is an example of a written instruction plan that can be personalized and provided to patients (Appendix 4).

77. Recommendation: We suggest against the routine use of premedications, such as AH, prior to each dose of SLIT-T to decrease the risk of LRs.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

There are no formal clinical trial studies that have evaluated whether premedications are beneficial for tolerance of SLIT therapy, and it is not a standard recommendation for pretreatment. LARs may occur in some patients in the first few weeks of starting SLIT. Given that this can lead to treatment discontinuation, oral AH have occasionally been given either as pretreatment or for the treatment of these LARs. There are no clinical studies that have formally evaluated whether AH are efficacious. There was a case report published in Canada describing the successful use of rupatadine to treat/mitigate SLIT-T LARs.[582] In this series, pretreatment with standard second-generation H1-AH was not sufficient to prevent bothersome LAR, resulting in patient discontinuation of SLIT-T. Rupatadine, an H1-AH with platelet activating factor activity inhibition that is not currently available for use in the US, was trialed with successful restart and tolerance of SLIT-T with minimal local symptoms.[582]

EoE and SLIT

78. Recommendation: We suggest screening for symptoms of EoE prior to starting SLIT, and monitoring patients receiving SLIT for symptoms suggestive of EoE.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

79. Recommendation: We recommend withholding SLIT in patients with suspected EoE and discontinuing SLIT in patients with confirmed EoE.
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

EoE is a potential risk when taking SLIT-T or SLIT-L. EoE has been reported more often in the food SLIT-L literature, but there have been some limited case reports of it occurring with aeroallergen SLIT-Ts and SLIT-Ls as well. A history of EoE is considered a contraindication to beginning SLIT-T in all the FDA package inserts;[313, 340, 583, 584] therefore, SLIT-Ts are not recommended if there is a preexisting history of EoE. Patients should be provided information on symptoms that may develop after starting SLIT, including dysphagia, chest discomfort upon eating, food impaction, and abdominal pain after starting SLIT. If these symptoms develop, patients should discontinue SLIT and notify the specialist for further evaluation, including consideration of referral to a gastroenterologist. There is no currently available, quality evidence to support starting or restarting SLIT after EoE has been treated and controlled; of the 3 cases where SLIT was started or reintroduced in symptomatically controlled EoE, all 3 cases had a relapse of symptoms.[286, 585, 586]

A total of 17 cases were identified pertaining to pollen SLIT and the development of EoE (Appendix 6).[286, 585, 587-596] Sixteen were published from outside the US. See Appendix 6 for a description of the cases, including products used. There was no specific pattern as to the type of aeroallergen SLIT that was associated with EoE, as various grasses, trees (cedar, hazel, birch, olive, eastern cottonwood, mesquite, orange), HDM, and mold/fungal SLIT were all associated with the development of EoE. There was also no pattern as to whether the allergen SLIT was in the form of SLIT-T versus SLIT-L.

After confirmation of EoE via biopsy (15 or more eosinophils per high power field), various treatment strategies were attempted, including proton pump inhibitors, swallowed topical corticosteroids, transition from SLIT-swallow to SLIT-spit method, decrease in dose of SLIT, and discontinuation of SLIT. Thirteen of 17 (76%) of the cases reported that discontinuation of SLIT was necessary for the resolution of symptoms, usually confirmed by a negative esophageal endoscopy (EGD) with biopsy. Proton pump inhibitor therapy was not successful in any of the cases.[585, 587, 588, 590-592, 595] Swallowed corticosteroids were trialed in three of the cases.[286, 590, 593] There were 5 cases from Japan where modifying the administration technique from SLIT-swallow to SLIT-spit was trialed.[592, 595, 596] Of these 5 cases, 4 cases resulted in resolution of symptoms, with a negative follow-up biopsy confirmed in 3 of the 4 cases. In the remaining case, there was no improvement in symptoms despite switching from SLIT-swallow to SLIT-spit method, ultimately resulting in the discontinuation of SLIT. Given there is limited current evidence to support this strategy at this time, in agreement with SLIT-T package inserts, we recommend that SLIT be discontinued if EoE is confirmed via EGD, regardless of whether symptoms are controlled, until further studies are performed on this method to evaluate clinical efficacy.

In terms of onset of symptoms upon starting SLIT, 59% of the cases (10/17) occurred within weeks of starting SLIT.[286, 585, 587-590, 594-596] Of those 10 patients, there was a patient who had received and tolerated HDM SLIT for 1 year, but subsequently developed symptoms within 4 weeks of beginning Grazax (Timothy grass, standardized, Spain),[585] which is mentioned in the postmarketing report in the package insert.[597] The remaining 7 of 17 patients developed EoE after an average of 13.6 months of SLIT.[592, 593]

There is now one case of EoE reported in the literature in 2025, utilizing a US product (Grastek), noted in the postmarketing experience of the package insert.[583, 591] It describes a 14-year old male with known EoE (diagnosed Jan 2022 by EGD with biopsy showing 31 eosinophils/high powered field [hpf]). He was treated with omeprazole 20 mg twice daily with symptomatic improvement. Repeat EGD in July 2022 revealed eosinophils of 23/hpf. Then, in August of

2023, the patient developed symptoms of generalized abdominal pain and nausea with EGD showing 45 eosinophils/hpf. It was discovered that the patient had been started on Grastek in June of 2023, with onset of symptoms within a month of SLIT-T. Discontinuation of the SLIT-T and continuation of proton pump inhibitors twice-daily resulted in resolution of symptoms and repeat EGD biopsy showed eosinophils of 1-2/hpf in December of 2023.

Cofactors as risk factors for SLIT

80. Recommendation: We suggest that upper respiratory tract infections are not a reason to withhold SLIT-T administration.
Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

There is no convincing evidence to withhold SLIT in the setting of an upper respiratory viral infection. Given this, there is consideration to follow similar guidelines as with SCIT where the decision to recommend to patients to withhold SLIT in the setting of a viral infection can be at the discretion of the specialist, given it may be more difficult to distinguish whether symptoms are due to a SR or local AE/LAR from SLIT treatment versus the viral infection.

A web-based retrospective European survey study published in 2021 evaluated the safety of the administration of AIT during the COVID-19 pandemic.[481] In this survey, most participants followed the EAACI recommendation to avoid administration of AIT during an active COVID infection. There were 16 physicians who did report continuing AIT (SLIT or SCIT), of which 14 of the 16 reported continuing SLIT despite (early) symptoms of COVID-19 and/or a positive test result. No AEs were reported in the SLIT group.[481]

81. Recommendation: We suggest exercise need not be avoided after SLIT-T administration.
Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

There is no formal recommendation in the prescribing information for the FDA-approved SLIT-Ts to withhold administration before or after exercise. This differs from SCIT, where there is a suggestion to withhold exercise in proximity to the time of SCIT (see Recommendation 63).[598] There is one study published in 2005, that specifically looked at 11 patients being treated with a pollen SLIT-L.[599] Upon reaching maintenance dose, the patients underwent an exercise test. Various parameters were measured and there was no increase in AEs, including decrease in FEV_1 and/or blood pressure or increase in blood tryptase level after exercise. The authors concluded that there was no reason to advise against exercise when receiving SLIT for aeroallergens.[599]

82. Recommendation: We suggest that it is reasonable to withhold SLIT during acute GI infections.
Strength of Recommendation: Conditional
Certainty of Evidence: Very Low

Although the risk with SLIT-T during an acute GI infection is not apparent with scant data, it is advised in the package inserts of FDA approved SLIT-T products[313, 340, 583, 584] and the JTF 2017 SLIT PP update[3] to discontinue use if experiencing symptoms of severe stomach cramps, abdominal pain, vomiting, and diarrhea. Therefore, to avoid potential confusion of associating

the symptoms of an acute GI infection with an AE from the SLIT-T, it is advantageous to hold SLIT-T during an acute infection.

83. Recommendation: We suggest against administering SLIT in the presence of oral mucosal ulcerations or dental extractions.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

The recommendation to temporarily stop treatment with SLIT if oral inflammation lesions are present is largely derived from expert opinion and theoretical risk, discussed in the package inserts of the FDA-approved SLIT-Ts,[313, 340, 583, 584] JTF 2017 SLIT PP update,[3] and European AIT guidelines.[69] Oral inflammatory lesions refer to patients who have recently undergone oral surgery or dental extraction, and conditions such as oral ulcers, thrush, or oral lichen planus. Studies were not identified that specifically investigated this risk, and there are no known cases of adverse outcomes. The recommendations from the JTF 2017 SLIT PP update are shown in **Table 18**.[3]

Table 18. Recommendations regarding SLIT and oral health.[3]

After professional dental cleaning	It is suggested to resume SLIT 24 hours after a dental cleaning procedure
After brushing and flossing of teeth	No caution is usually advised for brushing teeth. Because flossing and gum hygiene can be associated with gum bleeding, it is recommended that the patient delay the administration of SLIT for a few hours after the cessation of gum bleeding.
After dental extraction and gum surgery	The FDA advises waiting for complete healing. Although adequate healing will usually occur after 10-14 days (e.g., when stiches are often removed), it is advised to discuss with the dentist when adequate healing will occur.
Aphthous stomatitis, herpes, oral lichen planus	The FDA advises waiting for complete healing. Recovery can vary from days to longer than 1 week. If longer than 2 weeks, return to office for examinations and SLIT tablet administration under supervision

84. Recommendation: We suggest that beta-blockers or ACEi/ARBs may be used during SLIT following a shared decision-making discussion.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

There is no evidence for an increased risk of anaphylaxis or an increase in severity of reactions in patients treated with ACEi, ARBs, or beta-blockers, while receiving aeroallergen SLIT, although caution is mentioned in the prescribing information of all SLIT monographs. The potential concern with SLIT is theoretical, based on extrapolated data from SCIT, of which there is conflicting evidence. A comprehensive review of the recent data involving ACEi and beta-blockers in SCIT can be found in Recommendation 67 in this PP. Previously considered to be contraindications to SCIT, the recommendation has changed to a process of shared decision-making, weighing the risks/benefits of stopping these often-important medications with the patient's desire for the AIT treatment. This is also discussed in the JTF 2023 Anaphylaxis PP update.[39]

The JTF 2017 SLIT PP update previously suggested that an ACEi does not need to be stopped if a patient were to initiate SLIT, given the lack of evidence for risk in the SLIT literature and the conflicting evidence of potential risk of a more severe or unresponsive anaphylaxis occurring in the venom SCIT-treated population.[3] For patients treated with beta-blockers, despite the risk that a patient may be less responsive to epinephrine when treating anaphylaxis, the risk of anaphylaxis is exceedingly low with SLIT. Thus, the specialist should document shared decision-making discussions with patients pursuing SLIT, taking into account the individualized risk-benefit ratio, the value of beta-blocker or angiotensin pathway inhibition, the alternative therapeutic options, and patient preferences.

85. Recommendation: We recommend against SLIT administration in patients with active asthma exacerbations.
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

In the clinical trial studies for SLIT, patients with severe, uncontrolled or unstable asthma were excluded. This is largely based on concern from data derived from the SCIT literature, where it has been noted that the severe, uncontrolled asthma population comprise a significant portion of patients with near-fatal and fatal reactions to SCIT. Thus, there was concern that with SLIT, there was also an increased risk for systemic adverse reactions in severe, uncontrolled asthmatics. Therefore, we recommend against SLIT administration in patients with active asthma exacerbations.

86. Recommendation: We suggest HDM SLIT-Ts are an option for patients with mild to moderate partially controlled asthma (not during an active exacerbation).
Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

In patients with mild to moderate uncontrolled asthma, the Global Initiative for Asthma (GINA) guidelines recommend add-on HDM SLIT for asthma (HDM-related) adult patients who are not controlled with pharmacotherapy, who are on low- to high-dose ICS, as long as the FEV_1 is >70% predicted.[600] The EAACI guidelines[407] suggest consideration of SLIT on a case-by-case basis in those with partially controlled asthma, after weighing the risks and benefits, based on the limited reports on administering HDM SLIT in partially controlled asthma patients.[321] The study by Virchow et al.[321] evaluated the efficacy and AEs of HDM SLIT-T versus placebo for patients who had asthma that became uncontrolled, employing an ICS reduction period. This was a RDBPC trial performed across 109 European trial sites that included 834 adults with HDM AA not well controlled by ICS or combination products, and with HDM AR. Patients were receiving an ICS equivalent to budesonide of 400-1200 mcg and had an ACQ score above 1.5 (not-well-controlled). With the addition of HDM SLIT-T, there was a reduction in the time to first moderate or severe asthma exacerbation. Reviewing the AEs reported in this study, there were more AEs in the HDM SLIT group compared with placebo, as expected, but the majority of all adverse reactions were mild. Of note, no anaphylaxis or severe SRs occurred, no AEs required epinephrine, no deaths were reported, and only one LAR with laryngeal edema but without airway obstruction or dyspnea in the 6 SQ-HDM group.[321] Thus, this study provides safety evidence for the use of HDM SLIT in not-well-controlled asthma, as well as benefit in the delayed time to first exacerbation, although further study is warranted.

There was a post-hoc analysis study published in 2014 that looked at how HDM SLIT-T treatment affected various asthma endpoints in a subgroup of partially controlled asthma patients.[324] The original study was an ALK-funded phase II/III RDBPC trial, where patients with

mild-moderate HDM AA were randomized to various doses of SQ-HDM (1, 3, 6) or placebo daily. There was a smaller subgroup of patients analyzed (N=108, out of 604 patients) who were on a daily ICS dose of 400-800 mcg of budesonide and had an ACQ score of 1-1.5, which corresponded to partially controlled asthma. Looking at various endpoints (reduction in ICS use, AQLQ, and ACQ), the study suggested that there was a significantly higher benefit in asthma control and QoL with treatment using SQ-HDM SLIT-T in this subgroup of partially controlled asthma, compared to those with better control of their asthma. The difference in change from baseline daily ICS use between the placebo and 6 SQ-HDM group was 327 mcg per day (95% CI: 182, 471; p<0.0001). Seventeen subjects (59%) in the 6 SQ-HDM group were able to reduce ICS use by 75-100% without impairment in asthma control. Thirteen subjects (45%) withdrew ICS use completely. Only 1 subject (4%) in the placebo group was able to withdraw ICS use. None of the subjects in the 6 SQ-HDM group needed to increase their ICS use during the trial, compared to 5 subjects (19%) in the placebo group. There was also a treatment difference in the AQLQ of 0.52 (p=0.010) in the 6 SQ-HDM group compared to placebo, which was primarily related to the symptom domain and to the activity limitation domain. The overall ACQ score was also statistically significantly lower in the 6 SQ-HDM group at the end of the trial ICS stable period compared to the placebo group (difference -0,41, p=0.0002), suggesting better asthma control after treatment with the 6 SQ-HDM. In terms of adverse safety events, this group was similar in number, severity, and causality of AEs to the full analysis set, with the exception of a higher incidence of asthma being reported as an AE in the subgroup (11 subjects, 10%) compared with the full analysis set (18 subject, 3%).[324]

There was a RDBPC study by Tanaka et al.[320] that evaluated the efficacy and safety of SQ-HDM SLIT-T at doses of 10,000 or 20,000 JAU (equivalent to 12 SQ-HDM) or placebo, in 826 Japanese adults, aged 18-64 years old, with partially controlled AA (ACQ 1 - 1.5) despite being on a daily ICS equivalent of 200 to 400 mcg of fluticasone propionate. The trial design included an ICS reduction phase (50% to 100%) over 6 months. No significant difference in time to first asthma exacerbation (primary endpoint), as well as other secondary endpoints including symptom score, was found. Reviewing the AEs, there were no serious AEs in the active group, including no reports of anaphylaxis.[320]

There was a small study from Japan published in 2022 regarding the efficacy and safety of adding 6 SQ-HDM SLIT-T for 48-weeks to patients with not well-controlled asthma with high dose ICS-LABA or LTRA (ACQ-5 >1.5), already on dupilumab, in a real-life world setting.[601] The addition of SLIT resulted in significant improvement in asthma control scores (MCID of >0.5 points), as well as patient-reported end points. Due to the low annualized rate of exacerbations in the year prior to the study, as well as during the 48-week treatment period, evaluating the asthma exacerbations in this study was unable to be completed. From a safety perspective, there were no serious AEs or anaphylaxis reported in this patient population with asthma that was not well-controlled.[601]

There are also studies that include well-controlled, seasonal asthma, with no significant SLIT AEs reported. For example, in one of the large ragweed SLIT-T trials, 43% of the study population of 1,025 children aged 5-17 years old with ragweed pollen-induced AR/C, had controlled asthma.[79] There were no significant AEs; no deaths or events of anaphylaxis, no SLIT-T-related local swelling of the mouth or throat, nor SLIT-T-related asthma events reported.[79]

In summary, based on the above, we suggest that HDM SLIT-T for HDM-induced rhinitis can be carefully considered on a case-by-case basis in patients with partially controlled, HDM IgE-dependent AA. This has not been evaluated with other SLIT products, therefore this

recommendation cannot be applied to other aeroallergen SLIT products. It is important to emphasize that HDM SLIT-T is not approved for asthma, and therefore the decision to initiate HDM SLIT-T in a patient who has partially controlled HDM IgE-dependent AA would be for the indication of HDM-induced AR only.

Preparation of allergen extract vial sets

87. Recommendation: We recommend adherence to the standards defined in USP<797>, Section 21—the Allergy Exception, when compounding allergenic extract prescription sets.

Strength of Recommendation: Strong

Certainty of Evidence: High

The U.S. Federal Drug Administration (FDA) defines an allergen extract prescription set as a "vial or set of vials of premixed licensed standardized and non-standardized allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent prepared by a licensed physician for an individual patient according to instructions from a valid prescription (including a chart order) in a health care setting."[602] The FDA requires that the prescription be part of the patient's medical record and that the vials are prepared, labeled, and documented in accordance with U.S. Pharmacopeia <797> Pharmaceutical Compounding—Sterile Preparations, Sections 21—*the Allergy* Exception, which became effective 11.1.23.[603] USP <797>, Section 21 sets standards for the compounding of allergenic extract prescription sets, which include: 1) personnel qualifications; 2) personnel hygiene and garbing; 3) requirement for facilities where compounding is performed; 4) cleaning and disinfecting; 5) establishing by use dates; 6) labeling of extract prescription sets; 7) shipping and transporting; and 8) documentation for compounding. Furthermore, the following procedures are outlined: 1) gloved fingertip and thumb sampling; 2) media-fill testing; 3) hand washing; and 4) compounding records. While access to the full USP<797>, including Section 21 requires a USP subscription to access, the key changes and implementation details for compounding allergenic extracts are available at the ACAAI website (https://college.acaai.org/2023-usp-797-implementation-nov-1/) and the AAAAI website (https://education.aaaai.org/sites/default/files/media/2023-05/Section%2021%20Allergen%20Extracts.pdf). If requirements outlined in USP <797>, Section 21 are met, the more comprehensive requirements for compounding sterile preparations outlined in the remainder of USP <797> do not apply to preparation of allergen extract treatment sets.

The scientific background, supporting evidence, and methods used to determine allergen extract composition, potency, cross-reactivity, proteolytic enzyme activity, sterility, and safety of allergen extracts have been thoroughly reviewed in the JTF 2011 AIT PP.[2] In addition to fulfilling the competency requirements specified in USP <797>, Section 21, compounding personnel should have a basic working knowledge of aerobiology cross-reactivity principles; types and composition of aeroallergen extracts; allergen extract vial prescriptions; extract mixing; and vial dilution, reconstitution, labeling, and maintenance of documentation for all compounding procedures.

The AAAAI and the ACAAI have readily available guidelines and toolkits on the development of allergen extract vials within the office. The workgroup and JTFPP refer the reader to the respective member section of these websites for detailed information regarding allergen extra-vial preparation. The following summary describes the resources that are available as of 2026.

On the AAAAI member website, within the practice tools section, on the "Immunotherapy Forms" page, (https://www.aaaai.org/practice-management/practice-tools/immunotherapy-forms) there is a link to a downloadable referenced 30-page PDF guideline on allergen extract preparation, last updated in 2023, titled "Chapter 9. Allergen-Immunotherapy-Extract-Preparation-for-Aeroallergens and Venom". In addition to discussing the compounding standards required by USP <797>, Section 21, this guideline includes a full description of extract formulations,

diluents, stability, and storage; the development of allergen extract vial prescriptions (with examples); determination of maintenance dose; preparation of individual patient allergen vial treatment sets; color-coding and labeling of extract vials; and by-use date labeling. In addition to inhalant allergens, the guideline has a section on stinging-insect allergen extracts. It also includes useful appendices which include forms for 1) documenting initial and ongoing competency assessment-allergen extract compounding; 2) determining effective dose range for allergen extracts; and 3) sample forms for compounding stock extract volumes for 5- and 10-ml vials. This AAAAI resource page also provides a link to a list of media-fill test vendors (see URL link provided above).

The ACAAI member website also had an extensive website toolkit on allergen extract mixing (https://college.acaai.org/toolkits/allergen-extract-mixing-toolkit/). In addition to the summary of USP<797>, Section 21, this 44-page 2025 update toolkit provides resources/forms for developing the allergen extract prescription form; a checklist for AIT renewal; clinical indications for AIT and for AIT beyond 3 years; complaint/AE documentation form; AIT consent form; AIT label requirements; AIT mixing log; primary engineering control hood certification; and a refrigerator temperature log (see URL link provided above).

Some specialists may prefer not to manually calculate the extract volume to add when compounding allergen extract vials, instead opting to use a dosing guide that provides a predetermined extract volume and diluent to add for minimal, moderate, or maximum potency of the included allergens.[604, 605] Extract manufacturers may, upon an individual specialist's request, provide resources for compounding allergen extract vials, although these are not available on their websites for all professionals to access.

While the minimal requirements for extract vial labeling are provided by USP <796>, Section 21, the specialist may want to consider some additional elements (**Table 19**).

Table 19. Allergen vial label components.

Components	Individual allergy extract USP vial <797>, Section 21 requirements	Extended labeling of allergy extract vial suggestions	Example
Patient's name	X	X	Mary Wheeze
Date of birth		X	06.11.65
Type and fractional dilution and corresponding vial number	X	X	A Vial # 3 (Blue) 1:100 v/v
Concentration in v/v		X	1:100 v/v
Allergens included by category		X	T, G, W
Color code		X	Blue
Vial letter in vial set		X	A Vial
Vial number (potency)	X	X	Vial # 3
Date prepared		X	Made: 6/1/23
By-use date	X	X	Exp. Date: 12/10/23
Storage conditions	X	X	Store at 4-8 °C (refrigerator)
Practice name		X	

Practice phone number		X	

T, trees; G, grass; W, weeds.

The remainder of this section will emphasize new scientific information since the JTF 2011 AIT PP update,[2] respond to frequently asked questions, and reinforce some important clinical recommendations regarding allergy extract vial preparation, storage, and administration.

88. Recommendation: We suggest that the specialist should use standardized allergen extracts, when available, and follow the maintenance dosing recommendations for each allergen as specified in the JTF 2011 AIT PP.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Since the publication of the last JTF AIT PP in 2011,[2] there are no additional dose-response studies using the current standardized and nonstandardized US commercial extracts. The dose and safety studies since the JTF 2011 AIT PP[2] have been performed on modified allergen extracts, with a larger body of literature focused on HDM-extracts of different formulations, including glutaraldehyde polymerized allergen extract, tyrosine-adsorbed HDM extract, high-dose HDM allergoid (Acaroid®), none of which are available in the US. Thus, the specifics will not be discussed here.[151, 606-610] Information addressing the historical dose-response studies can be reviewed in the JTF 2011 AIT PP.[2] The table providing the basis for the extract dosing recommendations in the JTF 2011 AIT PP[2] is included in this document for reference (**Table 20**).

For the nonstandardized extracts, there are no established criteria for biologic potency nor dose-response studies. When these nonstandardized extract potencies have been evaluated, there is wide variability in allergen content, and thus, these products should not be considered equipotent. Dua et al.[611] published a small study in 2021 that compared the weight per volume and PNU concentrations for birch, ragweed, dog, and Alternaria, using extracts commercially available in the US and Canada. The study supported the substantial variability seen in prior studies. The authors suggested that dosing nonstandardized extracts closer to 1:200 w/v, rather than 1:100 w/v, may be safer given the variability they found in extract potency.

For cockroach and mold/fungi extracts, which are nonstandardized, there remains insufficient quality evidence regarding proper target dosing to achieve efficacy, other than to administer glycerinated extracts at the highest tolerated dose. As outlined thoroughly in the efficacy section on molds/fungi extracts, there is insufficient evidence to recommend for or against SCIT with mold/fungi extracts. Most of the literature on mold immunotherapy has been focused on *Alternaria*, with only 2 controlled studies on *Cladosporium*. The studies unfortunately lacked uniformity, were underpowered, and used widely variable dosing.[612] And the literature published since the last parameter have used different formulations of *Alternaria*, including depot formulations and purified isoforms, which are not available in the US, making it difficult to make any firm dosing recommendations.[185, 613] There have been limited studies on the nonstandardized cockroach extract since the JTF 2011 AIT PP. The main study was a SCIT RDBPC trial conducted by Zoratti et al.,[614] in which nonstandardized glycerinated German cockroach extract was utilized to see if cockroach SCIT for one year would be beneficial for TNSS after NAC in children with mild-moderate AA and AR in urban sites. Findings demonstrated that cockroach SCIT only increased cockroach-specific IgG4 levels but did not significantly alter NAC-induced TNSS responses.

For dog extract, the prior recommendation has been to achieve 15 micrograms of Can f 1 for a probable effective dose of immunotherapy.[2] Recently, the non-standardized acetone-precipitated dog extract (1:100 w/v) from the manufacturer Hollister-Stier was discontinued and replaced with ultra-filtered (UF) dog extract (1:650 w/v). It was demonstrated in a small study to have 35 times more Can f 1 major allergen compared to conventional dog extract.[210] The manufacturer has recommended a one-to-one conversion of the AP dog to the UF dog extract to achieve the maintenance dose of 15 mcg Can f 1, which translates to 1 ml of UF dog in a 5 ml vial at a 0.50 ml injection dose, although the actual Can f 1 content is not formally reported. Additional details concerning this can be found in Recommendation 17.

Table 20. Effective dose range for US-licensed allergen extracts.

Probable effective dose range for US licensed allergen extracts[i]			**Math-free volumes to achieve effective dose range**		
Allergen extract	**Major allergens**	**Probable effective dose range or target AIT dose ranges**	**Concentrate**	**Minimum extract volume[a] in 5 ml maintenance vial with 0.5 ml 1:1 v/v injection**	**Maximum extract volume[a] in 5 ml maintenance vial with 0.5 ml 1:1 v/v injection**
HDM[b]	*D. farinae* (Der f 1) *D. pteronnyssinus* (Der p 1)	500-2000 AU	10,000 AU/ml (30,000 AU/ml)	0.5 ml (0.17 ml)	2 ml (0.67 ml)
Pasture grasses, standardized[c]	Timothy (Phl p 5)	1000-4000 BAU	100,000 BAU/ml (10,000 BAU/ml)	0.1 ml (1 ml)	0.4 ml (4 ml)
Bermuda grass	Cyn d 1	300-1500 BAU	10,000 BAU/ml	0.3 ml	1.5 ml
Short ragweed	Amb a 1	6-12 micrograms of Amb a 1	200 mcg[d] of Amb a 1 (AgE U/ml)	0.3 ml	0.6 ml
Pollens[e]		1:100-1:200 w/v	1:10 w/v 1:20 w/v 1:40 w/v	0.25 ml 0.5 ml 1 ml	0.5 ml 1 ml 2 ml
Cat	Fel d 1	1000-4000 BAU	10,000 BAU/ml	1 ml	4 ml
Dog, ultrafiltered	Can f 1	15 mcg Can f 1	1:650 w/v	NA	1 ml
Cockroach[f,g]		Unknown			Unknown
Fungi[h]		Highest tolerated dose unknown	1:10 w/v 1:20 w/v 1:40 w/v	Unknown	Highest tolerated dose unknown

w/v, weight-to-volume ratio; AgE, Antigen E or Amb a 1; U, Unit; AU, Allergy Unit; BAU, Bioequivalent Allergy Unit; HDM, house dust mite.

[a]Cross-reactive allergens are additive and contribute to minimum to maximum extract volumes.

[b]*D. farinae* and *D. pteronnyssinus* are additive and contribute to minimum to maximum extract volumes if both used.

[c] Kentucky blue/June, meadow fescue, orchard, perennial rye, red top, sweet vernal, timothy. Choosing one species is typically sufficient. If use multiple northern pasture grasses, each of these are additive and contribute to total maximum volume.

[d] Minimum and maximum extract volume also applies to Ragweed mix (short/giant) products at 1:20 w/v and approximately 100 AgE U/mL.

[e]Cross-reactive pollens are additive and contribute to minimum to maximum extract volumes. If using a pollen mix, utilizing knowledge of cross-reactivity of species is required to calculate minimum and maximum extract volumes in order to achieve target concentration and to avoid exceeding maximum target concentration.

[f] Caution in mixing with certain pollens and environmental extracts due to degradation of potency secondary to proteolytic enzymes found in cockroach extracts.

[g]American (*Periplaneta americana*) and German cockroach (*Blatella germanica*) extract.
[h]Caution in mixing with certain pollens and environmental extracts due to degradation of potency secondary to proteolytic enzymes found in mold extracts.
[i]Basis for dosing recommendations are provided in Table X in the JTF 2011 AIT PP.[2]

89. Recommendation: We suggest that the specialist should use the fewest allergens that can adequately treat the clinically pertinent sensitizations, avoiding multiple cross-reactive allergens when one allergen has been shown to provide equal efficacy, thereby enabling effective dosing.

Strength of Recommendation: Conditional
Certainty of Evidence: Moderate

The available standardized allergen extracts, their potency units, and recommended dosing ranges remain unchanged from the JTF 2011 AIT PP[2] and are detailed in the allergen extract preparation guidelines on the websites of the AAAAI and ACAAI. The only change in recommended extracts is the addition of non-standardized ultra-filtered dog (UF) extract and the removal of nonstandardized acetone precipitated dog extract (see Recommendation 17, which includes SCIT efficacy for dog dander for a full discussion).

In that many allergens are substantially cross-reactive, the selection of a single allergen within a cross-reactive genus or subfamily facilitates attaining optimal therapeutic doses of each vial component. Clinically significant allergen cross-reactivities among pollens are presented in **Table 21**.

Studies have found high cross-reactivity among grasses of the Pooideae subfamily and have suggested that timothy grass is sufficient for SCIT treatment.[615-618] However, other studies suggested that a mixture of five grasses of the Pooideae subfamily would be better due to variability in cross-reactivity among the major group 1 and 5 allergens.[619, 620] In 2013, Gangl et al.[621] reviewed all the *in vivo* and *in vitro* studies on this question and concluded that there are no relevant advantages of using multiple grass mixes as opposed to a single grass pollen extract. The authors concluded that the major limitation to producing a high-quality grass pollen allergen extract was due to the intrinsic features of natural allergen extracts, in general, which could only be overcome with recombinant allergen-based technologies.[621]

In direct opposition, Archila et al.[622] found that many of the T-cell epitopes of some Pooideae grass pollen are minimally cross-reactive and that patients allergic to these grasses have T cells that recognize these minimally cross-reactive epitopes. Therefore, not all Pooideae grass epitopes with sequence homology are cross-reactive.[622] If the CD4+ T cell responses directed against allergens are important for long-term tolerance, as has been suggested, the minimally cross-reactive T-cell epitopes on many pollen, e.g., grasses, that have heretofore been categorized as highly cross-reactive, may indicate that treatment with multiple cross-reacting allergens rather than a single allergen could be preferred. If confirmed in larger studies, it also raises the potential limitation of recombinant allergen and peptide-based approaches for SCIT.[619] The debate on using a single or mixed cross-reacting allergens will likely continue.

While up to 25% of AR patients living in the subtropics are sensitized to the storage mite, *Blomia tropicalis*, 93% of these patients are also sensitized to *Dermatophagoides*.[623, 624] Another study found that among AR and/or AA patients, 82% were positive to HDM and 66% to *Blomia tropicalis* but only 1.5% of the *Blomia* positive patients were negative to HDM.[625] *Blomia tropicalis* allergen extract is currently not available in the US.

Published cross-reactivity data for other pollen, cockroach, and fungi are even more limited. Furthermore, most of the cross-reactivity data for these allergens are based on *in vitro* studies

without clinical efficacy data to substantiate if it is better to use one or all of a group of cross-reacting allergens. One advantage of using a single allergen rather than multiple cross-reacting allergens is that the specialist can achieve the recommended maintenance dose of each clinically relevant allergen without an excessive number of allergen extract vials per set or an unacceptable number of injections per visit. In addition, needless treatment above recognized probable effective dose ranges could be prevented.

Table 21. Cross-reactivity (aeroallergens).[2, 191, 626, 627]

Category/Family	Individual extracts	Recommendation for allergen vial preparation
Grass (Poaceae Family)		
Pooideae subfamily	Kentucky bluegrass, perennial rye grass, orchard grass, timothy grass, meadow fescue, red top, sweet vernal grass,	Select one, e.g., timothy (preferred), perennial rye, or meadow fescue
Panicoideae subfamily	Bahia, Johnson	Select one most patient or locally important
Chloridoideae subfamily	Bermuda (cross-reacts with Goose and Rhodes grass- not major allergens)	Must be treated individually when patient or locally important
Trees		
Cupressaceous	Juniper, cedar, cypress, arborvitae	Select one with highest exposure risk
Betulaceae	Birch, alder, hazel or hazelnut, hornbeam	Select one from Betulaceae or Fagaceae, e.g., birch
Fagaceae	Oak, beech, chestnut	Select one from Betulaceae or Fagaceae, e.g. oak
Juglandaceae	Hickory, pecan, walnut	Select one with highest exposure risk
Aceraceae	Maple, box elder	Select one with highest exposure risk
Oxalidaceae	Poplar, aspen, cottonwood	Select one with highest exposure risk
Oleaceae	European olive, ash, privet, Russian olive	Select one with highest exposure risk
Salicaceae	Willow, cottonwood, poplar	Select one with highest exposure risk
Weeds		
Asteraceae/Asteroideae Genus: Ambrosia	Short, giant, false, western ragweed	Select one with highest exposure risk
Asteraceae/Asteroideae Genus: Xanthium	Southern & slender ragweed, cocklebur, burweed, marsh elder	Select one with highest exposure risk
Asteraceae/Asteroiodeae Genus: Artemisia	Sages, wormwood, mugworts	Select one with highest exposure risk
Amaranthus	Pigweed [Cross reacts with Russian thistle, lamb's quarters, and *Kochia*]	Strong cross-reactivity with Chenopodiaceae and often grouped together

Chenopodiaceae	Saltbush, lamb's quarter, Russian thistle, *Kochia*, firebush, iodine bush	Select one with highest exposure risk. Consider Russian thistle & *Kochia* if both are locally important
Plantago	English plantain, ribwort plantain	Weak cross-reactivity with Chenopodium/Amaranthus
Rumex	Dock, sheep sorrel, curly dock, broadleaf dock	Select either sorrel or dock for treatment when locally important
HDM	*D. farinae, D. pteronyssinus*	Use mixture if both locally important; highly cross-reactive with *Blomia tropicalis*
Cockroach	American and German	Use mixture, unless one accounts for most of the allergen exposure

90. Recommendation: We suggest that allergens with high proteolytic enzymatic activity should, with rare exceptions, be formulated separately from other extracts to prevent degradation of allergenic proteins in other extracts.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Allergens with high proteolytic enzymatic activity, e.g., fungi and cockroach, should, in general, be formulated separately to prevent degradation of allergenic proteins in other allergen extracts, e.g., pollen, dander, and HDM.[2, 628] However, the mixing of concentrated glycerinated (47.5% glycerin) cat, dog, HDM, and cockroach extracts as well as a 1:10 v/v dilution (4.75% glycerin) of the concentrated vial provides mixing compatibility and stability for up to 12 months when stored at 2–8°C.[629] The evidence demonstrating the reduced potency due to high protease extracts continues to be based primarily upon *in vitro* data and has not been confirmed with clinical efficacy studies. Studies since 2010 have shown that cockroach allergen extracts are subject to autodigestion of endogenous allergens unless they are constituted in 50% glycerin.[626, 629] Furthermore, the proteases in *Alternaria alternata, Aspergillus fumigatus, Bipolaris sorokiniana, Penicillium chrysogenum (notatum), and Cladosporium herbarum* reduce the allergenic potency of American and/or German cockroach extract.[629] Fungi, in general, are relatively resistant to autodigestion and maintain stability when mixed; however, there is a concern that *Cladosporium herbarum* reduces the allergenic potency of *Aspergillus fumigatus* when mixed in the same vial.[629] Unfortunately, there is limited knowledge about the stability of mixing other fungal extracts in the same vial.

Daigle et. al.[630] evaluated the mixing compatibilities of subcutaneous allergens (fungi, insects, mites, ragweed, grasses, trees, weeds, dog, other animals, and cat) used for SCIT after storage for 1-3 months at 2–8°C in 0–10% glycerin; 25% glycerin, or 50% glycerin. As the glycerin concentration was reduced, the incompatibilities increased. At 50% glycerin, all allergens, with the exception of fungi mixed with insects, are compatible when mixed. In 25% glycerin, additional incompatibilities are fungi mixed with grasses, trees, and weeds. At ≤10% glycerin, additional incompatibilities include fungi mixed with HDM.[630] In this study, ragweed and all the animal danders remained compatible with all other allergens at all three glycerin concentrations.

Therefore, it would be advisable to keep fungal extracts in a separate vial, not mixed with any other allergen extract. The stability of weaker concentrations of fungi has not been adequately evaluated.

91. Recommendation: We recommend assigning treatment vial expiration dates based on the earliest expiration date of any component but recognize that less concentrated vials (e.g. 1:1000 v/v) may lose potency before that date.

Strength of Recommendation: Strong

Certainty of Evidence: Low

The FDA defines glycerin concentrations below 50% as aqueous formulations. The FDA has determined that standardized extracts, all formulated in 50% glycerin, and non-standardized extracts with 50% glycerin are assigned an expiration of 6 years from the date of extraction, with a maximum of 3 years for manufacturer storage and 3 years for expiration dating of the shipped vial. For non-glycerinated extracts, these time limits are reduced by 50%; for example, the shipped vial expiration date is up to 18 months. Although most non-standardized allergen extracts are available in aqueous or 50% glycerinated forms, only glycerinated extracts should be used for fungi and cockroach due to autodigestion and may be preferred for all allergen extracts due to their superior shelf life compared to other diluents. For stock solutions, the specialist must follow the manufacturer's expiration date; for 1:10-1:200 v/v from stock, the by-use date should be 12 months from dilution, for <1:200 v/v, the expiration should be 3-6 months from dilution. However, the stability of 1:1000 and 1:10,000 v/v has not been extensively studied and likely depends on the diluent, e.g., with human serum albumin (HSA) providing greater stability than normal saline.[631, 632] The AAAAI and ACAAI mixing guidelines suggest labeling these more diluted vials with an earlier expiration date.

92. Recommendation: We recommend that the specialist maintain aseptic conditions during the compounding of allergen extract vials and select a bacteriostatic diluent.

Strength of Recommendation: Strong

Certainty of Evidence: Low

Maintaining aseptic conditions as close to sterility as possible during the preparation of allergy extract vials, within vials during storage, and during administration is important both for patient safety and to fulfill the requirements set forth by USP <797>, Section 21.[603]

To ensure bacteriostasis, diluents should have at least 0.25% phenol or 20% glycerin.[633] At these concentrations, phenol, glycerin, and HSA have a long history of safe use in AIT and are not associated with systemic toxicity; AEs are typically limited to local tolerability issues.[3] While glycerinated extracts promote increased shelf life and reduce the formation of precipitants compared to aqueous extracts, when used in high concentrations in allergen extract vials, the increased viscosity often produces injection site pain. Therefore, the final glycerin concentration should be considered when selecting the most appropriate diluent. Both glycerin and serum albumin provide structural stabilization of allergenic proteins.[2] Furthermore, the addition of HSA to phenol helps to protect potency by limiting phenol-induced denaturation of allergenic proteins and preventing adsorption of allergen on the inner surface of the glass vial.[2, 631, 634, 635] Diluents commonly used for preparing allergen extract vials are 10% or 50% glycerin-saline with 0.4% phenol-saline, 0.4% phenol-saline, and 0.03% HSA with 0.4% phenol, with the latter often being preferred as it combines bacteriostasis with protein stabilization and reduces the pain associated with the high viscosity of glycerin.

93. Recommendation: We suggest storing allergen extracts in accordance with manufacturer recommendations, typically 2–8°C; keeping cool during transport; preventing freezing; and maintaining extract manufacturer and patient treatment vials in the highest glycerin concentration that is feasible, to maintain potency with temperature variation.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

The specialist often asks about the effect of temperature on allergen extracts during shipping and storage. While keeping allergen extracts refrigerated at 2–8°C is ideal for maintaining extract potency, this is often not feasible. A 2010 study of summer shipping of standardized timothy extract vials (10,000 and 100,000 BAU/ml) in >38°C ambient temperature showed that an extract that was at >20°C for 11 days and >30°C for 6 hours in transit maintained the expected potency and skin test reactivity without significant difference when compared to control vials that were not shipped.[636] Repeat freeze-thaw cycles reduce the potency of HDM extracts.[636]

Another study looked at non-standardized aqueous and glycerinated extracts as well as standardized extracts kept at 2–8 °C, 25°C (room temperature) and 40°C for 3 and 6 days.[637] All glycerinated 1:20 w/v and standardized major allergens maintained their stability except for Bermuda Cyn d 1 at 40°C. Non-standardized aqueous 1:10 w/v extracts maintained >75% allergen content at room temperature for 3 days. At 40°C, aqueous ragweed, olive, and English plantain lost up to 50% of allergen content at 3 days. Human serum albumin provided more stability than saline at 1:100 v/v dilution when extracts were stored at room temperature. However, even with HSA, the grasses and Der p 1 decreased below 60% potency when stored at room temperature for 3 days.[637] The 1:10 w/v birch extract lost all Bet v 1 content after freezing.[637]

When ragweed, mugwort, Japanese hop, and sawtooth oak are stored at 4°C with 50% glycerin for 12 months, >90% of protein content is maintained.[638] When stored at room temperature, up to 42% of the potency was lost.[638] When ragweed extract in buffer solution was left at room temperature for 8 weeks, Amb a 1 was almost completely degraded.[638]

USP Chapter <797>, Section 21, permits up to 1 year dating for compounded allergen vials, provided they are made with aseptic technique and stored in the refrigerator (2–8°C).[603] Both maintaining the storage of allergen extracts at 2–8°C, except for rare occasions, e.g., removing from the refrigerator for preparation of patient vial sets or for administering SCIT, and utilizing the highest possible concentration of glycerin in both concentrated and diluted vials help to ensure that the potency of the allergen extract is maintained. When allergen extracts are transported outside the office, a cool pack is advised, but freezing should be avoided. More diluted vials or vials only partially filled lose their potency more rapidly, regardless of the storage temperature. All allergen extracts and allergen extract vials should be stored at 2-8°C in a refrigerator designated for medications.[633] Monitoring refrigerators for temperature variations is essential to ensure the maintenance of potency of stock and patient treatment sets of allergen extracts.

Additional office decisions, documentation, and forms used for allergen extract compounding and SCIT administration

94. Recommendation: We suggest that when specialists compound allergen extracts, they maintain appropriate documentation of standard operating procedures, mixing personnel qualifications and training, refrigeration temperature logs, compounding records, mixing adverse event records, primary engineering control hood functioning records (e.g., laminar airflow workbench or biological safety cabinet), as applicable.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

In addition to following the compounding and documentation required by USP <797>, Section 21,[603] the specialist should document or have protocols for: the dosage schedule (conventional or accelerated) for each patient; dosing adjustments for unexpected gaps in treatment; the use of a preinjection questionnaire or validated instrument as available on which information such as preinjection peak flow measurement is recorded; treatment of local and systemic reactions and procedures for these adverse events; consent process; standard operating procedure (SOP) for compounding of allergen extract vials, administering, and documenting SCIT; justification or shared decision-making for extending SCIT for longer than 3 to 5 years; and transportation of allergen extract vials out of the office for administration, e.g., college student health or a primary care physician. The appendices of the JTF 2011 AIT PP[2] and the AAAAI and ACAAI websites provide resource materials with sample forms that facilitate this planning. Some of the current available sample forms and the hyperlinks are listed in **Table 22**.[2, 443, 444, 506, 639-644]

Table 22. Sample SCIT forms and documentation resources.

Topic	AAAAI Resource	ACAAI Resource
Dosing adjustments for missed injections	Dose Adjustment After Gaps in Administration of Subcutaneous Immunotherapy[506]	Immunotherapy Sample Forms[443]
Preinjection health screening questionnaire	Immunotherapy Administration Forms[639]	Immunotherapy Sample Forms[443]
Preinjection peak flow measurement	Allergen Immunotherapy: A Practice Parameter Third Update[2]	Allergen Immunotherapy Extract Preparation Instructional Guide[640]
Treatment protocols for local and systemic reactions	Immunotherapy Systemic Reaction Treatment & Grading System[641]	Immunotherapy Sample Forms[443]
Consent forms for SCIT	Immunotherapy Consent and Instruction Forms[444]	Immunotherapy Sample Forms[443]
Standard operating procedures for compounding and administration	Standard Operating Procedure for Preparation of Allergy Immunotherapy Extracts[642]	Allergen Immunotherapy Extract Preparation Instructional Guide[640]
Documentation for extending SCIT beyond 3–5 years	Allergen Immunotherapy: A Practice Parameter Third Update[2]	New Guidelines for Insurers Help Patients Receive Necessary Allergen Immunotherapy Treatment[643]

Procedure for sending allergy extract vials for out-of-office administration	Immunotherapy Administration Forms[639]	Immunotherapy Administration Instructions[644]

Throughout the allergen extract vial set production and documentation process, a recognized best practice is to have several quality checks involving a second staff person, in addition to the staff person preparing the allergen extract vial set. The details of these quality checks should be included in the SOP manual. When properly completed, a copy of the prescription for each allergen extract vial set produced can be used as documentation for the required "mixing log". (Examples of blank and completed extract vial prescription forms are included on the AAAAI and ACAAI websites and in Appendix 7.)

95. Recommendation: We recommend that the specialist determine that all facilities that will be administering SCIT have medical staff who have been trained in the prompt recognition and management of adverse reactions to AIT, including anaphylaxis; are equipped with emergency supplies to treat anaphylaxis; and that medical personnel capable of treating anaphylaxis are present onsite for the AIT administration and during the 30 minutes of observation. Ideally, acknowledgment of adherence to these standards by the administering facility should be received before allergen extract vials are transferred.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

96. Recommendation: We suggest that specialists who transfer AIT care to a remote facility should provide: 1) patient and physician identification and contact information; 2) signed patient consent form; 3) list of contents of each allergen extract vial; 4) dosage schedule for AIT; 5) administration recording form; 5) prescription (order) for AIT; 6) guidelines for dose adjustment for gap in treatment, adverse reactions, etc.; 7) pertinent patient medical records; and 8) office preparedness, safety, and monitoring recommendations, including minimal required emergency resuscitation equipment; and 9) packaging and labeling as specified by USP <797>, Section 21. The administering facility should be asked to acknowledge receipt of the allergen extract vials and the above information, and the ability to comply with recommended treatment and conditions.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

When the allergen extract vial set is transferred from the allergist's office to another provider, e.g., college student health, the exterior of the shipping container must specify handling instructions.[603] For international travel, the patient's name must match the passport ID. It is necessary to determine the maximum supply permitted by foreign countries, as some countries only allow a 30-day supply to enter the country.

The allergen extract vials must also be labeled with all the items specified in USP <797>, Section 21, e.g., patient's name; type and fractional dilution of each vial, with a corresponding vial number, by-use date, and storage conditions.[603] Most specialists also indicate a general category of the vial contents on the label, e.g., grasses or HDM. While there is no standardized list of items to include when transferring an allergen extract vial set, **Table 23** provides considerations for the following: patient identification, prescribing physician information, vial set

information, dosing documentation, clinical records, safety and monitoring, and transfer confirmation forms.

The specialist may also want to include a summary of potential local and systemic adverse reactions to SCIT, as well as guidance on recognizing and treating these reactions. A detailed listing of signs and symptoms, medications and equipment for emergency care were detailed in the JTF 2015 Anaphylaxis PP.[459]

When transferring total AIT care permanently to another physician, more extensive records would need to be provided. Details on what to send and decision points for the accepting physician are provided in the JTF 2011 AIT PP update and will not be restated here.[2]

Table 23. SCIT transfer packet: Items to include when transferring allergy extract vial sets for SCIT administration.

Category	Item	Required	Best Practice (not required)	Description
Patient identification	Patient's full name and date of birth	X		Must match vial label, prescription, and all forms
Patient identification	Copy of photo ID		X	Optional; helps verify identity, especially at student health center
Patient identification	Emergency contact information for <18yrs	X	X	Include parent/guardian or local contact if under 18. Best practice for adults.
Prescribing physician info	Physician's name, practice name and phone # of practice	X		For verification and clinical questions
Vial set information	Allergy extract vials (original, labeled)	X		Include full patient info, concentrations, contents, and beyond use date
Vial set information	Cold pack & refrigeration instructions	X		Ensure stability during transport
Vial set information	Extract preparation date and beyond use date	X		Required for compliance and safety
Dosing documentation	SCIT build-up and maintenance schedule	X		Specify dilution sequence and maintenance target for each extract vial. Indicate if current vials are for build-up or maintenance. Indicate if adjustments are to be made for specific allergy seasons or patient specific conditions.

				Indicate at what point and mechanism an extract refill request should be sent to the specialist.
Dosing documentation	Administration and adverse reaction log for use by facility	X		Include separate form for each extract vial, includes time and date of AIT, vial # and dilution (v/v), dose (mL), site (L/R arm), observation time, reaction (Y/N), reaction description and treatment (in any), staff initials. Form should indicate that pre-injection screening is required.
Dosing adjustment	Missed dose adjustment protocol		X	Based on PP or AAAAI/ACAAI guidance
Dosing adjustment	For repeated large locals; for systemic/anaphylaxis		X	Based on pt history of reactions, specify if dose reduction is to be made.
Dosing adjustment	Systemic/Anaphylaxis	X		Make contact with specialist for anaphylaxis reaction to AIT prior to any more AIT
Dosing adjustment	For patient's pollen season (s)		X	Guidelines for each patient on when and how to reduce dose during patient's high pollen season.
Dosing adjustment	For pregnancy	X		Follow specialists recommended schedule, e.g., no dose escalation during pregnancy. Contact prescribing specialist if patient becomes pregnant following transfer
Clinical records	Injection administration log (copy) from prior clinical records		X	Include previous doses, timing, reactions (at least for prior 6 months)
Clinical records	Adverse reaction log		X	Detail reaction type, severity, treatment of previous adverse reactions
Clinical records	Allergy testing summary		X	Provides rationale for extract components
Clinical records	Immunotherapy prescription form		X	Optional best practice. Standardized form

				recommended (e.g., AAAAI/ACAAI)
Clinical records	Standing orders/protocols		X	Dose adjustments, anaphylaxis treatment, observation
Safety and monitoring	Physician or Physician extender required onsite for AIT		X	JTF 2011 AIT PP recommended[2]
Safety and monitoring	Emergency protocol		X	Includes epinephrine dose, observation policy; whether epinephrine for self-administration has been prescribed and if required to be present prior to receiving SCIT; A list of the required components of emergency kit (e.g., medications, oxygen, O2 saturation monitor, IV fluids and administration equipment) or a reference to the JTF 2015 Anaphylaxis PP[459]
Safety and monitoring	Consent to treat/SCIT consent form	X		Signed by patient or legal guardian
Transfer confirmation	Documentation of transfer	X		Date/time, receiving party details
Transfer confirmation	Receiving clinic acknowledgment prior to transfer of allergen extract vials		X	Advanced verification of administering personnel training, emergency kit, refrigeration, anaphylaxis recognition and treatment capability
Transfer confirmation	HIPAA release or record sharing consent		X	Facilitates bidirectional communication
Request for allergy extract refills by facility	Procedure/forms for requesting refills	X		Specialist to specify refill request timing & process. Facility to specify clinic shipping/receiving requirements.

PP, practice parameter.

97. Recommendation: We recommend that the specialist and remote facilities use a standardized multi-step, verification protocol, including two patient identifiers, before administering SCIT.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

The AAAAI, the ACAAI, and the Joint Commission support a structured approach when administering SCIT to ensure patient safety.[2, 645] Prior to administering SCIT, the staff who draws up and administers the SCIT should review the chart to confirm the correct patient, current dose (volume and vial), date of last injection, planned injection schedule, interval since the last injection, and any adverse reactions to the last injection. In addition to adherence to USP vial labeling procedures, two-patient identifiers, e.g., name, date of birth, and/or medical record number, should be confirmed verbally with the patient and cross-checked against the vial label and chart. A best practice, although this may not be feasible in many office settings, is to use a 2-person (staff) verification process, with one staff member preparing the injection after verifying the patient, dose, and vial, and a second staff member independently checking and verbally confirming with the patient their name and matched labeled vial(s) and dose to be administered. This is similar to the “double-check” practices used in chemotherapy and high-alert medications. For practices with electronic medical records, barcode scanning of patient IDs and vials offers an alternative best practice that utilizes an automated verification layer, error prevention measures, and a comprehensive documentation system. The staff member(s) performing the verification process should initial or sign the administration form before each allergy injection. **Table 24** provides a summary of the “best practice” safety checklist for SCIT administration.

Table 24. Summary of best practice safety checklist prior to SCIT administration.

Step	Purpose
Two-patient identifier check	Confirms correct patient
Vial label review	Verifies correct extract and concentration
Vial particulate check	Assesses for interval sedimentation or contamination
Chart dose check	Ensures correct volume and sequence
Injection interval assessment	Prevents overdosing after long gaps
Dual staff verification	Reduces human error
Documentation and consent	Legal and safety recordkeeping
Adverse reaction history check	Ensures appropriate dose modifications

As part of the SOP, the office should maintain a system to ensure an adequate stock of extract, diluent, and mixing supplies, as well as a process for removing expired extract, diluent, and patient-specific treatment vials. There should be written documentation of the duties assigned to specific office personnel. A detailed, clearly stated set of step-by-step procedures for mixing that fulfills the requirements of USP Chapter <797>, Section 21 should be outlined in the SOP manual, which is reviewed and updated as needed on a frequent basis, e.g., every 6 months. The required personnel training and competency assessments should also be documented and maintained in each staff member’s personnel file.

Other administration methods for AIT

98. Recommendation: We recommend informing the patient when off-label immunotherapy is being prescribed, and documenting this in the consent form.
Strength of Recommendation: Strong
Certainty of Evidence: Low

Open discussions about both off-label and emerging immunotherapies, some with limited RDBPC trial efficacy data, promote progress in the field of immunotherapy and stimulate research and investment. Communication about how allergy specialists are addressing unmet needs sets the stage for pivotal studies for evidence-based practice advancements. Discussions about immunotherapy other than SCIT and SLIT-T vary widely due to specialists' contrasting viewpoints, training, and experience. This section was rewritten several times as the group aimed to reach a balance between those who felt it was outside the scope of a PP to mention off-label or emerging therapies and those who felt it is important to share how North American allergy specialists are practicing in the real world. The consensus was to provide balance by discussing these emerging AIT strategies.

As a rapidly growing field of study, new immunomodulation treatments continue to be studied and introduced to the market. Advancements aim to improve treatment efficacy, minimize AEs, and reduce the burden of lengthy treatment cycles, while maintaining the allergy specialist's central role in providing each patient an individualized treatment plan.

SLIT-L

Sublingual immunotherapy drops, or liquid formulations (SLIT-L), have been used globally for over 60 years and are discussed in more detail in the efficacy section of this document. Most evidence-based specialists who use off-label SLIT-L target extract dosing similar to FDA-approved SLIT-Ts, approximately the same amount of daily allergen as administered monthly with SCIT maintenance. Patients should be cautioned about online companies selling home-based SLIT-L at a discount. As a consumer, the patient should be wary and be educated about the importance of extract or vaccine allergen content in achieving efficacy. Effective dosing requires large volumes of commercially available extracts used off-label, which is generally reflected in higher out-of-pocket cost (more extract used, higher cost per vial) versus less expensive, lower dosing (less allergen extract used, lower cost per vial). For some patients who live in rural areas, whose lifestyle prevents frequent office visits, or whose insurance does not cover SLIT-Ts, many specialists consider shared decision-making for off-label use of SLIT-L.

99. Recommendation: We recommend that if using ILIT, it should be administered only by specialists trained in ultrasound-guided lymph node injections in settings with appropriate emergency preparedness for anaphylaxis.
Strength of Recommendation: Strong
Certainty of Evidence: Moderate

Intralymphatic immunotherapy is one of the newest forms of AIT. Its use is supported by a growing body of literature dating back a quarter of a century for human allergy studies and over half a century for animal studies. RCTs for ILIT are documented in 23 publications,[646] with nearly 250 ILIT scientific publications and citations dating back to the 1970s.[647] Clinical access to ILIT for treating environmental allergies emerged in the United States during the COVID-19 pandemic.

ILIT is typically dosed as a series of 3 injections of aeroallergen extract in a superficial lymph node using ultrasound guidance. The treatment course is usually completed within 8 weeks. Clinical studies report symptom improvement within 12 weeks of starting treatment and long-lasting benefits, comparable to 3 years of SCIT. This is accomplished with side effects limited to mild reactions in studies using off-label, standardized allergen extract with reduced allergenicity, like allergen-adjuvant products or allergoids (not available in the US).[648-650] Senti et al.[650] performed a randomized, active-comparator, parallel-group, superiority study in 183 grass pollen-allergic adults, randomized 3:2 to receive either SCIT standard of care or ILIT, with both arms treated with an aluminum-adsorbed grass pollen extract commercially available in Switzerland (Alutard; ALK-Abello). Cumulative extract dosing for the ILIT treatment arm was 1000-fold less than SCIT dosing. ILIT patients had fewer serious AEs compared to SCIT patients ($p=0.001$), perceived pain to be significantly less than that of an intravenous puncture ($p=0.018$), and, at 4-months after starting treatment, tolerated 10-fold higher concentration of pollen exposure by NPT ($p<0.001$) compared to the SCIT group. The SCIT group exhibited no change compared to baseline in nasal provocation tolerance at the 4-month time point. Both groups showed significant improvement in subjective hay fever symptoms during the subsequent pollen season ($p<0.001$). The ILIT and SCIT groups did significantly differ in patient reported outcomes at both the 1-year and 3-year time point from starting treatment. ILIT participants used less AH therapy during the first pollen season ($p=0.02$) of the study compared to the SCIT group, and by the third pollen season, medication reduction was not significantly different between the groups.[650] A RDBPC trial of 20 adult, cat-allergic patients conducted by the same research group tested a novel recombinant cat protein administered by 3-injection ILIT protocol compared to placebo.[649] This was a first-in-human study of the fusion protein MAT-Fel d 1 vaccine in alum targeting the MHC II pathway within the lymph node. The treatment group tolerated injections without serious AEs and experienced a 74-fold increase in nasal tolerance of cat dander ($p<0.001$). Suspected treatment-related AEs were higher in the placebo group, but not to a statistically significant degree. Efficacy biomarkers in the ILIT treated group were significantly higher than the placebo group for cat-dander serum sIgG4 ($p=0.003$) and in vitro T-reg cell response to allergen challenge ($p=0.026$) and IL-10 production ($p<0.001$).[649]

Patterson et al.[648] further investigated the safety of ILIT for treating grass pollen ARC in a younger study population (15–24 years olds), using extract sourced in the US (commercially available alum-adjuvanted grass pollen extract), and tested the safety of an escalating dose strategy in line with standard of care therapies. Previous ILIT allergy studies had been done only in adults with European extract concentrations using fixed-dose regimens. Seven patients were randomized to treatment with 20,000 PNU Center-Al *Phleum pratense* (ALK), and 8 patients were randomized to placebo (saline with phenol), each dosed once every 4 weeks for a total of 3 preseasonal injections (0.1 ml, 0.3 ml, and 0.5 ml). Adherence in this study was 100% with all 15 participants completing all 3 injections. Safety was measured by a Total Symptom Score (TSS), which were similar between active treatment and placebo groups at baseline ($p=0.8$). Reactions in both groups were local to injection sites and resolved without treatment. Although very small, this RDBPC trial found lymph node injections to be safe using an extract available in the US. Furthermore, inguinal lymph node injections were well-tolerated in a pediatric adolescent population. While primarily a safety study, a secondary endpoint included patient-reported daily diary entries collecting data for a Total Combined Score (TCS; symptom + medication scores), the usual gold standard for determining efficacy in AIT studies. During the two peak weeks of pollen season, when pollen counts were the highest, mean TCS was 8 in the treatment group and 16 in the placebo group (effect size = 0.97[651]), a very large magnitude of difference.[648]

Most ILIT studies report it to be a well-tolerated procedure, with lower risk of SR attributed to a low injection dose (allergen content and volume), to using extract with adjuvant providing a potential local depot effect, and to expert sonography and injection technique. Systemic reactions are rare. Two highly sensitized patients treated with non-adjuvant, standardized, aqueous HDM extract experienced severe SRs with ILIT.[652]

Clinical adherence rates for ILIT are high (with 100% adherence in this author's clinical practice and published studies[653]), exceeding published adherence rates for SCIT (~54% for 3+ yrs treatment, ranging 16-89%)[47, 578, 654-656] and SLIT (~57% for 3+ yrs treatment, ranging 7-89%)[342, 578, 657-662], and long-term medication adherence (~50%, studies range widely from 0% to 100%).[663, 664] Evidence demonstrates efficacy and safety for single allergen, and very limited evidence for up to 3 simultaneous allergens, including pollen, cat, dog, and HDM extracts.[652, 665-670] The proposed immune mechanism is that direct allergen delivery into a lymph node enhances the immune response,[671] down-regulating the allergic response with a much lower total dose of allergen. Dosing intervals of every 4 weeks, rather than every 2 weeks, and use of adjuvant in extracts, compared to non-adjuvant extracts, contribute to the effectiveness and safety of the procedure.[652, 672-674] Similar findings are seen in SCIT studies using adjuvant extracts, where reduced dosing can provide enhanced efficacy and safety compared to non-adjuvant extracts.[675] The maintenance dose usually administered with ILIT is less than a typical SCIT maintenance dose. Comparison of the studies is difficult due to various dosing schedules, inconsistent use of adjuvants, and potential variability of the clinician's skill in precisely delivering the allergen to the lymph node.

ILIT procedural precision, which requires ultrasound guidance and training, is crucial for its effectiveness. In a European training program where allergy specialists had not yet completed formal ultrasound and ILIT procedural training, only 58 of 156 ILIT injections went into the lymph node.[676] The majority of injections were determined to have missed the lymph node on post-procedural review of ultrasound video clips. There was an association between the number of successful injections into the lymph node and clinical effect.[676]

Benefits for patients undergoing ILIT include relief within two months after completing 3 allergen injections[650, 677] and persistent symptom improvement at least 3 years after completing treatment.[650, 678] In one study, 76% of grass-pollen allergic, ILIT-treated patients reported continued reduction or complete resolution of ARC symptoms when surveyed 19 years post-treatment with aluminum hydroxide-adsorbed grass pollen extract.[679] These results were not inferior to SCIT-treated patients in the study and represent one of the longest follow-up studies of AIT completed to date.

Translating the safety and efficacy of ILIT into clinical practice requires special training and expertise. Since most practicing allergists are not trained in ILIT, and procedural accuracy strongly influences outcomes, specialized training in ultrasound-guided lymph node injection and standardized dosing protocols is essential for safe and effective ILIT. For allergy specialists to maintain leadership as experts in the ILIT procedure, an active learning health network (LHN) for ILIT was instituted in 2023 for establishing standardized competency and quality metrics for clinical practice (*Patterson AAP Manuscript #AAP340-25 PMID: pending*). This LHN developed a master curriculum for training allergy specialists in this specialized procedure and implemented a standardized certification program for maintaining quality and safety standards. It is feasible to train allergy specialists — fellows and both academic and community-based allergy specialists — and ultrasound equipment can be reasonably incorporated into a private practice setting in a cost-effective manner. This LHN functions in the US as an academic-private practice collaborative for safe implementation of ILIT.

Learning Health Networks

A LHN is a collaborative community of patients, clinicians, researchers, and patients' families working together to accelerate improvements in healthcare. Allergy specialists are working within LHNs for advancing science of and patient access to treatments for neglected diseases and underfunded treatments, including pediatric asthma, food allergy, and ILIT (*Patterson AAP Manuscript #AAP340-25 PMID: pending*). Challenges with bringing new and emerging treatments to clinical practice include determining when enough efficacy and safety data are achieved; patient demand is sufficient, and implementation is economically feasible. The FDA approval process is a well-respected route of providing consumer and specialist confidence in medical treatments and technology by rigorously demonstrating safety and efficacy. It is also a multi-year, multi-million-dollar pathway that by default serves as a funnel for producing products with the most commercial viability. Active LHNs are an emerging pathway and powerful tool for bridging a gap between early-stage innovation and translatable patient access.[680-685] LHNs provide an organized network of specialists providing advanced, off-label medical care, in a systematic fashion that utilizes group data to modify protocols for safety and efficacy, with an end-goal of shortening the time between medical breakthrough and modern standards of care.

LNIT and EPIT

Other convenience-forward methods of administering AIT for inhaled allergens that have not been investigated in the recent literature include both local nasal (LNIT) and epicutaneous (EPIT) immunotherapy. EPIT is in clinical trials for food allergy. LNIT is a treatment whereby allergen extract is applied topically to nasal tissue. This was studied in the 1970s-1980s for treating AR due to tree, grass, weed pollen and HDM.[686-694] Variable efficacy was reported with preseasonal, daily application. Benefits appeared to be short-lived, and local side effects of treatment may have played a role in the lack of further development. There is no recent or current research on nasal application of allergen immunotherapy.

EPIT is a method of administering allergen via topical application, usually by patch, for repeated, prolonged periods of time (examples include several hours of skin contact at a time, once a week for a predetermined period, like 6 weeks). Grass pollen and cat aeroallergens have been studied.[695-700] Up to 10% of studied patients discontinued treatment due to local cutaneous side effects, and there have been no new publications of EPIT for aeroallergens in nearly a decade. EPIT for food allergy has had more favorable outcomes with prior and ongoing studies, but it is beyond the scope of this PP (prior studies include NCT02223182, NCT01197053, NCT01170286, NCT01489514, NCT04371627, and current studies include NCT07003919, NCT05424731 Search ClinicalTrials.gov for: Allergy;Food, Other terms: epicutaneous | Card Results | ClinicalTrials.gov).

Modification of Allergens, Allergen Carriers and Molecular Approaches

A variety of allergen modifications have been studied over the past 50 years, but several during the past 10 years. Regulatory approval for these approaches is complicated and may limit their commercialization, even if proven safe and effective, These include the synthetic Fel d 1 immunoregulatory peptide discussed in Recommendation #16 related to cat allergy (reference 196 is cited in Rec #16 but is not specific to the peptide, I suggest we add Patel, Deepen, et al. "Fel d 1–derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study." *Journal of Allergy and Clinical Immunology* 131.1 (2013): 103-109). The same group has also used this approach with HDM (Hafner, Rod, et al. "Persistent treatment effect achieved at one year after four doses of Der p

derived synthetic peptide immuno-regulatory epitopes in an exposure chamber model of house dust mite allergy." *Journal of Allergy and Clinical Immunology* 133.2 (2014): AB289.) Other strategies with very limited evidence of safety and efficacy include allergens attached to virus-like particles, mRNA-based allergy vaccines, DNA vaccines, allergen coupling to immune-modifying carriers, nanoparticle-based immunotherapy, and other synthetic peptide immunoregulatory epitopes (SPIREs).

Strategies to Improve AIT Tolerance: Adjuvants & Mast Cell Modulation

Alum-adjuvanted extracts are used globally and have been long touted for enhanced immunogenicity, shortened build-up schedule, and reduced AE profile. These were available in the US until 2023 when manufacturing ceased due to limited use in practice. Reasons for declining use included inability to mix adjuvant extracts with aqueous extracts, availability limited to only pollens, and increased cost compared to aqueous extracts. Newer developments in adjuvant technology seek to attenuate Th2 response in favor of more tolerogenic T-regulatory responses (**Table 25**).[675]

Table 25. Adjuvants for AIT. Reproduced under the Creative Commons Attribution-NonCommercial-NoDerivs License from Wise et al, 2023.[675]

TABLE XI.D.4.b Potential adjuvants for allergen immunotherapy

Category	Adjuvant	Examples and comments
Salts and crystals	Aluminum hydroxide (Alum)	Early studies showed augmented immune responses
	Calcium phosphate	Shown to have some immunogenicity enhancement with less IgE stimulation
	Microcrystalline structures	Microcrystalline tyrosine
Transfer vehicles	Liposomes	Oligo mannose-coated liposomes
	Nanoparticles	Poly lactose co-glycolide, many others
	Carbohydrate particles	Chitosan
	Amino acid particles	Cationic peptides, protamine
	Dendrimers	Highly ordered synthetic molecules that are typically spherical and can be made to be water soluble
	Oil-in-water emulsion	Oil emulsions such as MF59, AS03, CAF01, and Montanide ISA induce local inflammation while simultaneously acting as a long-term depot agent to prolong the distribution of allergen
Immunostimulatory	TLR-9 agonists	CpG oligodeoxynucleotide (CpG-ODN) has been employed in several direct disease modifying and allergen immunotherapy approaches by increasing tolerogenic cytokines including interferons. QbG10 is a synthetic virus like particle derived from bacterial DNA
	TLR-7 agonists	Virus like particles; single stranded viral RNA stimulates TLR-7 and stimulates the production of type I interferons can be used singly or in combination with allergens
	TLR-4 agonists	Monophosphoryl Lipid A fraction derived from bacterial lipopolysaccharide works as a TLR-4 agonist. Monophosphoryl lipid derived from bacterial DNA or RNA stimulate dendritic cells and other antigen-presenting cells to increase Th1 cytokines
	C-type lectin receptors	Mannan mannose polysaccharide that acts as C-type hectic ligand to enhance antigen presentation and increase tolerogenic cytokines
	DNA and mRNA vaccines	DNA and mRNA vaccines such as COVID-19 vaccine can be engineered to encode allergenic proteins but often are composed of CpG repeats that can also simultaneously induce TLR responses
	Imidazoquinones	Acts as functional adjuvant for TSLP mediated allergic T cell responses
	Heat killed bacteria	Heat killed mycobacteria, heat killed *E. coli*, heat killed *Listeria monocytogenes*
Natural derived	Probiotics	Ingested microbial products have shown some limited benefit in reducing eczema and other atopic disease. Microbial adjuncts proposed to enhance the efficacy of food allergen immunotherapy
	Vitamin D	Vitamin D3 has been shown to reduce effector T cell stimulation and cytokine production and promote the effect of allergoid in mice
	Amino acids	L-tyrosine bound to allergen acts a short-depot forming adjuvant and indirectly increases IgG production
	Chinese herbs	ASHMI

Abbreviations: ASHMI, Anti-Asthma Simplified Herbal Medicine Intervention; Ig, immunoglobulin; TLR, toll-like receptor; TSLP, thymic stromal lymphopoietin.

Combining mast cell modulating biologics and small molecules with AIT is an emerging strategy for improving tolerance of AIT. BTK, c-KIT and anti-IgE may make AIT less risky or allow treatment of subjects who are currently deemed too high risk to undergo AIT (see Recommendation related to biologics). None are approved for use with AIT but could be utilized to treat comorbidities and improve AIT tolerance and safety.

Future of Immunotherapy

100. Recommendation: We suggest that allergy specialists record objective measures of AR outcomes (e.g., RCAT or provocation tests) before and after initiating AIT to demonstrate real-world effectiveness, especially with multi-allergen immunotherapy.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

101. Recommendation: We suggest that allergy/immunology specialty societies invest in developing real-world databases to strengthen the evidence base for the safety and effectiveness of multi-allergen immunotherapy.
Strength of Recommendation: Conditional
Certainty of Evidence: Low

Research Call-to-Action Statements:

Extract Quality & Standardization

- Conduct large, multicenter, RCTs to evaluate the effectiveness and safety of multi-allergen immunotherapy with current standardized and non-standardized extracts. These studies should explicitly clarify mixing compatibility of allergens, dosing (including standardized terminology of dosing and comparisons among optimal dosing), and should be done over multiple years to capture batch to batch variability in raw materials across pollen seasons.
- Develop and validate novel extract manufacturing technologies that allow consistent, standardized dosing across allergens, including recombinant, adjuvanted, and modified extracts.
- Assess whether innovations in extract formulation can reduce SRs without compromising long-term immunomodulation.

Treatment Adherence

- Conduct large, multicenter, RCTs or real-world data to investigate strategies to improve adherence, including shorter treatment cycles and more convenient dosing mechanisms: ILIT, SLIT-T (for tree pollen, cat, dog), intradermal, oral, or biologic-assisted AIT.
- Define optimal ILIT dosing schedules for seasonal and perennial allergens, allergen extract formulations, and adjuvant use.
- Evaluate the impact of patient-centered approaches (convenient scheduling, remote monitoring, micro-climate–specific allergen guidance) on completion rates of full AIT courses.

Efficacy Assessment & Biomarkers

- Identify objective biomarkers and determinants of long-term immunomodulation to predict which patients are most likely to benefit from AIT.

- Invest in developing real-world databases to strengthen the evidence base for the safety and efficacy of multi-allergen immunotherapy.
- Validate and standardize an objective reference standard for outcome measures, such as RCAT, SNOT-22, nasal or conjunctival provocation testing, and CSMS (measured daily or once a week), to track response and durability.
- Examine the predictive value of immunologic markers (e.g., sIgG/sIgE ratios, T-regulatory cell responses) for sustained efficacy off therapy.

Safety Optimization

- Define ideal pre- and post-treatment regimens (AH, LTRAs, oral corticosteroids) for accelerated SCIT schedules to maximize safety without impairing immunomodulation.
- Study flexible dosing strategies for missed or delayed doses to maintain safety while improving adherence.
- Identify denatured or modified extracts and biologics that minimize the risk of anaphylaxis.

Personalized, Climate-Specific Treatment

- Expand local and automated pollen and environmental monitoring networks to optimize allergen exposure–based dosing in AIT.
- Research the integration of real-time micro-climate allergen data into treatment regimens for both SCIT and SLIT.

Integration of Innovative Therapies

- Conduct controlled trials on mast cell–modulating biologics, short synthetic T-cell or B-cell peptides consisting of immunoregulatory epitopes (SPIREs), hypoallergenic peptide vaccines, and passive monoclonal antibodies to determine safety, efficacy, and optimal dosing alone or in combination with AIT.
- Compare novel administration routes (ILIT, intradermal, OIT) with traditional SCIT/SLIT in terms of efficacy, safety, adherence, and patient preference.
- Evaluate mobile monitoring devices for collecting real-world data, enabling personalized care, and objectively monitoring response to AIT.

Systematic Approaches to Future Development

- Utilize clinical networks, like LHNs and large group practices with centralized databases, to systematically collect real-world data, monitor protocol adherence, and guide iterative improvements in AIT delivery.
- Promote collaborative efforts between national societies, academic centers, and industry to facilitate multi-center trials, novel extract development, and evidence-based regulatory pathways.

Allergy specialists advance the future of AIT and new AIT treatments by identifying knowledge gaps, translating them into innovative ideas, products, and protocols; investing in research; publishing findings in peer-reviewed literature; and advocating for reasonable reimbursement and coverage. Improving safety, efficacy, and convenience of AIT is important to patients and

allergy specialists. We stand confidently in an era where evidence-based AIT for respiratory allergens is effective and safe for most of our patients. This is thanks to a long history of successful outcomes and the research efforts of our predecessors regarding effective dosing, modern treatment schedules like rush and cluster, and standardization of some extracts. With these advancements come more questions about how to reduce SRs and fatality risks, while maintaining effective dosing, and understanding how to meet those goals with a convenient delivery model that maximizes adherence to a full treatment course. We are thinkers, so we also dream of a better future. We present a call to action for addressing gaps in current AIT evidence in **Table 26**.

Extract quality

Current extract quality is variable and depends on solubilizing a mixture of biological materials. Most extracts are regulated to some degree but not standardized. Nineteen of these allergen extracts are standardized. Mixing multiple extracts to compound personalized patient vials is an acceptable, off-label practice in North America. Multi-allergen immunotherapy risks inclusion of some unimportant allergens and insufficient dose of important allergens. Mixtures likely contain some clinically irrelevant allergens despite cutaneous or serum polysensitization, and there is insufficient data to support or refute the practice. Multi-allergen immunotherapy may be dose-limiting. Vial volume constraints, payor mixing requirements, diluting effects of mixing extracts, and presence of proteolytic enzymes - can result in a lower than anticipated final treatment dose for each individual allergen in a mixture. Lacking a preponderance of evidence for multi-allergen immunotherapy effectiveness, when allergy specialists compound mixtures of standardized and non-standardized extracts, we are extrapolating objective single-allergen data and extending confidence from the long history of subjective clinical improvement we see in our patients.

There are limitations to extract innovation due to the inability to modify payment structure for incremental change in a century-old treatment. Manufacturers have little to no incentive to fund the cost of regulatory approval for new extracts or for funding and organizing a study large enough to support current practice of mixing commercially available extracts.

In the future, allergen extract manufacturing technology may combine current knowledge about adjuvants and recombinant molecules to develop highly effective extracts with enhanced safety, less cumbersome treatment protocols, and standardization for all treated allergens. There are phase II and III clinical trials underway for evaluating the use of Toll like receptor agonists, peptides, nanoparticles, and biologics in AIT. One example of extract technology advancement is the development of a novel dog extract. A tetrameric structure, produced as a soluble fusion protein comprised of Can f 1, 2, 4, 6 is more efficient at binding sIgE to dog. When administered to mice, it induced higher concentrations of dog-specific IgG4 antibodies, but no human clinical trial has been completed.[216]

Easement in regulatory requirements for developing new extracts, and matched pacing of insurance reimbursement to our increasing cost of goods sold, will encourage extract manufacturers to develop novel standardized extracts to ensure consistent, effective dosing regimens. An organized effort between our national professional societies and industry support

is needed for designing and implementing a multi-center trial to study effectiveness of multi-allergen immunotherapy with currently available extracts.

Adherence

Many patients do not complete the duration of SCIT therapy required for long-term benefit, thus wasting resources. Novel antigens are being studied for their improved safety profile, targeted effectiveness, and resultant fewer doses needed for treatment. Passive immunotherapy with anti-cat IgG monoclonal antibodies,[207, 208, 701] SPIREs,[702, 703] and hypoallergenic B-cell epitope-based vaccines[704-707] could help reduce risks of treatment-related SRs as well as provide treatment in some cases as quickly as a single dose. Other research efforts are focusing on shorter treatment cycles like ILIT (discussed above), as well as exploring other administration methods like intradermal[708] and oral[709] administration.

Effectiveness

There is a lack of measurable determinants of long-term immunomodulation success, and there are no evidence-based biomarkers for evaluating AIT effectiveness. We also lack large, long-term studies showing effectiveness of multi-allergen immunotherapy, despite this being normal practice in North America. Improved, future AIT requires better objective measures for predicting response and measurable determinants predicting sustained immunomodulation off therapy. Our specialty and patients could benefit from allergy/immunology specialty societies investing in developing real-world databases to strengthen the evidence base for the safety and effectiveness of multi-allergen immunotherapy throughout the duration of treatment cycles.

Using a standard validated questionnaire for pre-, mid-, and end-of-treatment symptom and medication monitoring like the RCAT or SNOT-22 can provide means for evidence-based support of treatment efficacy. A total combined scoring system (symptom and medication scoring) is considered the gold standard for AIT clinical trial effectiveness.

Allergen provocation testing before and after AIT is another objective measure for comparing clinical response to treatment. Nasal provocation testing, also known as NAC, is one means for inducing clinical response to allergen.[413, 710-714] Conjunctival provocation testing is another way to objectively simulate allergen challenge for comparing pre- and post-treatment symptoms.[197, 715-722] Conjunctival provocation testing is considered safer, less labor intensive, and more cost effective than the nasal route. These tests use application of increasing dilutions of specific allergen to the nose or conjunctiva with the purpose of inducing an allergic response and then measuring symptoms with each successive exposure. After successful immunotherapy, NPT/NAC or conjunctival provocation testing can objectively measure reduced symptoms when challenged to their treated allergen. There is a high degree of concordance between the two methods, and patients consider them equally uncomfortable.[723] Provocation testing is used in some AIT clinical trials but are not routinely used in clinical practice as most allergists are not trained to perform the tests.

Safety

Current AIT poses inherent risk of anaphylaxis in diseases which are usually not life threatening. Safety measures for improvement include better data on ideal pre-treatment and/or post-treatment related to routine and accelerated SCIT schedules.

Our patients could benefit from a better understanding of pre- and post-rush and cluster treatment regimens such as knowing the best balance of immune dampening effects of antihistamines +/- LTM +/- OCS without causing immune suppression and subsequent reduced immunomodulation.

Longer intervals between maintenance SCIT aeroallergen doses may be effective and safe but have not been well studied. Some practices already use longer maintenance SCIT intervals (5 to 8 weeks) for patients who have completed at least 3 years of SCIT, have been compliant with their injection schedule, have not experienced severe SRs, and have difficulty maintaining a 4-week interval. As opposed to VIT, the only data available on aeroallergen maintenance intervals longer than 4 weeks was collected during the COVID-19 pandemic, and it is unclear whether this data (described below) can be applied to non-pandemic times.

The NAISS evaluated the impact of maintenance intervals on safety from 2021-2023 among 132 practices in North America given the lengthening of standard intervals in some practices during the COVID-19 pandemic.[509] For 2021-2022, there was a significantly increased rate of total SRs per 10,000 injection visits for practices that used a maintenance interval greater than 4 weeks, versus a 4-week maximum maintenance interval (chi-square $p<0.0001$). This finding was also seen for grade 2 (chi-square $p<0.0001$) and grade 3 SRs (chi-square $p=0.0005$). For 2022-2023, there were no significant differences in SR rates per 10,000 injection visits based on maintenance dosing intervals.[509] Data collected during the COVID-19 pandemic in Europe suggested that many patients tolerate a temporary extension of maintenance dosing to every 6 weeks, without an increase in SRs.[481, 724]

The importance of not straying too far from the recommended dosing intervals to maintain efficacy was verified in a real world study of 327 adults on maintenance SCIT during the COVID-19 pandemic.[725] One-hundred fifty-one patients continued to receive SCIT at their regular monthly interval (group 1), 72 received SCIT at intervals between 1 month to less than 2 months (group 2), and 104 patients received SCIT at intervals equal to or more than 2 months (group 3). The patients' symptom and QoL scores pre- and post-pandemic were compared within groups and between groups. The patients with injection intervals of 2 months or more had significantly higher (worse) VAS for symptoms ($p<0.001$), increased medication use scores, ($p=0.005$), and increased total symptom scores ($p<0.001$). When compared to other groups, group 3 also had the lowest VAS-QoL scores ($p<0.001$).[725]

Similarly, we need data to understand how to manage gaps in AIT when scheduled doses are missed for patients who are at low risk versus high risk for SR. If we could safely continue dosing after missed doses without significantly reducing the dose, we might improve adherence by encouraging patients to move forward in their build-up schedules despite real life gaps in treatment.

Allergy specialists need evidence-based strategies for advising co-factor management, such as beta-blocker therapy, concomitant exercise, fever, and acute illness during AIT. Our recommendations for how patients should manage these health and lifestyle factors and/or how we should adjust AIT schedules around illness should be better supported with evidence rather than extrapolations or empiricism.

Environmental monitoring

The future is a place where outdoor and indoor home micro-climate monitoring provides real-time pollen and air quality information. A micro-climate is the physical climate in a person's immediate vicinity (e.g., areas around home, work, school), including the surrounding air, and consumed food and water. Accessible advancements in pollen counting technology could make pollen counting automated and easier to adopt. Significantly, reducing barriers to establishing counting stations would resolve current technical difficulties associated with manual counting. Many of our aeroallergen testing panels are based on historical pollen count data from counting stations hundreds of miles from our communities or from colleagues' and extract manufacturer recommendations. Increasing the number of aeroallergen counting stations and developing automated counting stations can help us monitor changes in local pollen and other allergen counts that are possible with climate-change trends. Climate change pressures are impacting the time of onset and length of pollen seasons, expansion of pollen exposure maps, and dosing frequency for co-seasonal forms of AIT.[726] Historical pollen count trends inform specialists' testing panel selections which directly impact AIT prescribing.

Mobile monitoring devices can further enable personalized monitoring of symptoms and medication use for AR, providing objective measurements during AIT.[727]

A global pandemic taught us that patients have preferences about how and where they receive treatments, many desiring convenient treatments that reduce time spent in travel to our offices and time in clinics. Allergy specialists aspire to maintain access to treatments they can compound and administer in their offices, to utilize research-proven therapies, and to maintain or improve allergen extract availability. The future of allergy also depends on our partners in regulatory bodies and extract manufacturing to work with researchers to help move science-proven therapies into clinical practice and to keep pace with extract production needs, respectively.

The future of AIT lies in our ability to precisely diagnose allergies personalized to our patients' micro-climates; in access to safer, more effective allergen extracts for vaccines; in defining objective measures of effective immunomodulation for determining AIT efficacy; and in embracing a patient-centric, convenience-forward approach to AIT. AIT has an illustrious history of proven effectiveness and a bright future of innovation ahead.

Table 26. Call to action for allergy researchers.

Evidence Gap
Measurable determinants of long-term immunomodulation success in AIT
Data for prolonged SCIT maintenance dosing intervals for maximizing safety and efficacy
Data for how to manage dose adjustments for missed scheduled doses
Data regarding quality of non-standardized extracts
Clear predictors for increased risk of anaphylaxis

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