PROF. GRAHAM C ROBERTS (Orcid ID : 0000-0003-2252-1248)
PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)

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EAACI Guidelines on Allergen Immunotherapy: Allergic Rhinoconjunctivitis

Authors: Roberts G*[1,2,3], Pfaar O*[4,5], Akdis CA[6], Ansotegui IJ[7], Durham SR[8], Gerth van Wijk R[9], Halken S[10], Larenas-Linnemann D[11], Pawankar R[12], Pitsios C[13], Sheikh A[14], Worm M[15], Arasi S[16], Calderon MA[8], Cingi C[17], Dhami S[18], Fauquert JL[19], Hamelmann E[20], Hellings P[21], Jacobsen L[22], Knol EF[23], Lin SY[24], Maggina P[25], Mösges R[26], Oude Elberin H[27], Pajno GB[28], Pastorello EA[29], Penagos M[8], Rotiroti G[30], Schmidt-Weber CB[31], Timmermans F[32], Tsilochristou O[33], Varga E-M[34], Wilkinson JN[35], Williams A[36], Zhang L[37], Agache I[38], Angier E[39], Fernandez-Rivas M[40], Jutel M[41], Lau S[42], van Ree R[43], Ryan D[44], Sturm G[45], Muraro A[46].

*Denotes equal contribution

Affiliations:

1. The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK

2. NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. Clinical and Experimental Sciences and Human Development in Health Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK

4. Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;

5. Center for Rhinology and Allergology, Wiesbaden, Germany

6. Swiss Institute of Allergy and Asthma Research (SIAF), University Zurich, Davos Switzerland. Christine Kühne Center for Allergy Research and Education, Davos, Switzerand

7. Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Erandio – Bilbao, Spain

8. Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London, UK.

9. Section of Allergology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands

10. Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

11. Center of Excellence in Asthma and Allergy, Hospital Médica Sur, Mexicocity, Mexico

12. Dept. of Pediatrics, Nippon Medical School, Tokyo, Japan

13. Medical School, University of Cyprus, Nicosia, Cyprus

14. Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

15. Department of Dermatology and Allergy, Charité Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany

16. Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy; Molecular Allergology and Immunomodulation-Department of Pediatric Pneumology and Immunology, Charite Medical University, Berlin, Germany

17. Medical Faculty, Dept of Otorhinolaryngology, Eskisehir Osmangazi University, Eskisehir, Turkey

18. Evidence Based Health care Ltd, Edinburgh, UK

19. CHU Clermont-Ferrand University Hospital (CHU Estaing), Unité d'allergologie de l'enfant, INSERM, Clermont-Ferrand, France.

20. Children's Hospital Bethel, EvKB, University Bielefeld, Germany

21. Dept of Otorhinolaryngology, Univ. Hospitals Leuven, Belgium and Dept of Otorhinolaryngology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands.

22. Allergy Learning and Consulting, Copenhagen, Denmark

23. Depts. Immunology and Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

24. Johns Hopkins Dept of Otolaryngology-Head & Neck Surgery, Baltimore, USA

25. Allergy & Clinical Immunology Unit, 2nd dpt of Pediatrics, NKUA Athens University, Athens, Greece

26. Clinical Research International Ltd., Mühlenberg 64, 22587 Hamburg, Germany

27. University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands

28. Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy

29. University of Milano, Department of Allergy and Immunology, Asst Grande Ospedale Metropolitano Niguarda, Milano, Italy

30. Department of Allergy and Medical Rhinology, The Royal National Throat Nose and Ear Hospital, University College Hospital, London, UK

31. Center of Allergy and Environment (ZAUM) & Institute of Allergy Research, Helmholtz Center Munich, Munich, Germany

32. European Anaphylaxis Taskforce - Nederlands Anafylaxis Netwerk, Dordrecht, The Netherlands

33. Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, Children's Allergy Service, King's College London & Guy's and St. Thomas' National Health Service Foundation Trust, London, UK

34. Dept. of Paediatric and Adolescent Medicine, Respiratory and Allergic Disease Division, Medical University of Graz, Graz, Austria

35. Pharmaceutical Group of the European Union, Brussels, Belgium

36. Allergy Department Guys & St Thomas' NHS Foundation Trust, London, UK

37. Department of Otolarlyngology Head & Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing, China

38. Transylvania University Brasov, Faculty of Medicine, Department of Allergy and Clinical Immunology, Brasov, Romania

39. Department of Clinical Immunology and Allergy, Northern General Hospital, Herries Road, Sheffield, UK

40. Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

41. ALL-MED Medical Research Institute, Wroclaw Medical University, Poland

42. Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany

43. Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

44. Usher Institute of Population Health Sciences and Informatics, University of Edinburgh Medical School, Edinburgh, UK

45. Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria; Outpatient Allergy Clinic Reumannplaz, Vienna, Austria

46. Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Padua, Italy

Correspondence: Antonella Muraro, Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Via Giustiniani 3, 35128 Padua, Italy Tel.: +39-049-821-2538 Fax: +39-049-8218091 E-mail: muraro@centroallergiealimentari.eu

Short title: EAACI Guideline: AIT for Rhinoconjunctivitis

Key words: allergen immunotherapy, allergy, allergic conjunctivitis, allergic rhinitis, rhinoconjunctivitis

Abbreviations:

AR, allergic rhinoconjunctivitis; AIT, allergen immunotherapy; AGREE II, Appraisal of Guidelines for Research & Evaluation; ARIA, Allergic Rhinitis and its Impact on Asthma; EPIT, epicutaneous immunotherapy; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; HDM, house dust mite; ICER, incremental cost-effectiveness ratio; NARES, non-allergic rhinitis with eosinophilia syndrome; QALY, quality-adjusted life years; RCT, randomized controlled trial; SPT, skin prick test; SMD, standardized mean difference; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SmPC, summary or product characteristics.

ABSTRACT

Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes affecting about a fifth of the general population. Symptoms of AR can be controlled with allergen avoidance measures and pharmacotherapy. However, many patients continue to have ongoing symptoms and an impaired quality of life; pharmacotherapy may also induce some side-effects. Allergen immunotherapy (AIT) represents the only currently available treatment that targets the underlying pathophysiology and it may have a disease modifying effect. Either the subcutaneous (SCIT) or sublingual (SLIT) routes may be used. This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on AIT for AR and is part of the EAACI presidential project "EAACI Guidelines on Allergy Immunotherapy". It aims to provide evidence-based clinical recommendations and has been informed by a formal systematic review and meta-analysis. Its generation has followed the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included involvement of the full range of stakeholders. In general, broad evidence for the clinical efficacy of AIT for AR exists but a product-specific evaluation of evidence is recommended. In general, SCIT and SLIT are recommended for both seasonal and perennial AR for its short term benefit. The strongest evidence for long-term benefit is documented for grass AIT (especially for the grass-tablets) where long-term benefit is seen. To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used. Many gaps in the evidence base exist, particularly around long-term benefit and use in children.

INTRODUCTION

Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes, resulting in a chronic, mostly eosinophilic, inflammation of the nasal mucosa and conjunctiva [1,2]. Allergic rhinitis, with or without conjunctivitis, is one of the most prevalent allergic diseases affecting around a fifth of the general population [3,4,5]. It is associated with considerable loss of productivity and impaired school performance [6].

AR can usually be diagnosed from its typical presentation (Figure 1). Symptoms include itching, sneezing, watery nasal discharge and nasal congestion [2]. Commonly, there are associated ocular symptoms (watery, red and/or itchy eyes). Symptoms may be described as seasonal and/or perennial; as intermittent or persistent; or mild, moderate or severe according to their impact on the quality of life [8]. Symptoms are related to exposure to the offending allergen as well as to non-specific triggers such as smoke, dust, viral infections, strong odors and cold air [2]. Symptoms on exposure to one or more aeroallergens

supported by evidence of allergen-specific IgE sensitisation to the relevant allergens confirms the diagnosis. AR may co-exist with other forms of rhinitis (Figure 1). Additionally, AR may be associated with symptoms of sinusitis, hearing problems and asthma [2].

The aims of AR management are to control symptoms and reduce inflammation. Where possible, allergen avoidance can be recommended. Effective allergen avoidance is however often not feasible [9,10]. Many patients rely on pharmacotherapy with, for example, oral or topical antihistamines, intranasal corticosteroids, topical cromoglycate or leukotriene receptor antagonists [2]. However, these therapies do not alter the natural history of AR and may also induce side-effects. Additionally, despite medication, a significant number of patients continue to experience symptoms that impair their quality of life. Allergen immunotherapy (AIT) with the subcutaneous (SCIT) or sublingual (SLIT) administration of the culprit allergen(s) may not only desensitize a patient, thereby ameliorating symptoms, but also deliver long-term clinical benefits that may persist for years after discontinuation of treatment [11,12,13].

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Guideline on Allergen Immunotherapy: Allergic Rhinoconjunctivitis Taskforce and is part of the EAACI Guidelines on Allergy Immunotherapy. This Guideline aims to provide evidence-based recommendations for the use of AIT for patients with allergic rhinitis with or without conjunctivitis. The term AR will henceforth be used to denote either allergic rhinitis or allergic rhinoconjunctivitis (see Box 1 for definitions of key terms). The primary audience are clinical allergists (specialist and subspecialists); the document may also provide guidance to other healthcare professionals (e.g. physicians from other disciplines, nurses and pharmacists working across a range of primary, secondary and tertiary care settings) dealing with AR. The development of the Guideline has been informed by a formal systematic review (SR) and meta-analysis of AIT for AR [14], with systematic review principles being used to identify additional evidence, where necessary.

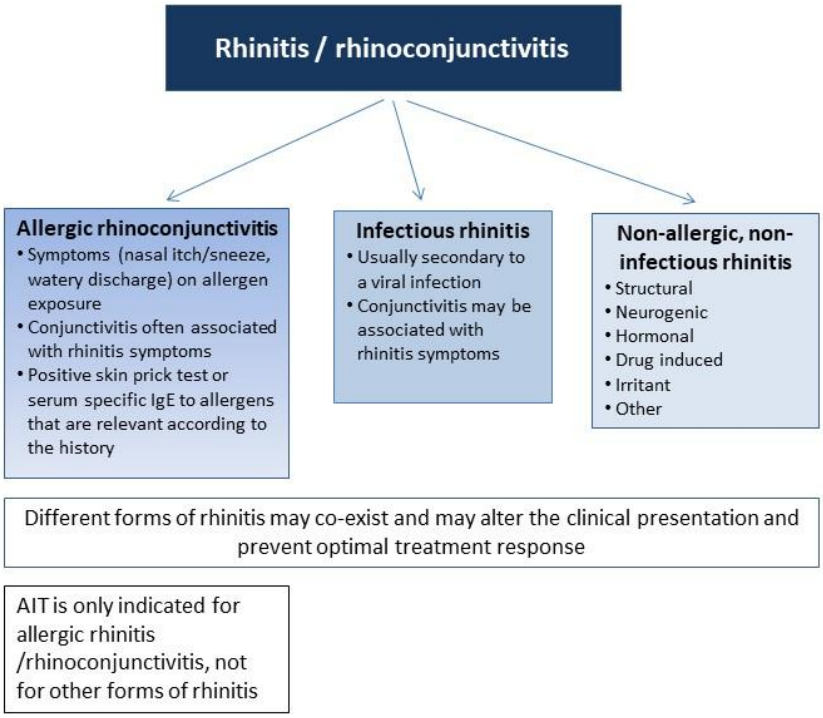

Figure 1. Differential diagnosis of allergic rhinoconjunctivitis

Adapted from Roberts 2013 [7]. Local allergic rhinitis may be seen where there is only evidence of local nasal allergic sensitization [15,16,26]. There are numerous other causes of non-allergic, non-infectious rhinitis, an example is non-allergic rhinitis with eosinophilia syndrome (NARES) [7]. In individual patients, symptoms may be driven by more than one trigger. Rhinosinusitis is not included in the scope of this Guideline.

Box 1. Key terms	
Allergen immunotherapy (AIT)	Repeated allergen administration at regular intervals to modulate immune response in order to reduce symptoms and the need of medication for clinical allergies and to prevent the development of new allergies and asthma. This is also sometimes known as allergen specific immunotherapy, desensitization, hypo-sensitization or allergy vaccination.
Conjunctivitis	Inflammation of the conjunctiva characterized by watery, itchy, red eyes.
Efficacy	**Short-term treatment efficacy:** clinical benefit to the patient while they are receiving AIT. **Long-term treatment efficacy:** clinical benefit to the patient for at least one year after cessation of the AIT course [14].
Rhinitis	Inflammation of the nasal mucosa resulting in at least two nasal symptoms: rhinorrhea, blockage, sneezing or itching.
Sensitization	Detectable allergen specific-IgE antibodies, either by means of skin prick test (SPT) and/or specific-IgE antibodies in a serum sample.
Subcutaneous immunotherapy (SCIT)	Form of AIT where the allergen is administered as subcutaneous injections.
Sublingual immunotherapy (SLIT)	Form of AIT where the allergen is administered under the tongue with formulation as drops or fast dissolving tablets which are administered through the sublingual route.

METHODOLOGY

This Guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach [17,18], a structured approach to guideline production. This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations and steps to ensure that the risk of bias is minimized at each step of the process. The process started on April 2015 beginning with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face meetings and regular web-conferences in which professional and lay representatives participated.

Clarifying the scope and purpose of the guidelines

The scope of this EAACI Guideline is multifaceted, providing statements that assist clinicians in the optimal use of AIT in the management of patients with AR and identifying gaps for further research.

Ensuring appropriate stakeholder involvement

Members of the EAACI Taskforce on AIT for AR represented a range of 18 countries and disciplinary and clinical backgrounds, including allergists (specialist and subspecialists), pediatricians, primary care specialists, ophthalmologists, otolaryngologists, pharmacists, immunologists, nurses and patient representatives. Methodologists took the lead in undertaking the underpinning SR while clinical academics took the lead in formulating recommendations for clinical care. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guidelines as part of the peer review and public comment process at the final stage. These comments were considered by Taskforce members and, where appropriate, revisions were made.

Systematic reviews of the evidence

The initial full range of clinical questions that were considered important were rationalized through several rounds of iteration to agree on one key question: What is the effectiveness, cost-effectiveness and safety of AIT in patients with AR? This was then pursued through a formal SR of the evidence by independent methodologists as previously published [19,14]; only double-blind RCTs were included in the effectiveness analyses. We continued to track evidence published after our SR cut-off date of October 31, 2015 and, where relevant, studies were considered by the Taskforce chairs. This evidence will formally be considered

in the systematic review update that will precede the update of this Guideline (discussed below).

Formulating recommendations

We graded the strength and consistency of key findings from the SR and performed meta-analyses, using a random-effects model to take into account the heterogeneity of findings [14]. These were used to formulate evidence-based recommendations for clinical care [20] (Box 2). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. Where the systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, i.e.: (i) other systematic reviews on the subject to see if these provided any clarity on the topic; (ii) RCTs within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach within the Taskforce. This evidence was graded as described in Box 2 using the SR results [14] and clearly labelled in the recommendation tables. Recommendations apply to all ages unless otherwise indicated in the tables. When there were insufficient pediatric data, we extrapolated from the adult recommendation where it was biologically likely that the intervention would also be effective in children, but downgraded the recommendation by at least one level. Taskforce members identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, adviced on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guideline was made available on public domain on the EAACI Website for a three week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce members and, where appropriate, final revisions were made in the light of the feedback received. We will be pleased to continue to receive feedback on this guideline, which should be addressed to the corresponding author.

Identification of evidence gaps

The process of developing this Guideline has identified a number of evidence gaps which are prioritized (Table 10).

Editorial independence and managing conflict of interests

This Guideline was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents or on the decision to publish. Taskforce members' conflicts of interest were declared at the start of the process and taken into account by the taskforce chairs as recommendations were formulated. Final decisions about strength of evidence for recommendations were checked by the methodologists who had no conflict of interests in this area.

Updating the guidelines

EAACI plans to update this guideline in 2022 unless there are important advances before then.

Box 2: Assigning levels of evidence and strength of recommendations

Level of evidence

Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g., cohort, case–control)
Level III	One group, non-randomized (e.g., before and after, pretest, and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements

Grades of recommendation

Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

Strength of recommendations

Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong: “is recommended”; moderate: “can be recommended”; weak: “may be recommended in specific circumstances”; negative: “cannot be recommended”.

Approach adapted from Oxford Centre for Evidence-based Medicine – Levels of Evidence and Grades of Recommendations [20]. The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information.

GENERAL CONSIDERATIONS BEFORE INITIATING AIT FOR AR

General considerations

AIT is only indicated in the presence of symptoms strongly suggestive of AR, with or without conjunctivitis (Table 1) [14,21]. Many patients will also have co-existing asthma. There should be symptoms on aeroallergen exposure with evidence of allergen specific IgE-sensitzation (positive SPT or serum specific-IgE) [14]. Identification of the allergen(s) driving symptoms is the first level of patient stratification ensuring that the correct allergen is used for AIT. Occasionally, SPT or specific-IgE results may not clearly identify the key allergen(s) causing the AR symptoms in polysensitized patients. Component resolved diagnostics may have a role in deciding which aeroallergen(s) should be chosen but definitive trials are awaited. An alternative approach is to use nasal or conjunctival provocation testing to prove the clinical relevance of the allergic sensitization in the relevant (target) organs before initiation of AIT but again definitive evidence is awaited.

AIT is indicated in those patients with moderate-to-severe symptoms (e.g. Allergic Rhinitis and its Impact on Asthma (ARIA) categories moderate-to-severe intermittent or persistent [22]), despite avoidance measures and pharmacotherapy, that interfere with their usual daily activities or sleep. AIT may also be considered in cases with less severe AR where the patient wishes to have the benefit of its long-term effect on rhinitis and a potential disease modifying effect to prevent asthma [23]. AIT products with evidence of efficacy for AR should be used when available [11,24].

Absolute and relative contraindications

Even when AIT is suitable for a patient with AR, clinicians must consider if there are any specific patient-related absolute or relative contraindications (Table 2), where the risk from AIT may outweigh the expected benefits. The summary of product characteristics (SmPC) should be reviewed for specific contraindications for individual preparations.

Table 1. General considerations for AIT for allergic rhinoconjunctivitis*

General indications	Key references	Contextual considerations
AIT should be considered when all of these criteria are met: • symptoms strongly suggestive of AR, with or without conjunctivitis • there is evidence of IgE-sensitization (positive SPT and / or serum specific-IgE) to one or more clinically relevant allergen • experience moderate-to-severe symptoms which interfere with usual daily activities or sleep despite regular and appropriate pharmacotherapy and/or avoidance strategies	Dhami 2017 [14]	A diagnosis of AR and evidence of IgE-sensitization were entry criteria for RCTs in the systematic review.
AIT may also be considered in less severe AR where a patient wishes to take advantage of its long-term effect on AR and potential to prevent asthma with grass pollen AIT	Kristiansen 2017 [25] Halken 2017 [23]	AIT has the potential to alter the natural history of disease reducing AR symptoms after completing an adequate period of immunotherapy and preventing the development of asthma in the short term, up to 2 years post AIT.
Standardized AIT products with evidence of efficacy in the clinical documentation should be used	Dhami 2017 [14]	These products have consistent formulations and so different batches are likely to have similar effects. The meta-analysis [14] reveals a considerable heterogeneity in effectiveness between products and therefore a product-specific evaluation

	of efficacy is recommended.

*The Summary of Product Characteristics (SmPC) should be checked for licensed indications which may differ between preparations.

Table 2. General contraindications for AIT for allergic rhinoconjunctivitis*

	Key references	Contextual considerations
The following are considered to be contraindications:		
Uncontrolled or severe asthma	Bernstein 2004 [31]; Bousquet 1989 [29]; Calderon 2012 [34]; Cox 2011 [28]; CSM 1986 [32]; Lockey 2001 [30]; Normansell 2015 [33]; Pfaar 2014 [11]; Pitsios 2015 [27]	Weak evidence of risk with uncontrolled asthma, active systemic autoimmune disease and malignancy from case reports or case series of adverse events with AIT. Taskforce considered that these were contraindications to AIT. Though initiation of AIT is contraindicated during pregnancy, an ongoing AIT is permissible when having been well tolerated by the patient in the past
Active, systemic autoimmune disorders (unresponsive to treatment)	Cabrera 1993 [35]; Fiorillo 2006 [37]; Pfaar 2014 [11]; Sánchez-Morillas 2005 [36]; Pitsios 2015 [27]	
Active malignant neoplasia	Larenas-Linnemann 2016 [39]; Pfaar 2014 [11]; Wöhrl 2011 [38]	
AIT initiation during pregnancy	Metzger 1978 [40]; Pfaar 2014 [11]	

With the following, AIT should only be used with caution when benefits outweigh potential risks in an individual patient:		
Partially controlled asthma	Virchow 2016 [41]	One trial with SLIT tablet [41] included some subjects with partially controlled asthma without compromising safety; it is important that confirmatory evidence is acquired.
Beta-blocker therapy (local or systemic)	Cleaveland 1972 [44]; Hiatt 1985 [42]; Lang 1995 [45]; Pfaar 2014 [11].	Weak evidence of risk. May compromise a patient's ability to tolerate an episode of anaphylaxis. This must be considered when deciding whether AIT is appropriate.
Severe cardiovascular diseases, e.g. coronary artery disease	Larenas-Linnemann 2016 [39]; Linneberg 2012 [46]	
Systemic autoimmune disorders in remission or organ specific	Larenas-Linnemann 2016 [39]. Pitsios 2015 [27]	Weak evidence of risk from case reports, case series of adverse events with AIT or expert opinion based on clinical experience. Taskforce considered that careful consideration on a case-by-case basis with discussion between patient and the treating physician is required before deciding whether or not to commence AIT.
Severe psychiatric disorders	Pitsios 2015 [27].	
Poor adherence	Pitsios 2015 [27]; Pfaar 2014 [11].	
Primary and secondary Immunodeficiencies	Larenas-Linnemann 2016, [39], Pitsios 2015 [27]	
History of serious systemic reactions to AIT	Calderon 2012 [34]	

*The Summary of Product Characteristics (SmPC) should also be checked for product specific contraindications which may differ between preparations.

ALLERGEN IMMUNOTHERAPY FOR AR: EVIDENCE-BASED, CLINICAL RECOMMENDATIONS

To underpin this guideline, a SR of the AIT literature was undertaken [14]. In general, the meta-analysis suggested that both SCIT and SLIT are effective for AR. They were associated with reductions in symptoms and with medication use. There were insufficient data to determine which of SCIT and SLIT are most effective.

Moderate to substantial heterogeneity was observed in some outcomes evaluated in the meta-analysis [14]. This heterogeneity can be explained by the study design (particularly the different outcomes used), study population and the products evaluated. There are data to indicate which preparations are most likely to be effective; so an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated. Not all AIT products provide sufficient data to support their efficacy in clinical practice [14]. As a result of this, the recent German, Austrian and Swiss guideline has followed a product specific approach [11]. This approach is more difficult across Europe with differing local regulations [47] and availability of products [48]. The specific recommendations in this guideline need to be seen in this context with only standardized AIT products with evidence of efficacy in the clinical documentation prescribed. The only exception should be orphan allergens where only a few patients are affected; these are discussed below in the specific allergen section.

SCIT immunotherapy is in general recommended for the treatment of AR in children and adults with moderate-to-severe disease that is sub-optimally controlled despite pharmacotherapy [14](Table 3). The evidence for short-term benefit for continuous SCIT is stronger for seasonal rhinitis (Grade A for adults) than for perennial rhinitis (Grade B for adults), where fewer studies have been performed and results are more heterogeneous (Table 3). SCIT is recommended for seasonal disease whether pre- or pre/co-seasonally (Table 3, Grades A for adults). Pre/co-seasonal therapy benefits from a shorter course of treatment but the one head-to-head trial suggests that continuous therapy may be more effective [49].

SCIT may be administered in aqueous formulation (rarely in Europe) or as a depot adsorbed on aluminum hydroxide or tyrosine. SCIT using either unmodified or modified allergen extracts is recommended for treatment of AR and provides short-term benefit (Table 3, Grade A for adults). This is based on evidence from the meta-analysis [14] that showed both unmodified allergen extracts (SMD [95%CI] -0.65 [-0.93, -

0.36]) and allergoids/polymerized extracts (-0.60 [-0.89, -0.31]) to be effective in reducing symptoms compared to placebo, with additional support from reduced medication requirements and combined symptom-medication scores. Although clinical trials of modified allergens involved shorter courses of treatment, there have been no head-to-head comparisons with unmodified preparations evaluating efficacy or adverse events using a placebo-controlled, randomized design.

In general, SLIT can be recommended for the treatment of seasonal AR in adults and children. SLIT has been shown to provide short term benefit during therapy with moderate-to-severe disease that is sub-optimally controlled despite pharmacotherapy (Table 3) [14]. SLIT is recommended to be taken either continuously or pre-/co-seasonally commencing a minimum of two months and ideally four months prior to the start of the pollen season (Grade A for adults).

SLIT may be taken daily either as fast-dissolving tablets or drops that are retained under the tongue for at least one minute and then swallowed. Both are recommended (Grade A and B respectively for adults) based on short-term reductions in symptoms and rescue medication for sublingual tablets for seasonal AR (Table 3). There are only convincing evidence for effectiveness of SLIT tablet in perennial AR (Grade A)(Table 3).

Sublingual grass pollen tablet immunotherapy for at least three years is recommended (Grade A) for the short-term treatment of grass polen driven AR in adults [86,87,108,109]. Sublingual house dust mite (HDM) tablet immunotherapy for at least one year is recommended (Grade A) for the short-term treatment of perennial HDM AR in adults [50,51,52,53,54,55].

While higher doses and/or increased cumulative doses may be more effective, they may be associated with more side-effects [56,57,58]; decisions on dose must be made balancing efficacy and side-effects [59].

Table 3. Recommendations: AIT for treatment of allergic rhinoconjunctivitis: schedules, products, formulations

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results.							
Recommendation	**Adults**		**Children and adolescents**		**Strength of recommendation**	**Other considerations**	**Key references**
	Evidence level	**Grade of recommendation**	**Evidence level**	**Grade of recommendation**			
SCIT							
Seasonal allergic rhinitis							
Continuous SCIT is recommended for seasonal AR for short-term benefit in those with moderate-to severe disease	I	A	I	B	Strong recommendations for adults based on low risk of bias studies [60,61,62]. Moderate recommendation for children as just one one open RCT with risk of bias reporting solely pediatric data [63].	Consistent results, low risk of severe systemic allergic side-effects. Most studies reported pediatric and adult data together.	Dhami 2017 [14], e.g. **Adult:** Dolz 1996 [64], Charpin 2007 [61], Ferrer 2005 [62], Jutel 2005 [75], Scadding 2017 [65], Walker 2001 [60] **Paediatric:** Jacobsen 2007 [63].
Pre- and pre-/co-seasonal SCIT is recommended for seasonal AR for short-term benefit	I	A	I	B	Strong recommendation for adults based on low risk of bias studies [69,70,71,72]. Moderate recommendation for children as only combined adult/pediatric data, one study with low risk of bias [73] and with one with unclear risk of bias RCTs [74] available.	Consistent results in adult studies; low risk of severe systemic allergic side-effects.	Dhami 2017 [14] SR, e.g. **Adult:** Balda 1998 [69], Bodtger 2002 [70], Bousquet 1990 [74], Frew 2006 [58], Varney 1991 [71], Zenner 1997 [72]. **Adult/pediatric:** Bousquet 1990 [74], Weyer 1981 [73].

Continuous grass pollen SCIT is recommended for seasonal AR for short and long-term benefit	I	A	I	B	Strong recommendation for adults based on above evidence plus two low risk of bias long-term studies [83,84]. Moderate recommendation for children as one long-term open RCT with risk of bias [63].	A few adult studies and one pediatric study (designed to assess whether SCIT prevents asthma) demonstrating long-term effectiveness.	Dhami 2017 [14] SR, e.g. **Adult:** Durham 1999 [83], James 2011 [84]. **Pediatric:** Jacobsen 2007 [63].
Perennial allergic rhinitis							
Continuous SCIT is recommended for perennial AR due to HDM for short-term benefit	I	B	I	C	Strong recommendation for adults based on one study with low risk of bias [67] plus one with high risk of bias [68]. No exclusive pediatric data. Moderate recommendation for children, based on extrapolation from adult studies.	Few small adult studies, considerable heterogeneity [66] and risk of systemic allergic side-effects.	Dhami 2017 [14] SR, e.g. **Adult:** Dokic 2005 [67], Ewan 1988 [68], Varney 2003 [66]
All							
Modified (allergoids) and unmodified allergen extracts for pollens and HDM SCIT are recommended for AR for short-term benefit	I	A	I	B	Strong recommendation for adults based on high quality studies for both modified [61,67,76,77,78] and non-modified [60,61, 69,70,71, 72,73,76,79,80] allergen extracts. Weak recommendation for children as no exclusive pediatric randomized, placebo-controlled data.	Consistent results, low risk of severe systemic allergic side effects. No exclusive pediatric randomized, placebo-controlled data.	Dhami 2017 [14] SR, e.g. **Modified:** Ceuppens, 2009 [81]; Corrigan 2005 [77], Dokic 2005 [67], Klimek 2014 [78], Riechelmann 2010 [82]. **Non-modified:** Balda 1998 [69], Bodtger 2002 [70], Brunet 1992 [76], Charpin 2007 [61], Frew 2006 [58], Ortolani 1994 [79], Scadding 2017 [65], Varney 1991 [71], Walker 2001 [60], Weyer 1981 [73], Zenner 1997 [72]. **Modified and non-modified**: Bousquet 1990 [74].

SLIT							
Seasonal allergic rhinitis							
Pre-/co-seasonal SLIT is recommended for seasonal ARs for short-term benefit	I	A	I	A	Strong recommendation based on high quality adult [86,87,88,89] and paediatric [90,91,92,155,156] studies.	Consistent results, low risk of severe systemic allergic side-effects.	Dhami 2017 [14] SR, e.g. **Adult:** Dahl 2006 [85], Dahl 2006 [86], Didier 2007 [56], Durham 2006 [87], Palma-Carlos 2006 [96], Worm 2014 [89] **Pediatric:** Blaiss 2011 [99]; Bufe 2009 [98]; Caffarelli, 2000 [90], Halken 2010 [97], Pajno, 2003 [91], Wahn 2009 [156].
Continuous SLIT can be recommended for seasonal AR for short-term benefit	I	A	I	A	Moderate-to-strong recommendation based on low [100] and high [101,102] risk of bias adult studies plus low [111], moderate [103] and unclear [57] risk of bias paediatric studies.	Some heterogeneity between studies particularly pediatric ones, low risk of severe systemic allergic side effects.	Dhami 2017 [14] SR, e.g. **Adult:** Amar 2009 [100], Ariano, 2001 [101], Creticos 2013 [93], Panzner, 2008 [102]. **Pediatric:** Bufe 2004 [103], Valovirta 2006 [57], Valovirta 2017 [111].
SLIT with aqueous solutions can be recommended for seasonal AR for short-term benefit.	I	B	I	A	Moderate recommendation for adults based on a mixture of low [104] and high [101,105,106] risk of bias studies. Strong recommendation for pediatrics based on low risk of bias studies [91, 92].	Some heterogeneity between adult studies, low risk of severe systemic allergic side-effects.	Dhami 2017 [14] SR, e.g. **Adult:** Ariano 2001 [101], Bowen 2004 [105], Feliziani 1995 [104], **Pediatric:** Pajno 2003 [91], Stelmach 2012 [92]
SLIT with grass pollen tablets is recommended for AR for short-term benefit.	I	A	I	A	Strong recommendation based on low risk of bias adult [86,87,108,109] and pediatric [97,98,99,111] studies.	Non-important heterogeneity between studies, low risk of severe systemic allergic side effects.	Dhami 2017 [14] SR, eg **Adult:** Dahl 2006 [86], Didier 2007 [56], Didier 2013 [108], Durham 2006 [87], Durham 2012 [109] **Pediatric:** Blaiss 2011 [99], Bufe 2009 [98], Halken 2010 [97], Valovirta 2017 [111]

Grass pollen SLIT tablets or solution with continuous therapy is recommended for AR for long-term benefit.	I	A	I	A	Strong recommendation for adults based on low risk of bias studies [108,109]. One low risk of bias pediatric study [110,111]	Effective up to 2 years after cessation in adults [108,109]. One pediatric study was designed to look at prevention of asthma.	Dhami 2017 [14] SR, eg **Adult:** Didier 2015 [94], Durham 2012 [109] **Pediatric:** Valovirta 2011 [110] & 2017 [111] **Adult & pediatric:** Ott 2009 [145]
Perennial allergic rhinitis							
SLIT with aqueous solutions may not be recommended for perennial AR for short-term benefit.	I	C	I	A	Weak recommendation against use for adults based on one high risk of bias RCT. [107] Cannot be recommended in children based on 4 negative RCTs and 1 positive RCT.	Low risk of severe systemic allergic side-effects. Studies of low [106,139,140,146] and high [144] risk of bias suggest that it is not effective in children.	Dhami 2017 [14] SR, e.g. **Adult:** Guez 2000 [107], **Pediatric:** Bahçeciler 2001 [139], de Bot 2012 [146], Hirsch 1997 [140], Marcucci 2003 [144], Tari 1990 [106]
SLIT with HDM tablets is recommended for AR for short-term benefit.	I	A	I	A	Strong recommendation based on low risk of bias adult [50,51,52,53,54] and mixed adult/pediatric [51,55] studies.	Non-important heterogeneity between studies, low risk of severe systemic allergic side effects.	Dhami 2017 [14] SR, eg **Adult:** Bergmann 2014 [53], Demoly 2015 [52], Mosbech 2015 [54], Passalacqua 2006 [50], Passalacqua 1998 [147 **Adult and pediatric:** Nolte 2016 [51], Okubo 2017 [55]
HDM SLIT tablet with continuous therapy can be recommended for AR for long-term benefit.	I	B	-	C	Moderate recommendation based on one large, low risk of bias study [53]. No pediatric data.	One study demonstrates effectiveness for a year post-treatment [53]; data requires replication especially as 3 years therapy required for grass pollen. No pediatric data, extrapolated from adult data.	**Adult:** Bergmann 2014 [53].

Continuous: year round therapy. Pre-seasonal: before a pollen season. Co-seasonal: during a pollen season. Not all AIT preparations are licensed for children and adolescents. Long-term is defined as at least one year after cessation of the AIT course. See allergen factors section for other specific allergens.

Other approaches of AIT for AR

Other approaches aim to improve patient convenience and adherence with shorter courses, whilst improving or maintaining efficacy and reducing the risk of systemic side effects (Table 4). As such, adjuvants to AIT extracts are possible candidates [112]. For example, TLR-4 agonists (Th1-inducing adjuvant monophosphoryl lipid A) in combination with a grass allergoid has demonstrated effectiveness [113], although in a phase three trial efficacy was modest [114] (Grade A for adults, B for children) and there are no head-to-head comparisons with conventional preparations. There is also one trial demonstrating efficacy for this approach with ragweed pollen [172]. The TLR-9 agonist (Bacterial DNA oligonucleotides containing a CpG motif) fused to Amb a 1, the major allergen of ragweed showed efficacy in a phase two trial [115] although this was not observed in a subsequent phase three trial. The combination of anti-IgE injections with conventional and rush AIT with non-modified extracts has been proven to be effective with a marked reduction in systemic side-effects in studies of children [116] and adults [117] (Grade A recommendation). This is an expensive approach and there is concern as to when and how to discontinue the anti-IgE when AIT maintenance therapy is achieved [118].

Recombinant AIT is attractive as it allows accurate standardization of allergen products, has potential for personalized therapy based on individual allergen sensitivities and a hypothetical lower risk of inducing new sensitizations. Subcutaneous recombinant birch (Bet v 1) [119] and a five-recombinant grass allergen mix [75] have been shown to be efficacious with no safety concerns (Grade A for adults, B for children). However, there are no commercially products available at present. A recombinant B cell epitope-based vaccine, comprising a recombinant hybrid grass allergen mix combined with a hepatitis B domain surface Pre-S protein as an immunologic carrier has shown efficacy in a phase two trial [120]. T cell peptide immunotherapy for cat allergy using mixtures of short T cell epitopes via the intradermal route, had promising

results in environmental chamber phase two studies [121]; however, it has been reported that a subsequent phase three study did not demonstrate effectiveness [122]. Studies with other allergen peptide approaches are in progress [124].

There has been recent interest in the use of alternative modalities of delivery including the epicutaneous, intradermal and intra-lymphatic routes. In RCTs, epicutaneous grass pollen immunotherapy (EPIT) has shown modest benefit [125] although accompanied by local eczematous reactions at the patch application site. Intradermal grass pollen immunotherapy inhibited allergen-induced cutaneous late responses although in a subsequent RCT it was ineffective and there was evidence of exacerbation of seasonal outcomes and Th2 inflammation in the skin [126]. The intra-lymphatic route, using a grass pollen extract and a modified cat allergen extract, showed efficacy in some trials [127,128] but not in others [129].

Table 4. Recommendations: other approaches for AIT for treatment of allergic rhinoconjunctivitis

For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in the meta-analysis results.							
Recommendation	**Adults**		**Children and adolescents**		**Strength of recommendation**	**Other considerations**	**Key references**
	Evidence level	**Grade of recommendation**	**Evidence level**	**Grade of recommendation**			
A combination of the TLR-4 agonist monophosphoryl lipid A with pollen allergoid is recommended for AR	I	A	III	B	Strong recommendation for adults based on four low risk of bias studies [113,114,131,172]. Weak recommendation for children [130].	Consistent randomized controlled data; only one ragweed pollen study, others grass pollen. Only one uncontrolled before and after study pediatric study [130].	**Adult:** Drachenberg 2001 [113], DuBuske 2011 [114], Patel 2013 [172], Patel 2014 [131] **Pediatric:** Drachenberg 2003 [130],
Combining anti-IgE injections with AIT for AR is recommended for reducing side-effects	I	A	I	A	Strong recommendation based on one low risk of bias adult [117] and one low risk of bias pediatric [116] study.	Consistent evidence but the required length of co-therapy unclear.	**Adult:** Casale 2006 [117] **Pediatric:** Rolinck-Werninghaus 2004 [116]
Recombinant AIT can be recommended for birch and grass pollen allergy	I	A	-	B	Moderate recommendation based on 2 double-blind placebo-controlled RCTs of unclear risk of bias [75,119].	Some evidence of benefit for adults, no pediatric data.	**Adult:** Jutel 2005 [75], Pauli 2008 [119]

ALLERGEN FACTORS THAT MAY AFFECT THE EFFICACY OF AIT for AR

Standardization of allergen extracts

For the common allergens, many companies now provide characterized, standardized, stable preparation for AIT as recommended by EMA [47,132]. For others, such as molds, there are problems with the complexity, variability and stability of the allergens [133]. The lack of standardized extracts may hamper the diagnosis of eligible patients for AIT and may impede the effectiveness of AIT [133,134]. Additionally, non-standardized preparations may vary between batches increasing the potential for side effects. Further purification and characterization of such allergens [134,135,136] may result in better extracts for the future. Where possible, standardized allergen products should be used for AIT. Further discussion is available in a position paper on regulatory aspects of AIT [47].

Formulation of SLIT preparations

In deciding on the appropriate preparation to use for AIT, the formulation should be taken into account. For example, three large studies have shown efficacy for HDM SLIT tablets [52,53,137] whereas three HDM SLIT studies with sublingual drops were negative [107,140,146], and another only demonstrated efficacy in the first and not the second year [50]. However, many factors such as differences in allergen content [141], administered volume, number of participants and statistical power of the study may explain the differences between tablets and drop trials. We recommend that AIT products with evidence of efficacy in the clinical documentation should be used when they are available.

Allergen mixtures

Both mixtures of grass pollen and mixtures of tree pollen are frequently used in AIT and such an approach is effective [14]. The use of different, non-taxonomically related allergens mixed in one AIT product has been evaluated in a very limited number of studies. One SCIT study showed that a depigmented-polymerized mixed grass/birch pollen extract was effective over placebo [142]. A small study in children demonstrated efficacy using a mixture of grass pollen and HDM SLIT [143]. SLIT drops that employed a momomeric *Phleum pratense* grass pollen extract

was more effective when given alone compared to when given in an equivalent dose as part of a combination with a nine-pollen, multi-allergen, sublingual extract [100].

There are a number of potential drawbacks of mixing allergens including a dilutional effect, potential allergen degradation due to enzymatic activity of some allergens and the difficulties of adequately demonstrating efficacy of a high number of allergen combinations and/or different products. The EMA has recommended that only homologous allergens (usually ones that are taxonomically related, for example a mixture of grass pollen extracts [56]) should be mixed and that allergens with enzymatic activity (e.g. HDM) should be never used in a mixture. We therefore recommend only homologous allergens to be mixed in AIT preparations until further evidence is available substantiating the efficacy of other mixtures (Grade A)(see online supplement, Table S1). Alternatively, extracts should be given separately.

Specific allergens

In the recent meta-analysis, there were sufficient SCIT and SLIT studies for subgroup analyses by specific allergens [14]. Short-term effectiveness was demonstrated for HDM (symptoms score SMD -0.73; 95%CI -1.37, -0.10), grass pollen (-0.45; -0.54,-0.36); tree pollen (-0.57; -0.92, -0.21) and weed pollen (-0.68; -1.06, -0.30). However, there was substantial heterogeneity for all allergens, particularly molds (-0.56; -2.29, 1.18), suggesting that different preparations may be more or less effective. Before a product is used, an individual product-based evaluation of the evidence for efficacy is recommended.

There are some orphan allergens where robust data from RCTs are sparse or non-existent. Where there is a clinical need, the available evidence of efficacy and safety needs to be weighed against the needs of the individual patient. Where therapy is considered in the patient's best interest, an early evaluation of its impact on the patient's clinical symptoms is required to determine whether or not therapy should be continued. The generation of controlled clinical trial data to assess efficacy and safety of these orphan products should be encouraged. There will always be rare allergens where such studies are uneconomic and have to be regulated as named patient products [47].

Table 5. Recommendations: allergen factors that affect the efficacy of AIT for allergic rhinoconjunctivitis

Recommendation	Adults		Children and Adolescents		Strength of recommendation	Other considerations	Key references
	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation			
Either a single allergen species or a mixture of well-documented homologous allergens from the same biological family are recommended for patients with AR who are allergic to grass pollens, tree pollens or HDM	I	A	I	A	Strong recommendations on basis of low risk of bias grass pollen (single grass, e.g. [85,98,99]); mixture of grasses, e.g. [56, 145]), tree pollen (single tree, e.g. [70, 61]; mixture of trees, e.g. [69]) and house dust mite (single, e.g. [66]; mixture, e.g. [147]) studies.	Strong RCT evidence that these are effective approaches. Supported by regulators.	Demoly 2016 [137], Dhami 2017 [14], EMA 2008 [132] **Adult:** Balda 1998 [69], Bodtger 2002 [70], Charpin 2007 [61], Dahl 2006 [85], Didier 2007 [56], Ott 2009 [145], Passalacqua 1998 [147], Varney 2003 [66], Varney 1991 [71] **Pediatric:** Bufe 2009 [98]
Mixtures of allergens from non-related biological families are not recommended for AIT.	I	B	-	C	Strong recommendation against use of allergen mixtures is based on the little available evidence.	No evidence of effectiveness for almost all mixtures. Exception is one positive low risk of bias study in adults (grass and tree pollen mix) [142], this product would therefore be indicated for use for AIT.	Bonertz 2017 [47], EMA 2008 [132] **Adult:** Amar 2009 [100], Nelson 2009 [151], Pfaar 2013 [142]

Examples of homologous, taxonomically related allergens from the same biological family are the grasses or tree pollens. Also see Table 3.

PATIENT FACTORS THAT MAY IMPACT ON THE EFFICACY OF AIT FOR AR

The approach to immunotherapy is a good example of patient stratification. Immunotherapy will only work when directed to the specific allergen(s) driving symptoms. So identifying the driving allergen(s) with a thorough history and assessment of allergic sensitization is an essential example of patient stratification. Not all patients benefit from AIT [14] and further stratification approaches to indentify the responders would be useful.

Polysensitized patients

Epidemiological data indicate that most patients with AR are polysensitized [148]. Consequently, consideration needs to be given as to whether patients are: (i) clinically mono-allergic (where only one allergen is driving symptoms) and polysensitised; or (ii) poly-allergic (symptoms with overlapping exposure to multiple different allergens) and polysensitized. Immunotherapy with a single allergen extract is effective in the first [149] while immunotherapy has been shown to be ineffective [150] or less effective in the last situation [151]. This may be apparent from the history or may need investigation with component resolved diagnostics or assessment with nasal or conjunctival provocation challenges where the clinician is experience in these diagnostic procedures [137]. Polysensitized patients who are mono-allergic are recommended to receive AIT for the specific allergen that is driving their AR symptoms (Grade A).

For a polysensitized patient who is poly-allergic for homologous (biologically related) allergens (e.g. two grass pollens), a single allergen preparation or a mixture of two homologous allergens is recommended (Grade B)[137]. For poly-allergic patients where allergens are not homologous, separate AIT preparations for one or two of the clinically most important allergens might be recommended with doses given 30-60 minutes apart at separate locations when two are selected (Grade C)[137,32]. This represents a trade-off between efficacy and safety as both seem to be dose-dependent. More studies are needed to further address this important clinical challenge.

Co-existing asthma

Co-existing asthma is seen in many participants in the published AR AIT studies [14]. Co-existing asthma has no impact on the efficacy of AIT for AR [103] and may also lead to improvement in asthma [43]. When controlled, mild-to-moderate asthma does not seem to be a safety issue with AIT (Grade A recommendation) [41,43]. In one large recent asthma SLIT trial, participants with not well controlled asthma based on an Asthma Control Questionnaire (ACQ-6) were included safely in the study [41]. We await confirmatory evidence and emphasize that efforts should be taken to control asthma before commencing AIT. Uncontrolled or severe asthma are definitely considered to be an absolute contraindication to AIT [25,26,27,28,29,30,31].

Specific pediatric issues

Similarly to adults, AIT should be considered in pediatric patients with AR with evidence of IgE-sensitization to clinically relevant allergens (Grade A)(Tables 1, 3).

The evidence for the efficacy of AIT for AR is limited in children younger than five years of age. Some clinical studies have shown the efficacy and safety of both SCIT and SLIT in preschool children [88,152,153,154,155], and children were included from five years onward in several of the well-powered SLIT tablet trials [98,156]. Experience suggests that repeated injections of SCIT may be stressful in pre-school children. It is recommended that the decision to start the treatment has to be taken on a case by case basis together with the patients and their family (Grade D). The decision should depends on several factors, such as the severity of the allergic disease, the clear exposure-symptoms pattern supported by allergic sensitization testing, the impairment of the health-related quality of life and the expected acceptance and adherence to the AIT.

There are more data to drive recommendations for school age children and adolescents although major gaps still exist (Table 3). Many of the SCIT trials are now relatively old, many enrolled only a few children and/or did not present pediatric only analyses. Continuous and pre-

and pre/co-seasonal SCIT can be recommended (Grade B) for children with seasonal AR (Table 3). Continuous SCIT is also recommended for perennial AR but with a weaker grade due to the lack of exclusive pediatric data (Grade C)(Table 3). There are no exclusive pediatric, placebo-controlled data for allergoid preparations but one controlled trial with a pre-seasonal treatment regimen has indicated long-term efficacy of pre-seasonal grass pollen immunotherapy in this age group [157]. Two further open RCTs also suggest that SCIT for grass pollen driven AR does have a long-term benefit [63,158].

For SLIT, there are more recent pediatric trial data to support this approach. In general, pre-/co-seasonal and continuous SLIT is recommended for seasonal AR (Grade A) (Table 3). Both tablet and aqueous formulations are recommended (Grade A)(Table 3). There is now one recently published trial supporting the long-term effectiveness for a grass pollen tablet and reduction in asthma symptoms [110,111](Grade A). For perennial allergic rhinitis, the evidence is not as good. There are no consistent data to recommend SLIT with aqueous solutions for perennial allergic rhinitis but the SLIT tablet approach has been desmontrated to be effective in the short term in mixed adult/paediatric studies [51,55](grade A).

Elderly

A detailed allergy history is especially important when evaluating older adults suffering with rhinitis as other types of rhinitis may mimic AR symptoms. There are very few studies specifically evaluating the use of AIT in the elderly (defined here as >65 years as this is usually an exclusion crtieria in AIT trials) but SLIT with grass pollen and HDM has been demonstrated to be effective and safe in two studies [159,175]. AIT elicits clinical responses comparable to studies with younger patients. Another important consideration in this age group, when contemplating treatment with AIT, is the higher prevalence of comorbidities. Examples are hypertension, coronary artery disease, cerebrovascular disease, malignancy and/or cardiac arrhythmias. Also, treatment with medication such as beta-blockers that may impair the treatment of anaphylaxis with adrenaline (epinephrine) (see Table 2). AIT can be recommended in otherwise healthy elderly patients with AR whose symptoms cannot be adequately controlled by pharmacotherapy (Grade A for SLIT, B for SCIT).

Pregnancy

There is one prospective study investigating the safety of AIT in pregnancy [161] and several retrospective studies that suggest that there is no greater risk of prematurity, fetal abnormality, or other adverse pregnancy outcome in women who receive AIT during pregnancy [39]. Observations about anaphylaxis in pregnant and breastfeeding women are largely derived from case reports and are generally reassuring [162]. However, the balance between benefits and potential risks in pregnant patients needs to be discussed with the patient. Systemic reactions and their resultant treatment can potentially harm the baby and/or mother. It is therefore recommended that AIT is not initiated during pregnancy (Grade D) but, if already initiated, AIT may be continued during pregnancy or breastfeeding in agreement with the patient's general practitioner (GP) and obstetrician if former AIT treatment has previously been tolerated well (Grade C).

Adherence

There is a great variance between studies (both real life studies and clinical trials) in the criteria used for evaluating adherence and in the rates of adherence [163,164,165,166,167,168,169]. The range of reported adherence varied from 18% to over 90%, higher in clinical studies than real-life surveys with overlapping ranges for SCIT and SLIT. The main causes for poor adherence are reported to be side effects, inconvenience, lack of efficacy or forgetting to use [163,164,165,167,168,170]. A few other factors have been associated with poor adherence, for example age and patient's educational level. Potential ways to improve adherence are the use of reminder mechanisms (e.g. alarm on mobile phone, internet-based tools, short message service (SMS) electronic reminders, social networks, mobile applications (apps) and monitoring systems – this approach should be tailored to the patient)(Grade C). Patient education and good communication between physican and patient are key (Grade C)[169,137]. One randomized study suggests that adherence is much better with three monthly follow up appointments compared to six or 12 monthly follow-up (Grade B)[171]. Recommendations are summarized in Table 6.

Table 6: Recommendations: patient factors that affect the efficacy of AIT for allergic rhinoconjunctivitis

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Polysensitized patients					
Polysensitized patients who are mono-allergic are recommended to receive AIT for the specific allergen that is driving their AR symptoms	I	A	Strong recommendation, based on RCTs with low risk of bias [56, 109]	Expert review of RCTs [137,149]	Didier 2007 [56], Demoly 2016 [137], Durham 2012 [109], Nelson 2013 [149]
Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens	II	B		Expert review of RCT data	Demoly 2016 [137], EMA advice [132]
Patients who are poly-allergic for non-homologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the two clinically most important allergens	II	C		Expert review of RCT data	Demoly 2016 [137], EMA advice [132]; Pfaar 2013 [142]
Co-existing asthma					
Controlled asthma is not a contraindication to AIT	I	A	Strong recommendation based on low risk of bias studies [43]	Evidence described in asthma AIT systematic review [43].	Dhami 2017 [14], Virchow 2016 [41], Dhami 2017 [43]
Specific pediatric issues					

Consideration of AIT is recommended in pediatric patients with AR with evidence of IgE-sensitization to clinically relevant allergens	I	A	Strong recommendations from low risk of bias studies [eg 90,91,92,98]	See Table 3 for detailed review.	Bufe 2009 [98], Caffarelli 2000 [90], Pajno 2003 [91], Stelmach 2012 [92]
In children aged 2-5 years of age, it may be recommended that consideration should be given to likely benefits and risks associated with AIT for AR	IV	D	Weak recommendation based on little available evidence	May be more difficult to make a definitive diagnosis of AR in pre-school children. Safety seems to be similar in this age group as per older patients.	Rienzo 2005 [173], Rodriguez-Santos 2008 [174]
Elderly					
AIT can be recommended in otherwise healthy elderly patients (>65 years) with AR	I	A (SLIT), B (SCIT)	Moderate recommendation for SLIT based on two consistent RCT studies of unclear risk of bias [159, 175]. Moderate recommendation for SCIT based on only one relatively small, low risk of bias study [160].	Detailed clinical assessment is recommended to exclude other types of rhinitis in elderly patients.	Bozek 2012 [175], 2014 [159], 2016 [160]
Pregnancy					
Immunotherapy is not recommended to be initiated during pregnancy	V	D		Based on balance of additional risk versus benefits.	Expert opinion
Maintenance immunotherapy may be recommended to be continued (at the achieved dose) during pregnancy	III	C	Weak recommendation based one cohort study [161] and one case series [40]		Shaikh 2012 [161], Metzger 1978 [40]

Adherence					
It is recommended that patients should be informed about how immunotherapy works and the need to take regular doses and complete the course of treatment.	IV	C	Based on a survey of allergists.	Based on observational data	Scurati 2010 [164]
Reminders are recommended for patients on immunotherapy to improve treatment adherence.	III	C	One interventional study (educational session, phone calls, emails)	Consider mobile phone texts, social media and applications (apps)	Savi 2013 [169]
Patients receiving SLIT can be recommended to be followed up every 3 months to improve treatment adherence	II	B	Moderate recommendation based on one quasi-randomized study [171].	Method of randomization unclear.	Vita 2010 [171]

HOW LONG AIT SHOULD BE CONTINUED FOR IN AR?

Most clinical studies evaluating the efficacy of AIT follow participants for one or two years on therapy. The EMA currently recommends an experimental, randomized, controlled design involving three years of therapy with a two year follow-up period off treatment. These studies demonstrate a sustained benefit for three years of SLIT-tablet grass pollen therapy for two years off therapy [94,109,111,176]. There are some data to suggest that HDM SLIT tablets give sustained benefit for at least one year after one year of therapy in one RCT [108] and also after three years of therapy in a SLIT drop RCT [177]. More data are required for HDM and evidence is required on the optimal duration of therapy. Grass pollen SCIT for three to four years has been shown to result in long-term efficacy for three years after discontinuation [83]. In a recent study, either SCIT or SLIT tablets were effective compared to placebo over two years but two years was insufficient for long-term efficacy as measured one year off treatment (65). In another adult study, participants randomized to three years of ragweed continued to benefit after two years post SCIT [178]. Similarly, children randomized to three or five years HDM SCIT had similar outcomes at five years [179]. So, in summary, for patients with AR a minimum of three years of AIT is recommended in order to achieve long-term efficacy after treatment discontinuation (Grade A)(Table 7).

Table 7. Recommendations: How long should AIT for allergic rhinoconjunctivitis be continued?

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Contextual comments	Key references
AIT is recommended as benefit is seen from the first year of therapy	I	A	Strong recommendation based on low risk of bias studies (eg [53,56,58,69, 72,74,85,94])	Generally consistent data	Dhami 2017 [14], Bergmann 2014 [53], Bousquet 1990 [74], Didier 2015 [94], Dahl 2006 [85], Frew 2006 [58]
It is recommended that in order to achieve long-term benefits, immunotherapy should be continued for a minimum of 3 years.	I	A	Strong recommendation based on low risk of bias longterm adult studies [56,83,84,94,108,56,109 ,145], one high risk of bias pediatric study (due to its open design although it was randomized) [63] plus one recently published low risk of bias pediatric study [111].	Consistent data	**Adult:** Arroabarren 2015 [179], Didier 2007 [56], Didier 2013 [108], Didier 2015 (94], Durham 1999 [83], Durham 2012 [109], James 2011 [84], Lin 2016 [177], Naclerio 1997 [178], Ott 2009 [145], Scadding 2017 [65] **Pediatric:** Jacobsen 2007 [63], Stelmach 2012 [223], Valovirta 2017 [111]

ADVERSE EVENTS WITH AIT FOR AR

SCIT

SCIT is a safe and well-tolerated treatment when the injections are given in a medical setting by experienced personnel trained in the early recognition of systemic reactions and how to manage them [11,180,181,182]. There must be immediate access to resuscitation equipment and a physician trained in the management of anaphylaxis (Grade C).

Systemic allergic adverse reactions to SCIT can range between mild to severe adverse reactions of the skin, upper and lower airways, gastrointestinal tract, or the cardiovascular system ((see Table S2 in online supplement for details of classification [123]. In a three year real life US survey study that included over 20 million injection visits, systemic reactions were reported in 0.1% of injections; there were no fatalities [182] although four were reported in a follow-up survey by the same group [183]. Fatal allergic adverse reactions have though been reported in earlier surveys [30,31]. Over 80% of reactions occurred within 30 minutes after injection; very few of the delayed ones were severe. It is therefore recommended that patients stay in clinic for at least 30 minutes after an injection (Grade C).

A European real life, prospective, survey performed by members of the Immunotherapy Interest Group of EAACI on 4316 patients in France, Germany and Spain was published after our SR was completed [184,185]. It demonstrated that SCIT and SLIT for respiratory allergy are safe in general in the pediatric and adult population and found only a low number of systematic reactions (SRs). For SCIT, SRs were found in 2.1% of all SCIT treated patients. Independent risk factors for SRs during SCIT were the use of natural extracts, the absence of symptomatic allergy medications, asthma diagnosis, sensitization to animal dander or pollen, cluster regimens (versus rush) and a previous episode of anaphylaxis. Further possible risk factors for systemic adverse reactions have been described (Table 9, [11]). When one or more severe adverse reactions occur, the allergist (specialist and subspecialists) should re-evaluate the benefits and risks of SCIT therapy with the patient and decide whether or not treatment should be continued (Grade D). In any case, cessation of treatment or adaptation of the dosing-schemes for the next injection should follow the summary of product characteristics (SmPC).

Redness, itching or swelling represent local reactions at the injection site and occur frequently after around half of injections [14]. Local measures (e.g., cooling or topical glucocorticoids) or oral antihistamines may be helpful for these reactions. Increased local adverse reactions do not predict an increased individual risk of a systemic adverse reaction [186]. In case of enlarged local adverse reactions (redness and/or swelling >10 cm in diameter) occur at the injection site, the SmPC provides adaptation of the dosing-schemes for the next injection. When local adverse effects occur, pre-medication with an H1-antihistamine can be used to reduce the frequency and severity of adverse reactions (Grade A recommendation) but this prophylactic treatment does not prevent the onset of SRs or anaphylaxis [187,188]. Also, case series indicate that modified allergen extracts are associated with less adverse effects [189,190,191,192]. For aluminum hydroxide containing SCIT products, granulomas have been described from a foreign body reaction mainly caused by incorrect intradermal administration as well as contact allergic reactions, new onset of protein contact dermatitis or a vasculitic inflammatory reactions have been reported [193,194,195]. If these reactions to SCIT occur, treatment with another aluminum hydroxide-free product is preferred (Grade D)[11].

SLIT

SLIT is regarded to be a safe and well-tolerated treatment [11,14,196,197].

Severe SRs with SLIT appear to be much less likely than with SCIT although the overall rate of any adverse reactions is similar in both SCIT and SLIT [184, 14] (see Table S2 and S3 in online supplement for details of classification [198,199]). In a review of 66 SLIT studies (over 4000 patients who received over a million doses), there was one SR for approximately every four years of treatment and only one severe SR per 384 treatment years [198]. There are no new safety concerns in more recent studies [14]. Several severe reactions - in some cases with anaphylaxis - are described in the literature occurring within 30 minutes of sublingual administration of allergens in droplet or tablet form [34]. In these cases, SLIT was not administered according to the standards (non-standardized extracts, rush protocols, excessive allergen dose, patients in whom SCIT had previously been interrupted due to severe reactions). Patients should be observed for at least 30 minutes after the first dose (Grade C) and supervised by staff able to manage anaphylaxis (Grade C). As in SCIT, concomitant, uncontrolled asthma has been

reported to be associated with severe systemic reactions after SLIT [34]. In the recently published European Survey [185] the rate of SRs under SLIT was also reported to be low (1.1% of all SLIT-treated patients) [184,185].

The majority of adverse events in SLIT develop at home without any medical observations. Patients should therefore be thoroughly informed about how to recognize and manage reactions, particularly severe ones (Grade D). Patients also need education on what to do if a dose is forgotten and when SLIT should be temporarily interrupted (e.g. oropharyngeal lesions) (Grade D)[11]. When one or more severe adverse reactions occur, the allergist (specialist and subspecialists) should re-discuss the benefits and risks of SLIT with the patient and decide whether or not treatment should be continued (Grade D). As for SCIT, cessation of treatment or adaptation of the dosage should follow the summary of product characteristics (SmPC).

The frequency of local adverse events during SLIT correlates with the dosage and has been reported to be 40-75%, for example temporary local mucosal reactions (oral pruritus or dysesthesia, swelling of the oral mucosa, throat irritation) or abdominal pain [34,197,198,199]. Most of these reactions occur during the initial phase of the treatment course (commonly in the first three weeks). They are commonly considered to be of mild intensity and self-limiting [34,97]. Nevertheless, these reactions may lead to cessation of treatment, as observed in 4-8% of cases reported in recent trials of SLIT tablets [56,85,99,138].(see section “adherence”). As in SCIT, local adverse reactions may be diminished by the intake of oral antihistamines (Grade A).

For SLIT, temporary cessation of therapy may be advised in a number of situations to reduce the potential for adverse effects. For example, for seven days following dental extraction or oral surgery or following shedding of a deciduous tooth; while an oral ulcer or open wound in the mouth heals; or during an upper respiratory tract infection in patients with asthma. Individual product SmPCs may list additional advice.

Box 3. Risk factors for systemic reactions during AIT

Current allergy symptoms and potential allergen exposure
Current infections
Mast cell disease
Previous systemic reaction to SCIT or SLIT
Uncontrolled or severe asthma
A high degree of sensitization
Excess dose escalation during initiation
Beta-blockers use
Poor injection technique
Overdose of allergen extract
Failure to follow manufacturer's recommendation for dose reduction when change to new production batch
High-intensity physical exercise

Adapted from Pfaar et al., [11]

Table 8. Recommendations: adverse events with AIT for allergic rhinoconjunctivitis

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Contextual comments	Key references
SCIT or SLIT					
For correctly selected patients, SCIT or SLIT is recommended as, appropriately administered, it is safe and well tolerated	I	A	Strong recommendation based on low risk of bias RCT studies and observational studies [14]	Consistent evidence	Dhami 2017 [14]
It is recommended that asthma should be controlled before commencing AIT as insufficiently controlled asthma is a risk factor for both SCIT and SLIT	III	C		Expert opinion from observational studies	Bernstein 2004 [31], Amin 2006 [200], Calderon 2012 [34]
Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions but does not eliminate the risk of other systemic adverse reactions including anaphylaxis	I	A	Strong recommendation based on low risk of bias RCTs [187,188].	Consistent strong evidence from RCT studies	Nielsen 1996 [187], Reimers 2000 [188]
When one or more severe adverse reactions occur, it may be recommended that the allergist (specialist and subspecialists) should re-discuss the benefits and risks of AIT therapy with the patient and decide whether or not treatment should be continued. This decision and continuation of treatment should be in line with the Summary of Product Characteristics (SmPC).	V	D		Expert opinion from clinical experience	Expert opinion
SCIT					

It is recommended that patients should remain under observation for at least 30 minutes after a SCIT injection	III	C		Consistent observational data	Epstein 2011 [182]
If subcutaneous granulomas develop with aluminum hydroxide containing SCIT products, it may be recommended that a replacement allergen extract that does not contain aluminum hydroxide should be used.	V	D			Expert opinion
It is recommended that SCIT should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.	III	C		Consistent observational data on adverse effects reported in SR	Dhami 2017 [14]
SLIT					
It is recommended that patients should remain under observation for at least 30 minutes after an initial SLIT dosage	III	C		Expert opinion based on consistent observational data	Calderon 2012 [34]
It is recommended that initial SLIT dosage should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.	I	C		Consistent observational data on adverse effects reported in SR	Dhami 2017 [14]
It is recommended that patients receiving SLIT should be informed about how to recognize and manage reactions, particularly severe ones. Patients also need to know what to do if a SLIT preparation is forgotten and when SLIT should be temporarily interrupted (e.g. oropharyngeal lesions).	V	D		Expert opinion from clinical experience	Expert opinion

PREVENTIVE EFFECTS OF AIT FOR AR

A three years course of AIT reduces the likelihood that children and adolescents with allergic rhinitis driven by pollen allergy go on to develop asthma up to two years post-AIT [23]. There is currently no convincing evidence for a preventive effect of HDM AIT or for prevention of new sensitivities [23]. This is further discussed in the EAACI AIT Prevention Guidelines [23].

PHARMACOECONOMIC ASPECTS OF AIT VERSUS PHARMACOTHERAPY FOR AR

Pharmacoeconomic studies that only analyze costs in monetary units have reported beneficial health care expenditure of AIT in the long-run although savings are not expected in the first year. The majority of pharmacoeconomics studies support the viewpoint that AIT gives value for money, with cost-effectiveness within six years of treatment initiation [201]. Retrospective and prospective observational studies have shown that SCIT and SLIT positively affects health care expenditure in pharmacotherapy with a reduction in expenditure of 12% to 80% [202,203,204,205,206]. A reduction in medical costs in the AIT versus placebo groups have been repeatedly reported but these savings did not compensate the costs of AIT [202,207,208].

In contrast to cost-only studies, cost-effectiveness and cost-utility analysis evaluates the effects of treatment in terms of clinical benefits or health-related quality of life (i.e., quality-adjusted life years [QALYs]). An incremental cost-effectiveness ratio (ICER), which is defined as costs divided by benefits, can be calculated to estimate the costs of a certain gain. Several health economics studies that include cost-effectiveness and cost utility calculations have demonstrated that SCIT and SLIT are economically advantageous to pharmacotherapy [209,210,211,212].

Seven studies based on RCT data conducted from a health system perspective and using QALYS as their outcome measure suggest that SLIT and SCIT would be considered cost-effective in this patient population in England at the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20,000 (€24616) per QALY [213,214,215,216,217,218,219]. The studies comparing SCIT and SLIT have given mixed results and do not allow us to conclude whether either treatment is more cost-effective [220]. ICERs for cost

evaluations of AIT seem to vary substantially between different health systems suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries [215]. Finally, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data should be taken into account when interpreting these results.

SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

The EAACI Taskforce on AIT for AR has developed this guideline as part of the EAACI AIT Guidelines Project. This guideline has been informed by a formal SR and meta-analysis of AIT for AR [14]. The guidelines provide evidence-based recommendations for the use of AIT for patients with AR with or without allergic conjunctivitis (Figure 2). Practical guidance is provided in Box 4 and a summary of the guidelines is provided in Box 5. An approach to the use of AIT for AR across the healthcare system is summarized in Figure 3. The recommendations should be of value to all healthcare professionals involved in the management of patients with AR. There are barriers to the wider use of AIT but equally there are facilitators that could be put into place to widen access to AIT (Table 9).

The key limitation of this guideline is the considerable heterogeneity seen in elements of the underpinning meta-analysis. For newer products, such as the SLIT grass pollen and house dust mite tablets, we have consistent low risk of bias data and very secure recommendations. For older products, such as house dust mite SCIT products, there is considerable heterogeneity in the meta-analysis weakening the strength of recommendations around those products. Many of these older studies were poorly designed and reported; for example it is often not clear whether intention-to-treat or per-protocol analyses were being reported making it impossible to combine similar analyses in the meta-analysis. Indirect comparisons within the meta-analysis strongly suggests that some products are more effective than others. A network analysis approach, which allows indirect comparisons across trials based on a common comparator (usually the placebo group), would allow us to improve our comparative estimates between products [221]. This would allow product specific recommendations to be made. The different local regulations [47] and availability of products [48] makes this difficult at a European level. So before treatment with a specific product is initiated, clinicians need to undertake an individual product-based evaluation of the evidence for efficacy, focusing on low risk of bias studies which are generally the larger, more recent ones [11].

There are a number of areas in this guideline where there is no low risk of bias evidence, these signify the gaps in the current evidence base. The key ones are highlighted here and in Table 10. There is a major gap in the evidence base for the clinical effectiveness of AIT in children and adolescents with recommendations at least one grade lower than for adults in most areas. As AR usually starts in childhood and AIT has the potential to change the natural course of the disease and prevent the development of asthma, this age group has most to benefit. Once safety is established in adult studies, pediatric studies need to be commenced using validated, common outcome measures [11, 34]. There are also little data in the elderly particularly for patients with multi-morbidity. Additionally, more RCTs need to follow participants post-cessation of therapy to establish long-term clinically effectiveness, especially for HDM respiratory allergy. Dose-finding studies are needed. Agreement about the clinically meaningful effect size of AIT treatment would assist in the interpretation of clinical trial data and help facilitate stratification studies to help predict which patients will respond best to which forms of AIT. The collection of patent reported outcomes in studies would ensure the patient experience is captured. Additionally we need data from randomized cost-effectiveness and cost-utility studies to use in discussions with healthcare funders. We need biomarkers to predict and quantify the effectiveness of AIT to assist in patient selection [222]. Suboptimal adherence with AIT is likely to impact on its effectiveness; novel approaches to improve effectiveness should be developed in partnership with patients. Also, to allow better comparison of safety between approaches, studies need to use a unified approach to classifying side effects is required. A common and international recognized language should be use when reporting severe adverse reactions, such as the MedDRA classification and AIT related local and systemic reactions should be reported in line with internationally standardized classification such as the WAO-grading system [198,199]. Filling these gaps would allow the generation of much clearer guidelines for clinicians allowing them to stratify patients to the best therapy. It may not be possible to achieve this with only randomized, controlled prospective data; large, real-life, controlled data needs to be examined although the potential for bias and confounding needs to be acknowledged.

Despite all these gaps we have clear evidence for the clinical effectiveness of AIT, for SCIT, SLIT-tablets and SLIT-drops, for adults and children with moderate-to-severe AR that is otherwise uncontrolled despite pharmacotherapy. We have evidence-based recommendations for specific patient groups and specific approaches. There is now a need to ensure that primary care healthcare professionals know which patients might benefit from AIT (Box 6), that national healthcare providers understand that AIT is cost-effective and that patients and patient support groups are aware of this approach. This will be supported by the implementation strategy for this guideline with efforts being put into

disseminating the guideline. This will be supported with materials such as schedules and country specific product evaluations as exemplified by the German, Austrian and Swiss guideline [11]. Finally as new evidence is published these guidelines will need to be updated with revision of specific recommendations to reflect the new data.

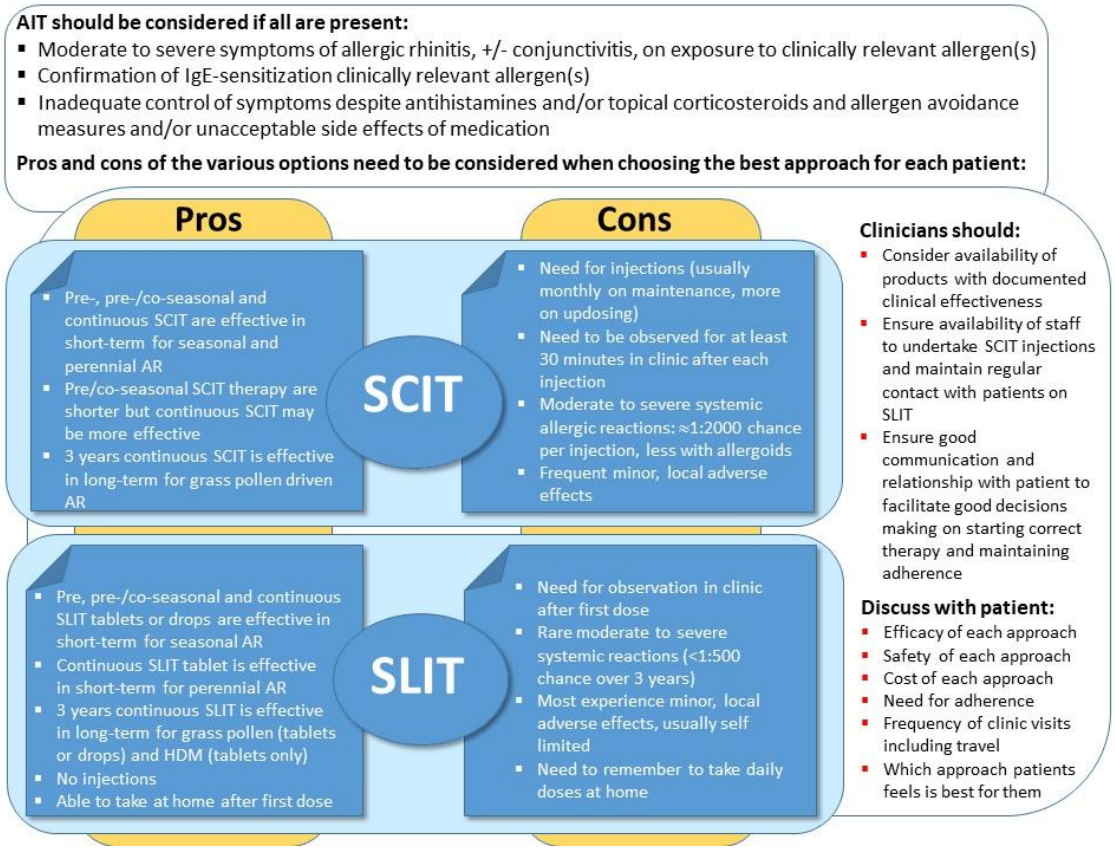

Figure 2. Schematic approach to deciding which approach to AIT is best to use in individual patients

For details to specific recommendations, see table 3. For details about local and systematic adverse reactions, see adverse event section above.

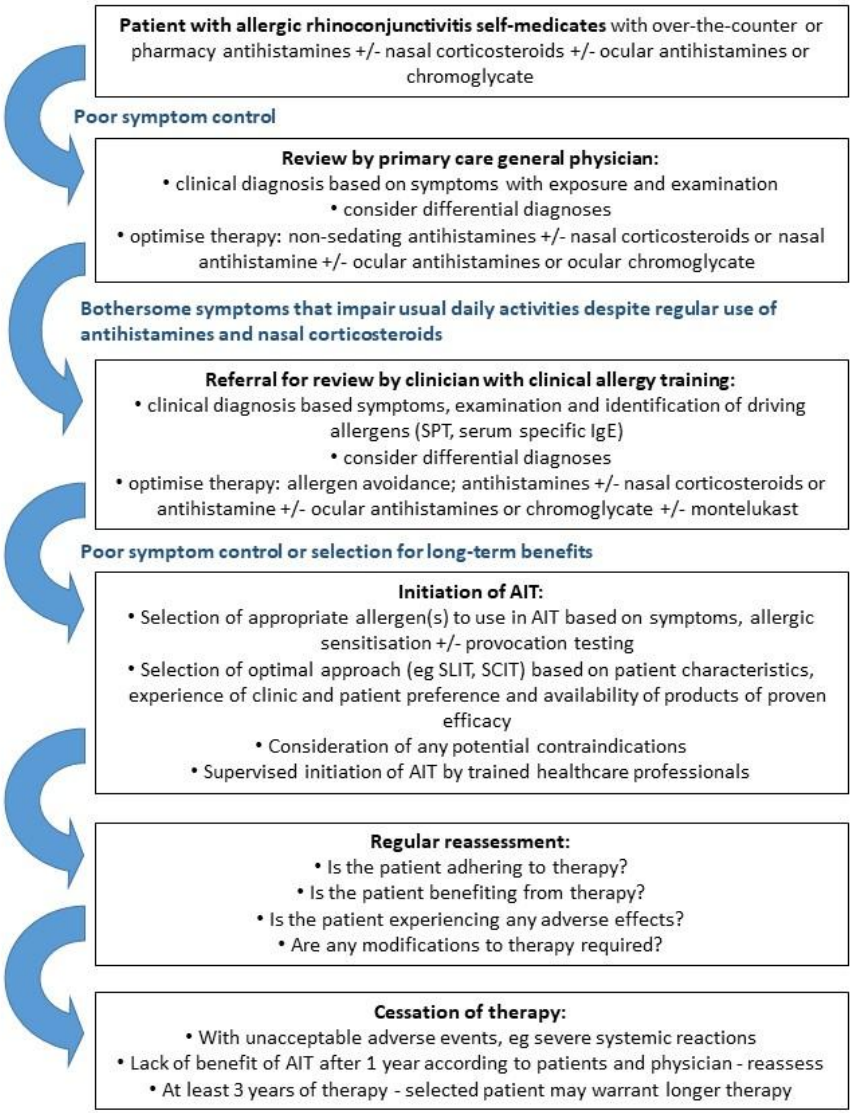

Figure 3. Approach to using AIT for allergic rhinoconjunctivitis
Schematic illustration of the approach to using AIT for AR starting with self-medication and management in primary care moving to assessment by a clinician trained in clinical allergy for consideration and initiation of AIT in suitable patients. Structure of healthcare systems differ between countries.

Table 9. Implementation considerations: AIT for treatment of allergic rhinoconjunctivitis

Recommendation areas	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
SCIT or SLIT therapy	Lack of awareness of how to assess severity of AR Appreciation of SCIT and SLIT as treatment options Access to providers offering SCIT and/or SLIT at convenient locations and/or affordable cost Lack of knowledge about the relative efficacies and safety of different products	Development of integrated care pathways for AR incorporating primary and secondary care Increase in number of specialists able and willing to provide SCIT and/or SLIT Subsidised provision of SCIT and SLIT Document detailing and training about the efficacy and safety of individual products	Proportion of patients with moderate-to-severe seasonal AR who are offered and use SCIT or SLIT	The resource implications include professional time to develop and agree integrated care pathways The costs of training and upskilling allergist (specialist and subspecialists) to deliver SCIT and/or SLIT Training of primary care nurses and doctors to deliver immunotherapy as shared care agreements where appropriate Financial costs of subsidizing access to SCIT and SLIT
Selecting the appropriate AIT in patients with polysensitisation +/- polyallergy	Lack of documentation for individual AIT products Effective identification of the key allergen(s) driving symptoms	Information to clinicians and patients about the better efficacy of single allergen or a mixture of well documented homologous allergens Use of component resolved diagnosis and provocation testing	Proportion of patients receiving either a single allergen or a mixture of well documented homologous allergens Proportion of patients where additional measures are taken to identify the driving allergen(s)	Training for clinicians Availability of appropriate AIT products Access to component resolved diagnostics and provocation testing

Using AIT in patients with controlled, co-existing asthma	Lack of education of clinicians and patients	Information to clinicians and patients about safety of AIT with co-existing asthma Control asthma before commencing AIT	Proportion of patients with co-existing asthma receiving AIT.	Available AIT service
Consideration of AIT in pediatric patients with AR	Available AIT clinical service for children	Information about the place of AIT in managing AR in children for health purchases, primary care clinicians and patients.	Proportion of pediatric patients with moderate to severe seasonal AR who use continuous SCIT.	Availability of a clinical service for children able to deliver AIT for AR.
Consideration of AIT in otherwise healthy elderly patients with AR	Lack of access to AIT for AR in general or specific products.	Information about the place of AIT in managing AR in the elderly for health purchases, primary care clinicians and patients.	Proportion of elderly patients with moderate to severe seasonal AR who use AIT.	Availability of a clinical service able to deliver AIT for AR.
Adherence to AIT	Lack of patient education about AIT	Information for patients and use of simple reminders Three monthly follow up for SLIT patients Good physician patient relationship and communication regarding side effects and time course of treatments	Assessment of understanding of patients on AIT Assessment of adherence and use of reminders by patients on AIT	Resources to educate patients Investment in written communication and regular follow up with access to advice redarding side effects if necessary
Use of premedication with an antihistamine to reduce adverse effects	Lack of knowledge by clinicians and patients	Training of clinicians using AIT	Proportion of patients who receive pre-medication with antihistamine	Resources for training clinical staff Availability of medication

Observation for at least 30 minutes after a SCIT injection or initial SLIT dosage by trained staff	Lack of understanding by clinicians of delayed effects Lack of trained staff and workforce time pressures	Training of clinicians using SCIT and SLIT Staff availability and rotas for administration and observations	Proportion of patients who wait 30 minutes after receiving SCIT or initial SLIT dosage Proportion of staff trained in management of severe adverse reactions	Resources for training clinical staff Time set aside for observation
Information for patients receiving SLIT about how to recognize and manage reactions and when therapy should be temporarily interrupted	Lack of understanding by patients receiving SLIT and clinicians administering	Training of patients and clinicians	Proportion of patients receiving SLIT trained in the self-management of severe adverse reactions	Resources for training patients and clinicians

Table 10. Gaps in the evidence for AIT for allergic rhinoconjunctivitis

Gaps	Plan to address	Priority
Lack of biomarkers to predict and quantify the effectiveness of AIT	Prospective observational studies to validate potential predictive biomarkers	High
Agreement about the clinically meaningful effect size of AIT treatment (active versus placebo treated patients)	Consensus discussion	High
Low risk of bias randomized controlled data for children and adolescents	More prospective controlled trials using standardized products	High
Evidence for long-term clinical effectiveness after treatment cessation	More prospective controlled trials with follow up post treatment cessation in adults and children	High
Standardization of grading of adverse effects of AIT	Future clinical trials should use the WAO systemic reaction grading system	High
Approaches to improve adherence with AIT	Working with patients to develop novel approaches that can be tested in prospective controlled trials and real life settings	High
Randomized cost-effectiveness and cost utility studies adjusted to socioeconomic differences within and between countries	Additional multinational studies with a health economics focus	High
For some AIT products there is little or no evidence for clinical effectiveness	Dose ranging studies to optimize dose for efficacy and safety; prospective controlled trials; use of patient reported outcomes; use of products with proven effectiveness	High
Approaches to minimize adverse effects	More prospective observation and controlled trials. A sub-analysis of different phenotypes populations in current RCTs and real life settings	Moderate
Effectiveness of mixtures of homologous allergens from the same, related or different biological families	More prospective controlled trials using the commonest allergens	Moderate
Good evidence base for contraindications to AIT	Registries recording patient details, AIT, outcome and adverse effects	Moderate
Value of provocation tests in identifying the most appropriate allergen to use in AIT	Prospective controlled studies to assess benefit of provocation testing	Moderate
Management of AIT in patients who become pregnant on therapy	More prospective observational studies	Low
Lack of standardized AIT preparations for orphan allergens	Multi-centre studies	Low

Box 4. Practical considerations for healthcare professionals delivering AIT

Training and facilities

- Expertise in the diagnosis and differential diagnosis of AR by history and supporting SPT or specific IgE testing
- Training in recognition and management of severe allergic reactions including anaphylaxis
- Availability of equipment and trained personal to manage severe allergic reactions
- Training in administration of specific AIT products
- Facilities to observe patient for at least 30 minutes with SCIT injections and initial dose of SLIT

Assessing patient and deciding on best approach

- Effective communication with patients and/or family about practicalities of AIT, expected benefits and potential adverse effects
- Identification of clinical contraindications to AIT
- Select an AIT product with documented evidence for efficacy and safety, for specific patients, whereever possible

Undertaking AIT

- Start AIT for seasonal AR at least 4, and preferably 2, months before the pollen season
- Preferably start AIT for perennial AR when allergen exposure is lowest and avoidance measures are in place
- Dose reductions (usually 50%) or split doses for adverse effects, intercurrent illness or delayed dosing as recommended by SmPC for SCIT

- Dose interruption with oral lesions and other issues as recommended by SmPC for SLIT
- Facilities to regularly follow up patient promoting adherences to therapy and watching for adverse effects

Box 5. Summary of the EAACI Rhinoconjunctivitis AIT Guidelines

- AIT should be considered with symptoms strongly suggestive of allergic rhinitis, with or without conjunctivitis; evidence of IgE-sensitization to one or more clinically relevant allergens; and moderate-to-severe symptoms despite regular and/or avoidance strategies
- AIT may also be considered in less severe AR where a patient wishes to take advantage of its long term effect on rhinitis and potential to prevent asthma with grass pollen AIT
- More standardized products with documented evidence for efficacy in clinical trials are needed
- Standardized AIT products with evidence of efficacy in the clinical documentation should be used when they are available
- An individual product-based evaluation of the tolerance and evidence for efficacy is recommended before treatment with a specific product is initiated
- Key contraindications are severe or uncontrolled asthma; active, systemic autoimmune disorders; active malignant neoplasia. Careful review of benefits and risks are required with beta-blocker or ACE-inhibitor therapy, severe cardiovascular disease, other autoimmune disorders, severe psychiatric disease, poor adherence and immunodeficiency. The individual patient's conditions should be considered when deciding whether to prescribe AIT and the summary of product characteristics (SmPC) should be reviewed for specific contraindications for individual preparations
- For each recommendation, an individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated given the heterogeneity in meta-analysis results:
    - Continuous SCIT is recommended for seasonal (Grade A for adults, B for children) or perennial (Grade B for adults, C for children) AR for short-term

benefit in those with moderate-to severe disease

- Pre- and pre-/co-seasonal SCIT is recommended for seasonal AR for short-term benefit (Grade A for adults, B for children)
- Both modified (allergoids) and unmodified allergen SCIT extracts are recommended for AR for short-term benefit (Grade A for adults, B for children)
- Continuous grass pollen SCIT is recommended for AR for short and long-term benefit (Grade A for adults, B for children)
- Pre-/co-seasonal or continuous SLIT is recommended for seasonal ARs for short-term benefit (Grade A)
- SLIT with tablets for pollens or HDM can be recommended for AR for short-term benefit (Grade A)
- SLIT aqueous solutions for pollens can be recommended for AR for short-term benefit (Grade B for adults, A in children)
- SLIT aqueous solutions for HDM cannot be recommended for AR for short-term benefit
- Continuous grass pollen SLIT tablets or SLIT solution is recommended for AR for long-term benefit (Grade A)
- HDM SLIT tablet can be recommended for AR for long-term benefit (Grade B for adults, C for children)

- Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens (Grade A)
- Patients who are poly-allergic for non-homologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic

rhinoconjunctivitis symptoms or separate treatment with the two clinically most important allergens (Grade C)

- In children aged 2-5 years of age, it is recommended that consideration should be given to likely benefits and risks associated with AIT for AR (Grade D)
- AIT can be recommended in otherwise healthy elderly patients with AR whose symptoms cannot be adequately controlled by pharmacotherapy (Grade A for SLIT, B for SCIT)
- If patients have not started AIT and are pregnant, it is recommended to wait until after pregnancy to initiate therapy (Grade D)
- It can be recommended that patients on SLIT are followed up every 3 months to maximize adherence (Grade B)
- To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used (Grade A)
- Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions but does not eliminate the risk of other systemic adverse reactions including anaphylaxis (Grade A)
- It is recommended that patients should wait in the clinic for at least 30 minutes after a SCIT injection (Grade C)
- It is recommended that SCIT should be administered by competent staff, trained to diagnosed symptoms of early systemic reactions or anaphylaxis, with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. (Grade C)
- It is recommended that patients should wait in clinic for at least 30 minutes after an initial SLIT dosage and staff and equipment should be available to manage any severe local or systemic reaction or anaphylaxis (Grade C)

- It is recommended that patients receiving SLIT should be informed about how to recognized and manage adverse reactions, particularly severe ones (Grade D)

Box 6. Key messages for primary care

- Diagnosis of AR is by history
- Where severe, treat with non-sedating, long-acting antihistamine and topical nasal corticosteroid (with appropriate nasal spray training) and/or topical ocular cromoglycate or antihistamine
- Check for any co-existing asthma; this should be properly controlled when using AIT
- AIT is effective for AR driven by pollens, house dust mite and animal dander
- AIT is indicated for AR with moderate to severe symptoms that are not controlled by pharmacotherapy or avoidance strategies (where appropriate)
- AIT may be given by subcutaneous (SCIT) or sublingual route (SLIT) as either SLIT tablets or SLIT drops
- AIT therapy needs to be continued for at least three years for post-cessation effectiveness
- Local adverse effects, which are mild in severity and self-limited without the use of rescue medication, are common with SLIT when starting therapy
- More severe systemic allergic adverse events are infrequently seen and more commonly with SCIT than SLIT
- SCIT injections and the initial SLIT dose should be given by healthcare personal who are trained in AIT and the management of any adverse events
- At least a 30 minute observation period is required for all SCIT injections and the initial dose of SLIT

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Conflict of interest:

G. Roberts has a patent issued: “Use of sublingual immunotherapy to prevent the development of allergy in at risk infants”; and his university has received payments for the activities he has undertaken giving expert advice to ALK, and presenting at company symposia for ALK, Allergen Therapeutics, and Meda, and serving as a member of an Independent Data Monitoring Committee for Merck outside of this work.

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REFERENCES

1. Eifan WO, Durham SR. Pathogenesis of rhinitis. Clinical & Experimental Allergy 2016; 46: 1139–1151.
2. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet 2011; 378(9809): 2112-22.
3. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010;126:778.
4. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, Simmons AL, Wingertzahn MA, Boyle JM. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009; 124:S43-70.
5. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy 2009; 64: 123-48.
6. Walker S, Khan W, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J Allergy Clin Immunol 2007;120:381–387.

7. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, Papadopoulos NG, Rotiroti G, Scadding G, Timmermans F, Valovirta E. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2013; 68: 1102-16.

8. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic rhinitis and its impact on asthma ARIA 2008 update in collaboration with the World Health Organization, GA2LEN and Aller Gen. Allergy 2008; 63: 8-160.

9. Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, Aalberse RC, Gerth van Wijk R. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. New Engl J Medicine 2003; 349: 237-46.

10. Sheikh A, Hurwitz B, Nurmatov U, van Schayck CP. House dust mite avoidance measures for perennial allergic rhinitis. The Cochrane Library. 2010 Jan 1.

11. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014; 23: 282-319.

12. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'Hehir R, Kleine-Tebbe J, Muraro A, Lack G, Larenas D, Levin M, Nelson H, Pawankar R, Pfaar O, van Ree R, Sampson H, Santos AF, Du Toit G, Werfel T, Gerth van Wijk R, Zhang L, Akdis CA. International consensus on allergy immunotherapy. J Allergy Clin Immunol. 2015; 136: 556-68.

13. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, Cox L, Demoly P, Frew AJ, O'hehir R, Kleine-Tebbe J. International consensus on allergen immunotherapy II: mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol 2016; 137: 358-68.

14. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy. 2017;00:1–35. https://doi.org/10.1111/all.13201

15. Rondón C, Canto G, Blanca M.Local allergic rhinitis: a new entity, characterization and further studies.Curr Opin Allergy Clin Immunol. 2010; 10:1-7.

16. Rondon C, Campo P, Herrera R, et al. Nasal allergen provocation test with multiple aeroallergens detects polysensitization in local allergic rhinitis. J Allergy Clin Immunol 2011; 128: 1192-7.

17. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18–23.

18. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Can Med Assoc J 2010;182:E839–E842.

19. Dhami S, Nurmatov U, Roberts G, Pfaar O,Muraro A, Ansotegui I et al. Allergen immunotherapy for allergic rhinoconjunctivitis: protocol for a systematic review Clinical and Translational Allergy 2016; 6:12 DOI: 10.1186/s13601-016-0099-6©

20. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. 2013. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ Last accessed 27 July 2017.

21. A. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases A WHO position paper. Journal of Allergy and Clinical Immunology. 1998; 102: 558-62.

22. Brozek JL, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol, 2010; 126: 466-476.

23. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Agache I, et al. EAACI Guidelines on Allergen Immunotherapy: Prevention of allergy. Allergy, *to be submitted*.

24. Bachert C, Larche M, Bonini S, Canonica GW, Kundig T, et al. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. World Allergy Organ J 2015; 8: 29.

25. Kristiansen M, Dhami S, Netuveli G, Halken S, Antonella M, Roberts G, Larenas-Linnemann D, Calderón MA, Penagos M, Du Toit G, Ansotegui IJ. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. Pediatric Allergy and Immunology. 2017; 28: 18–29.

26. Campo P, Rondón C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in non-allergic rhinitis. Clinical & Experimental Allergy, 2015 (45) 872–881.

27. Pitsios C, Demoly P, Bilò MB, Gerth van Wijk R, Pfaar O, et al. Clinical Contraindications to Allergen Immunotherapy: an EAACI Position Paper. Allergy, 2015; 70: 897-909.

28. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127:S1-55.

29. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract: systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989; 83: 797-780.

30. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001; 87: 47-55.

31. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee AaoAA, and Immunology: Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004; 113, 1129-36.

32. CSM Update: Desensitising vaccines. Br Med J 1986; 293: 948.

33. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD011293. DOI: 10.1002/14651858.CD011293.pub2.

34. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy 2012; 67: 302–11.

35. Cabrera GE, Citera G, Gutiérrez M, Scopelitis E, Espinoza LR. Digital vasculitis following allergic desensitization treatment. J Rheumatol 1993; 20: 1970-1972.

36. Sánchez-Morillas L, Reaño Martos M, Iglesias Cadarso A, Pérez Pimiento A, Rodríguez Mosquera M, Domínguez Lázaro AR. Vasculitis during immunotherapy treatment in a patient with allergy to Cupressus arizonica. Allergol Immunopathol 2005; 33: 333-334.

37. Fiorillo A, Fonacier L, Diola C. Safety of Allergenic Immunotherapy in Systemic Lupus Erythematosus J Allergy Clin Immunol 2006; 117(2 Suppl): S264.

38. Wöhrl S, Kinaciyan T, Jalili A, Stingl G, Moritz KB. Malignancy and specific allergen immunotherapy: The results of a Case Series. Int Arch Allergy Immunol 2011; 156: 313-319.

39. Larenas-Linnemann DES, Hauswirth DW, Calabria CW, Sher LD, Rank MA. American Academy of Allergy, Asthma & Immunology membership experience with allergen immunotherapy safety in patients with specific medical conditions. Allergy Asthma Proc 2016; 37: e112–e122.

40. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. Journal of Allergy and Clinical Immunology. 1978; 61: 268-72.

41. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA 2016; 315:1715-25.

42. Hiatt WR, Wolfel EE, Stoll S, Nies AS, Zerbe GO, Brammell HL, et al. beta-2 Adrenergic blockade evaluated with epinephrine after placebo, atenolol, and nadolol. Clin Pharmacol Ther 1985; 37: 2-6.

43. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Marek J, Muraro A, Roberts G, Akdis CA, Bonini M, Cavkaytar O. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy in press.

44. Cleaveland CR, Rangno RE, Shand DG. A standardized isoproterenol sensitivity test. The effects of sinus arrhythmia, atropine, and propranolol. Arch Intern Med 1972; 130: 47-52.

45. Lang DM. Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers. Drug Saf 1995; 12: 299-304.

46. Linneberg A, Jacobsen RK, Jespersen L, Abildstrom SJ. Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischemic heart disease, and mortality. J Allergy Clin Immunol 2012; 129; 413-419.

47. Bonertz A, Roberts G, Hoefnagel M, Timon M, Slater J, Rabin R, Bridgewater J, Pini C, Pfaar O, Akdis C, Goldstein J, Poulsen LK, van Ree R, Rhyner C, Barber D, Palomares O, Sheikh A, Pawankar R, Hamerlijnk D, Klimek L, Agache I, Angier E, Casale T, Fernandez-Rivas M, Halken S, Jutel M, Lau S, Pajno G, Sturm G, Varga EM, Gerth van Wijk R, Bonini S, Muraro A, Vieths S. Challenges in the implementation of EAACI Guidelines on Allergen Immunotherapy: A global perspective on the regulation of allergen products. Allergy, *in press*.

48. Ryan D, Gerth van Wijk R, Angier E, Kristiansen M, Zaman H, Sheikh A, Cardona V, Vidal C, Warner A, Agache I, Arasi S, Fernandez-Rivas M, Halken S, Jutel M, Lau S, Pajno G, Pfaar O, Roberts G, Sturm G, Varga EM, Van Ree R, Muraro A. Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy. Allergy, *in press*.

49. Tworek D, Bochenska-Marciniak M, Kuprys-Lipinska I, Kupczyk M, Kuna P. Perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. Am J Rhinol Allergy 2013; 27: 304-8

50. Passalacqua G, Pasquali M, Ariano R, et al. Randomized double blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. Allergy. 2006; 61: 849-54.

51. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, Rehm D, Kaur A, Li Z, Lu S. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2016;138: 1631-8.

52. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016; 137: 444-51 e8.

53. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. J Allergy Clin Immunol 2014; 133: 1608-14 e6.

54. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. Ann Allergy Asthma Immunol 2015; 114: 134-40.

55. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, Konno A. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite–induced allergic rhinitis. J Allergy Clin Immunol 2017;139: 1840-8.

56. Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, André C, de Beaumont O, Melac M. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol 2007; 120: 1338-45.

57. Valovirta E, Jacobsen L, Ljørring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy 2006; 61: 1177-1183.

58. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006; 117: 319-325.

59. Demoly P, Calderon MA. Dosing and efficacy in specific immunotherapy. Allergy 2011; 66 (Suppl. 95): 38–40.

60. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001; 107: 87-93.

61. Charpin D, Gouitaa M, Dron-Gonzalvez M, Fardeau MF, Massabie-Bouchat YP, Hugues B, et al. Immunotherapy with an aluminum hydroxide-adsorbed Juniperus ashei foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. Int Arch Allergy Immunol. 2007; 143: 83–91.

62. Ferrer M, Burches E, Peláez A, Muñoz A, Hernández D, Basomba A, et al. Double-blind, placebo-controlled study of immunotherapy with Parietaria judaica: Clinical efficacy and tolerance. J Investig Allergol Clin Immunol. 2005; 15: 283-92.

63. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Möller C; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007; 62: 943-8.

64. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A doubleblind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996; 51: 489-500.

65. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, Sever ML, Bahnson HT, Lawson K, Harris KM, Plough AG, Panza JL, Qin T, Lim N, Tchao NK, Togias A, Durham SR; Immune Tolerance Network GRASS Study Team. Effect of 2 Years of Treatment with Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients with Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. JAMA 2017;14: 615-625.

66. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. Clin Exp Allergy 2003; 33: 1076-82.

67. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. Makedon Akad Na Nauk Umet Oddelenie Za Bioloshki Meditsinski Nauki Pril. 2005; 26: 113–29.

68. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Exp Allergy 1988; 18: 501–8.

69. Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. Allergy 1998; 53: 740–8.

70. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002; 57: 297–305.

71. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ. 1991; 302 (6771): 265–9.

72. Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol. 1997; 100: 23–9.

73. Weyer, N. Donat, C. L'Heritier, F. Juilliard, G. Pauli, B. Soufflet, et al. Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. Allergy 1981; 36: 309–17.

74. Bousquet J, Hejjaoui A, Skassa-Brociek W, Guerin B, Maasch HJ, Dhiver Ht, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1990; 80: 591–8.

75. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005;116:608-13.

76. Brunet C, Bédard PM, Lavole A, Jobin M, Hébert J. Allergic rhinitis to ragweed pollen: I. Reassessment of the effects of immunotherapy on cellular and humoral responses. J Allergy Clinical Immunol 1992; 89: 76-86.

77. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A, for the Study Group. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy. 2005; 60: 801-807.

78. Klimek L, Uhlig J, Mosges R, Rettig K, Pfaar O. A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. Allergy. 2014; 69): 1629–38.

79. Ortolani C, Pastorello EA, Incorvaia C, Ispano M, Farioli L, Zara C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of Parietaria judaica in patients with Parietaria hay fever. Allergy 1994; 49: 13-21.

80. Tabar AI, Lizaso MT, García BE, Gómez B, Echechipía S, Aldunate MT, et al. Double-blind, placebo-controlled study of Alternaria immunotherapy: Clinical efficacy and safety. Pediatr Allergy Immunol. 2008; 19: 67-75.

81. Ceuppens JL, Bullens D, Kleinjans H, van der Werf J, Purethal Birch Efficacy Study Group. Immunotherapy with a modified birch pollen extract in allergic rhinoconjunctivitis: clinical and immunological effects. Clin Exp Allergy. 2009; 39: 1903-1909.

82. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. Am J Rhinol Allergy. 2010; 24: 104-109.

83. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999; 341: 468-475.

84. James LK, Shamji MH, Walker SM, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. J Allergy Clin Immunol. 2011; 127: 509-516.

85. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006; 61: 185–90

86. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, Rivas MF, Ribel M, Durham SR Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 118: 434-40.

87. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; 117: 802-9.

88. Pajno GB, Caminiti L, Crisafulli G, Barberi S, Landi M, Aversa T, Valenzise M, Passalacqua G. Adherence to sublingual immunotherapy in preschool children. Pediatr Allergy Immunol 2012; 23: 688-689.

89. Worm M, Rak S, de Blay F, Malling HJ, Melac M, Cadic V, Zeldin RK. Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study. Clin Transl Allergy 2014; 11; 4: 7.

90. Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. Allergy. 2000; 55: 1142-7.

91. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. Clin Exp Allergy. 2003;33:1641-7.

92. Stelmach I, Kaluzińska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P.Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. Allergy 2012; 67: 312-20.

93. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol. 2013; 131: 1342-9.e6.

94. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. Clinical Translational Allergy. 2015; 5: 12. `

95. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a 45tandardized grass pollen extract; a double-blind placebo-controlled study. Allergol Immunopathol (Madr). 1998; 25: 234-40.

96. Palma-Carlos AG, Santos AS, Branco-Ferreira M, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A doubleblind, placebo-controlled study. Allergol Immunopathol (Madr). 2006; 34: 194-8.

97. Halken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol. 2010; 21: 970-6.

98. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009; 123: 167-73.

99. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP.Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011; 127: 64-71, 71.e1-4.

100. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol. 2009; 124: 150-6.e1-5.

101. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in Cupressaceae allergy using an extract of Cupressus arizonica. A double blind study. Allergol Immunopathol (Madr). 2001; 29: 238-44.

102. Panzner P, Petras M, Sykora T, Lesna I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. Respir Med. 2008; 102: 1296-1304.

103. Bufe A, Ziegler-Kirbach E, Stoeckmann E, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. Allergy. 2004; 59: 498-504.

104. Feliziani V, Lattuada G, Parmiani S, Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. Allergologia et immunopathologia. 1995;23:224-30.

105. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Ann Allergy Asthma Immunol. 2004; 93: 425-30.

106. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr). 1990; 18: 277-284.

107. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. Allergy. 2000; 55: 369-375.

108. Didier A, Malling HJ, Worm M, Horak F, Sussman G, Melac M, Soulie S, Zeldin RK. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. Clin Exp Allergy. 2013; 43: 568-77.

109. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012; 129: 717-725.e715.

110. Valovirta E, Berstad AK, de Blic J, Bufe A, Eng P, Halken S, Ojeda P, Roberts G, Tommerup L, Varga EM, Winnergard I. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass Pollen–Induced allergic rhinoconjunctivitis. Clinical therapeutics. 2011; 33: 1537-46.

111. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sørensen HF, Klink R, GAP investigators. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol, J Allergy Clin Immunol. 2017 Jul 6. pii: S0091-6749(17)31088-6. doi: 10.1016/j.jaci.2017.06.014. [Epub ahead of print]

112. Pfaar O, Cazan D, Klimek L, Larenas-Linnemann D, Calderon MA. Adjuvants for immunotherapy. Curr Opin Allergy Clin Immunol 2012; 12: 648-657.

113. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001; 56: 498–505.

114. DuBuske L, Frew A, Horak F, Keith P, Corrigan C, Aberer W. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. Allergy Asthma Proc. 2011; 32: 239-247.

115. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R, Li H, Coffman R, Seyfert V, Eiden JJ, Broide D; Immune Tolerance Network Group. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med. 2006; 355: 1445-55.

116. Rolinck-Werninghaus C, Hamelmann E, Keil T, Kulig M, Koetz K, Gerstner B, Kuehr J, Zielen S, Schauer U, Kamin W, Von Berg A, Hammermann J, Weinkauf B, Weidinger G, Stenglein S, Wahn U; The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Omalizumab Rhinitis Study Group. Allergy; 2004; 59: 973-9.

117. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, Mokhtarani M, Seyfert-Margolis V, Asare A, Bateman K, Deniz Y; Immune Tolerance Network Group Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol. 2006; 117: 134-40.

118. Larenas-Linnemann D, Wahn U, Kopp M. Use of omalizumab to improve desensitization safety in allergen immunotherapy. J Allergy Clin Immunol 2014; 133: 937-937.

119. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, Purohit A, Arvidsson M, Kavina A, Schroeder JW, Mothes N, Spitzauer S, Montagut A, Galvain S, Melac M, André C, Poulsen LK, Malling HJ. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. J Allergy Clin Immunol 2008; 122: 951-60.

120. Zieglmayer P, Focke-Tejkl M, Schmutz R, Lemell P, Zieglmayer R, Weber M, Kiss R, Blatt K, Valent P, Stolz F, Huber H, Neubauer A, Knoll A, Horak F, Henning R, Valenta R. Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy. EBioMedicine 2016; 11: 43-57.

121. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larché M, Hafner RP. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. J Allergy Clin Immunol 2013; 131: 103-9.e1-7.

122. http://www.circassia.com/media/press-releases/circassia-announces-top-line-results-from-cat-allergy-phase-iii-study/.[Accessed on July 31st, 2017]

123. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125:569–74,574.e1–574.e7.

124. Spertini F, DellaCorte G, Kettner A, de Blay F, Jacobsen L, Jutel M, Worm M, Charlon V, Reymond C.Efficacy of 2 months of allergen-specific immunotherapy with Bet v 1-derived contiguous overlapping peptides in patients with allergic rhinoconjunctivitis: Results of a phase IIb study. J Allergy Clin Immunol. 2016; 138: 162-8.

125. Senti G, von Moos S, Tay F, Graf N, Sonderegger T, Johansen P, Kündig TM. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. J Allergy Clin Immunol. 2012; 129: 128-35.

126. Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Hay E, Lam EP, Kelly J, Peacock JL, Ying S, Shamji MH, Cousins DJ, Durham SR, Till SJ. Intradermal grass pollen immunotherapy increases TH2 and IgE responses and worsens respiratory allergic symptoms. J Allergy Clin Immunol. 2017; 139: 1830-9.

127. Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, Steiner M, Hothorn LA, Grönlund H, Tivig C, Zaleska A, Soyer O, van Hage M, Akdis CA, Akdis M, Rose H, Kündig TM. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol. 2012; 129: 1290-6.

128. Patterson AM, Bonny AE, Shiels WE, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. Annals of Allergy, Asthma & Immunology. 2016; 116: 168-70.

129. Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK. Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy?J Allergy Clin Immunol. 2013; 132: 1248-52.

130. Drachenberg KJ, Heinzkill M, Urban E, Woroniecki SR. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A (MPL) for children and adolescents. Allergol Immunopathol (Madr). 2003; 31: 270-7.

131. Patel P, Holdich T, von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. J Allergy Clin Immunol 2014; 133: 121-9.

132. European Medicines Agency. Guideline on allergen products: production and quality issues. London; 2008 EMEA/CHMP/BWP/304831/2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf [accessed 13th August 2017]

133. Coop CA. Immunotherapy for Mold Allergy. Clin Rev Allergy Immunol. 2014; 47: 289-98.

134. Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: From structure to therapy. Allergy Asthma Immunol Res. 2015; 7: 205-20.

135. Lizaso MT, Martínez A, Asturias JA, Algorta J, Madariaga B, Labarta N, et al. Biological standardization and maximum tolerated dose estimation of an Alternaria 45tandardi allergenic extract. J Invest Allergol Clin Immunol. 2006; 16: 94-103.

136. Slater JE, Zoch A, Newman-Gerhardt S, Khurana T. Comparison of total protein profile of alternaria extract obtained from various U.S. Allergenic extract manufacturers. J Allergy Clin Immunol. 2014; 133: AB100.

137. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. Allergy, Asthma & Clinical Immunology. 2016; 12: 2.

138. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2014; 134: 568-75 e7.

139. Bahceciler NN, ik UI, Barlan IB, Bas aran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001; 32: 49-55.

140. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Paediatr Allergy and Immunol. 1997; 8: 21-27.

141. Larenas-Linnemann, D., et al. Maintenance dosing for sublingual immunotherapy by prominent European allergen manufacturers expressed in bioequivalent allergy units. Ann Allergy Asthma Immunol 2011; 107: 448-4.

142. Pfaar O, Biedermann T, Klimek L, Sager A, Robinson DS. Depigmented–polymerized mixed grass/birch pollen extract immunotherapy is effective in polysensitized patients. Allergy. 2013; 68: 1306-13.

143. Swamy RS, Reshamwala N, Hunter T, Vissamsetti S, Santos CB, Baroody FM, Hwang PH, Hoyte EG, Garcia MA, Nadeau KC. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. J Allergy Clin Immunol. 2012; 130: 215-24.e7.

144. Marcucci F, Sensi L, Frati F, Bernardini R, Novembre E, Barbato A, et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. Allergy 2003; 58: 657–62.

145. Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L, Pfaar O, Merk H. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. Allergy. 2009; 64: 1394-401.

146. de Bot CMA, Moed H, Berger MY, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. Pediatr Allergy Immunol. 2012; 23: 151-159.

147. Passalacqua G, Albano M, Fregonese L, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet. 1998;351:629632.

148. Migueres M, Dávila I, Frati F, Azpeitia A, Jeanpetit Y, Lhéritier-Barrand M, Incorvaia C, Ciprandi G. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. Clinical and translational allergy. 2014; 4: 16.

149. Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. Allergy. 2013; 68: 252-5.

150. Adkinson Jr NF, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, Tonascia J. A controlled trial of immunotherapy for asthma in allergic children. New England Journal of Medicine 1997; 336: 324-32.

151. Nelson HS. Multiallergen Immunotherapy for Allergic Rhinitis and Asthma. J Allergy Clin Immunol 2009; 123: 763–69.

152. Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, Li Q, Cao LF. Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis. Am J Rhinol Allergy 2014; 28: 131-9.

153. Fiocchi A, Pajno G, La Grutta S, Pezzuto F, Incorvaia C, Sensi L et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann All Asthma Immunol 2005; 95: 254-258.

154. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. Allergy 2005; 60: 133-134.

155. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol. 2006; 117: 263-8.

156. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, Le Gall M; SLIT Study Group. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009; 123: 160-166.e3.

157. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy. 2006; 61: 198-201.

158. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. Pediatr Allergy Immunol 2006; 17: 396-407.

159. Bozek A, Kolodziejczyk K, Warkocka-Szoltysek B, Jarzab J. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. Am J Rhinol Allergy. 2014; 28: 423-7.

160. Bozek A, Kolodziejczyk K, Krajewska-Wojtys A, Jarzab J. Pre-seasonal, subcutaneous immunotherapy: a double-blinded, placebo-controlled study in elderly patients with an allergy to grass. Ann Allergy Asthma Immunol. 2016; 116: 156-61.

161. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. Allergy. 2012; 67: 741-3.

162. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. Allergy Asthma Clin Immunol. 2015; 11: 31.

163. Incorvaria—Incorvaia C, Masieri S, Berto P, Scurati S, Frati F. Specific immunotherapy by the sublingual route for respiratory allergy. Allergy Asthma Clin Immunol. 2010; 6: 29.

164. Scurati S, Frati F, Passalacqua G, Puccinelli P, Hilaire C, Incorvaia C; Italian Study Group on SLIT Compliance. Adherence issues related to sublingual immunotherapy as perceived by allergists. Patient Prefer Adherence. 2010; 4: 141-5.

165. Egert-Schmidt AM, Kolbe JM, Mussler S, Thum-Oltmer S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. Patient Prefer Adherence. 2014; 8: 1475-81.

166. Kiel MA, Röder E, van Wijk RG, Al MJ, Hop WC, Rutten-van Mölken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. Journal of Allergy and Clinical Immunology. 2013; 132: 353-60.

167. Vaswani R, Garg A, Parikh L, Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. Ann Allergy Asthma Immunol. 2015; 115: 241-3.

168. Leader BA, Rotella M, Stillman L, DelGaudio JM, Patel ZM, Wise SK. Immunotherapy compliance: comparison of subcutaneous versus sublingual immunotherapy. Int Forum Allergy Rhinol. 2016; 6: 460-4.

169. Savi E, Peveri S, Senna G, Passalacqua G. Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach. Allergy. 2013; 68: 1193-5.

170. Makatsori M, Scadding GW, Lombardo C, Bisoffi G, Ridolo E, Durham SR, Senna G. Dropouts in sublingual allergen immunotherapy trials – a systematic review. Allergy 2014; 69: 571–580.

171. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. Allergy. 2010; 65: 668-9.

172. Patel P, Holdich T, von Weikersthal-Drachenberg KJ, Huber B. Efficacy of a short course of specific immunotherapy in patients with allergic rhinoconjunctivitis to ragweed pollen. Journal of Allergy and Clinical Immunology. 2014 Jan 31;133(1):121-9.

173. Rienzo VD, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy 2005; 35: 560-564.

174. Rodriguez-Santos O. Sublingual immunotherapy in allergic rhinitis and asthma in 2-5-year-old children sensitized to mites. Rev Alerg Mex 2008; 55: 71-75.

175. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. Clin Exp Allergy. 2012;43:242-248.

176. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, Scadding GK, Andersen JS, Riis B, Dahl R. Long-term clinical efficacy in grass pollen–induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. Journal of Allergy and Clinical Immunology 2010; 125: 131-8.

177. Lin Z, Liu Q, Li T, Chen D, Chen D, Xu R. The effects of house dust mite sublingual immunotherapy in patients with allergic rhinitis according to duration. Int Forum Allergy Rhinol. 2016; 6: 82-7.

178. Naclerio RM, Proud D, Moylan B, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997; 100: 293-300.

179. Arroabarren E, Tabar AI, Echechipía S, Cambra K, García BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. Pediatr Allergy Immunol. 2015; 26: 34-41.

180. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. Immunotherapy 2012; 4: 601–16.

181. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. Drug Saf 2000; 23: 323–32.

182. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: year 2. Ann Allergy Asthma Immunol 2011; 107: 426–431.e1

183. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). Ann Allergy Asthma Immunol 2016; 116: 354-9.e2.

184. Calderon MA, Vidal C, Rodrıguez del Rıo P, Just J, Pfaar O, Tabar AI, Sanchez-Machın I, Bubel P, Borja J, Eberle P, Reiber R, Bouvier M, Lepelliez A, Klimek L, Demoly P on behalf of the EASSI Doctors' Group. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. Allergy 2017; 72: 462–72.

185. Rodríguez del Río P, Vidal C, Just J, Tabar AI, Sanchez-Machin I, Eberle P, Borja J, Bubel P, Pfaar O, Demoly P, Calderón MA. The European survey on adverse systemic reactions in allergen immunotherapy (EASSI): a paediatric assessment. Pediatric Allergy and Immunology. 2017; 28: 60-70.

186. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. Ann Allergy Asthma Immunol 2004; 92: 225–7.

187. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996; 97: 1207–13.

188. Reimers A, Hari Y, Müller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. Allergy 2000; 55: 484–8.

189. Brehler R, Klimek L, Pfaar O, Hauswald B, Worm M, Bieber T. Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts. Allergy Asthma. 2010; 31: 3138.

190. Cardona R, Lopez E, Beltran J, Sanchez J. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultrarush buildup. A retrospective study. Allergol Immunopathol (Madr). 2014; 42: 90-95.

191. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. Int Arch Allergy Immunol. 2006; 139: 153-158.

192. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of immunotherapy with therapeutic vaccines containing depigmented and polymerized allergen extracts. Clin Exp Allergy. 2007; 37: 434-440.

193. Vogelbruch M, Nuss B, Körner M, Kapp A, Kiehl P, Bohm W. Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. Allergy 2000; 55: 883–7.

194. Netterlid E, Hindsén M, Björk J et al. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. Contact Dermatitis 2009; 60: 41–9.

195. Frost L, Johansen P, Pedersen S, Veien N, Ostergaard PA, Nielsen MH. Persistent subcutaneous nodules in children hyposensitized with aluminium-containing allergen extracts. Allergy 1985; 40: 368–72.

196. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2010;(12):CD002893.

197. Canonica GW, Cox L, Pawankar R et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. The World Allergy Organization journal 2014; 7: 6.

198. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS: Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol. 2006, 117: 1021-35.

199. Passalacqua G, Baena-Cagnani CE, Bousquet J et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. J Allergy Clin Immunol 2013;132:93–8.

200. Amin HS, Liss GM, Bernstein DI: Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006, 117: 169-175.

201. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, Barton P, Dretzke J. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess. 2013; 17(27): vi, xi-xiv, 1-322.

202. Ariano R, Berto P, Tracci D, et al. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. Allergy Asthma Proc 2006; 27: 159–163.

203. Berto P, Bassi M, Incorvaia C, et al. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. Allerg Immunol (Paris) 2005; 37: 303–308.

204. Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G, et al. Allergy immuno- therapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. J Allergy Clin Immunol 2008; 121: 227-32.

205. Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. Ann Allergy Asthma Immunol 2010; 104: 79-85.

206. Hankin CS, Cox L, Bronstone A, Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. J Allergy Clin Im- munol 2013; 131: 1084-91.

207. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996; 334: 501-6.

208. Berto P, Frati F, Incorvaia C, Cadario G, Contiguglia R, Di Gioacchino M, et al. Comparison of costs of sublingual immunotherapy and drug treatment in grasspollen induced allergy: results from the SIMAP database study. Curr Med Res Opin 2008; 24: 261-6.

209. Schadlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. Pharmacoeconomics 2000; 17: 37-52.

210. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. Allergol Immunopathol (Madr) 2005; 33: 296-302.

211. Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G, et al. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. Ann Allergy Asthma Immunol 2006; 97: 615-21.

212. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis—a Northern European perspective. Clin Exp Allergy 2007; 37: 772-9.

213. Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. Allergy. 2008; 63: 1624-1629.

214. Poulsen PB, Pedersen KM, Christensen J, Vestenbaek U. [Economic evaluation of a tablet-based vaccination against hay fever in Denmark]. Ugeskr Laeger. 2008: 14; 170: 138–42.

215. Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. Curr Med Res Opin. 2007; 23: 1113–20.

216. Ronaldson S, Taylor M, Bech PG, Shenton R, Bufe A. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (Grazax) in children. Clin Outcomes Res. 2014; 6: 187–96.

217. Westerhout KY, Verheggen BG, Schreder CH, Augustin M. Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany. J Med Econ. 2012; 15: 906-17.

218. Verheggen B, Westerhout K, Schreder C, Augustin M. Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany. Clin Transl Allergy. 2015; 5(1).

219. Reinhold T, Brüggenjürgen B. Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment. Allergo J Int. 2017; 26: 7-15.

220. Asaria M, Dhami S, van Ree R, Gerth van Wijk R, Muraro A, Roberts G, Sheikh A. Health Economic Analysis of Allergen Immunotherapy (AIT) for the Management of Allergic Rhinitis, Asthma, Food Allergy and Venom Allergy: A Systematic Overview. Allergy. *in press.*

221. Nelson H, Cartier S, Allen-Ramey F, Lawton S, Calderon MA. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. J Allergy Clin Immunology: In Practice. 2015; 3: 256-66.

222. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, Bohle B, Chaker AM, Till SJ, Valenta R, Poulsen LK. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy 2017; 72: 1156-1173.

223. Stelmach I, Sobocińska A, Majak P, Smejda K, Jerzyńska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. Ann Allergy Asthma Immunol. 2012; 109: 274-8.