EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergen Immunotherapy Guidelines

Part 2: Recommendations

Translating knowledge into clinical practice

European Academy of Allergy and Clinical Immunology

EAACI GUIDELINES

Allergen Immunotherapy Guidelines Part 2: Recommendations

Editors

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The European Academy of Allergy and Clinical Immunology (EAACI) is a non-profit organisation active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. EAACI was founded in 1956 in Florence and has become the largest medical association in Europe in the field of allergy and clinical immunology. It includes over 10,000 members from 122 countries, as well as over 60 national and international member societies.

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For all EAACI Members
and to our patients

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Foreword

EAACI has a long history and strong ethos in implementing the latest research findings to deliver better healthcare for patients with allergies. Over the last decades this mission has become even more important with allergic diseases now affecting the lives of millions of people around the world. This represents a major burden for patients as well as their clinicians, governments, legislators and regulators. The current challenge is to deliver appropriate treatments that are able to prevent lifetime disabilities, shifting from "treating a disease" to "promote health" in a sustainable context.

Allergen immunotherapy (AIT) has been used for a century. Several terms including "desensitization", "hyposensitization" and "vaccines" have been used, and often misused, to indicate administration of incremental doses of allergenic substances to reduce the clinical manifestations of allergy. However AIT has also been the subject of considerable controversy in terms of its efficacy. The dispute has impacted on the dissemination of knowledge about AIT, the availability of the products in many countries and the relevant policies for their reimbursement. Some of these issues result from an inadequate translation of the scientific data into daily practice, with clinical judgment being established on expert opinion instead of the objective evaluation of valid scientific studies.

These Guidelines for clinical practice aim to define the current literature and they have synthesized the scientific evidence in a well-structured, systematic and reproducible process. This has been combined with the expertise of clinicians, the preferences of patients and the needs of policy makers. The purpose has been to develop clinically valid, operational recommendations which serve as a strong basis to help the allergist to advocate for AIT, practitioners to refer patients onto appropriate management, the patient to request the best standard of care for their disease and quality of life and the regulators to evaluate the sustainability for the health-care system. Of note, these recommendations cannot, and will not, stand forever but will need to be revised as soon as new research developments are available.

These guidelines follow the previous guidelines on Food Allergy and Anaphylaxis. Together, they have defined a crucial change resulting in a framework of a rigorous methodological approach for future guidelines. The ambition for EAACI is to drive the perception of clinicians and stakeholders from relying on old "pre-cooked recipes" to focusing on critical thinking and applicability of the recommendations.

Almost all the EAACI groups have worked on these AIT Guidelines. It is thanks to the tireless efforts of the many task forces Chairs, to the Sections and to the Interest Groups that we have been able to develop comprehensive Guidelines. We also need to thank the commitment of the EAACI members who contributed through the public comment, the Board of Officers and the Executive Committee and almost 100 experts from all over the world who have worked with enthusiasm and who have been instrumental to maintain the pace over the last 2 years. We feel privileged for their vision and continuous support.

This is, indeed, the start of the journey. Implementing the Guidelines both nationally and internationally will measure the success of this project. We are sure that EAACI members have the strength and dedication to accomplish this achievement.

Antonella Muraro

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Abbreviations

AAI	Adrenaline autoinjector
ACEI	Angiotensin-converting enzyme inhibitors
AD	Atopic dermatitis (atopic eczema)
AGREE II	Appraisal of Guidelines for Research & Evaluation
AIT	Allergen immunotherapy
AR	Allergic rhinitis / Allergic rhinoconjunctivitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BAT	Basophil activation test
CBA	Controlled before and after study
CCT	Controlled clinical trial
CI	Confidence interval
CM	Cow's milk
CRD	Component-resolved diagnosis
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
ELIFAB	Enzyme-linked immunosorbent facilitated antigen binding
EMA	European Medicines Agency
ENT	Ear nose and throat
EoE	Eosinophilic esophagitis
EPIT	Epicutaneous immunotherapy
FA	Food allergy
HDM	House dust mite
HE	Hen's egg
HVA	Hymenoptera venom allergy
ICER	Incremental cost-effectiveness ratio
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
LLR	Large local reaction
MAOI	Monoamine oxidase inhibitors
NARES	Non-allergic rhinitis with eosinophilia syndrome
OAS	Oral allergy syndrome
OFC	Oral food challenge
OIT	Oral immunotherapy
QALY	Quality-adjusted life years
QoI	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
SCIT	Subcutaneous immunotherapy
sIgE	Specific-IgE
SLIT	Sublingual immunotherapy
SMD	Standardized mean difference
SmPC	Summary or product characteristics.
SPT	Skin prick test
SR	Systematic review
SSR	Systemic sting reaction
VIT	Venom immunotherapy (subcutaneous, unless otherwise stated).
WAO	World Allergy Organization.

Preface

A third of the population in Europe now suffers from at least one allergic disease. Allergic rhinitis, asthma, food allergy and other allergies represent major burdens to individuals, families and to health services. We now have a good understanding of these diseases and how to manage them. Most patients have good disease control and quality of life with avoidance strategies and simple pharmacotherapy. Unfortunately, a minority still have persistent symptoms or remain at risk of life-threatening allergic reactions; they need additional therapy.

Allergen immunotherapy (AIT) is an approach where administration of allergen can be used to ameliorate a specific IgE associated response thereby controlling allergic disease symptoms. The therapy has been used for over a century and there have been considerable advances in the approach over the last decade. Typically the subcutaneous, sublingual or oral routes are used. AIT has the capacity to control allergic symptoms that are not responsive to avoidance strategies or pharmacotherapy; it may also change the natural history of allergic disease.

These AIT Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) AIT Guidelines Taskforces in a project chaired by Antonella Muraro and coordinated by Graham Roberts. They aim to provide evidence-based recommendations for the use of AIT for patients with allergic disease. As such, their primary audience are clinical allergists, although the guidelines will be of relevance to other healthcare professionals (e.g. primary care workers, other specialist doctors, nurses and pharmacists working across a range of clinical settings) dealing with allergic disease. We have tried to anticipate the patient journey across the health system and potential pathways to envisage the potential service delivery in different contexts and countries.

The Guidelines have been generated using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach which is a structured approach to developing guidelines. In following this approach, the Taskforces have ensured that there has been 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 in April 2015 beginning with detailed face-to-face discussions agreeing 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.

Part 1 of the book focused on the systematic reviews with chapters covering the prevention of allergy (Chapter 1), insect venom allergy (Chapter 2), IgE-mediated food allergy (Chapter 3), allergic asthma (Chapter 4) and allergic rhinoconjunctivitis (Chapter 5). This part 2 of the book includes the AIT guideline documents for prevention (Chapter 1), venom allergy (Chapter 2), IgE mediated food allergy (Chapter 3), allergic rhinoconjunctivitis (Chapter 4); plus position papers focused on primary care (Chapter 5) and regulatory (Chapter 6) and a systematic review of socioeconomics of AIT (Chapter 7). A considerable amount of supplementary materials are available for each of the chapters. These can be downloaded from the EAACI website. All the documents have been published in Allergy, Pediatric Allergy and Immunology or Clinical and Translational Allergy; they are reproduced with permission of the publishers.

This massive project has only been possible with the active engagement of numerous friends and colleagues. We would like to thank the Taskforce Chairs who have successfully steered each of the chapters to completion: Susanne Halken (Prevention) with support from Desiree Larenas-Linneman and Moises Calderon, Gunter Sturm and Eva-Maria Varga (Venom), Giovanni Pajno and Montserrat Fernandez Rivas (Food allergy), Ioana Agache, Susanne Lau and Marek Jutel (Allergic Asthma), Oliver Pfaar and Graham Roberts (Allergic Rhinoconjunctivitis), Stefan Vieths and Andreas Bonertz (Regulatory paper) and Dermot Ryan, Liz Angier, Ronald van Ree and Roy Gerth van Wijk

(Primary care and health economics papers). Also, we would like to thank Frans Timmermans of the EAACI Patient's organizations committee for coordinating the input of the patient representatives into the guideline process. The Taskforces have been supported by a team of methodologists led by Aziz Sheikh; we are especially indebted to the help of Sangeeta Dhami and Stefania Arasi. We would like to thank EAACI for funding this project and the headquarters for supporting it. We are very grateful to all the Taskforce members who have dedicated time to be actively involved in this project, reviewing evidence and then generating recommendations. Also, a huge thanks to our external experts and EAACI members who have taken time to review the draft guidelines and provide feedback; this has helped us ensure that the final versions are accurate and relevant for healthcare professionals and patients.

These Guidelines have been an exciting and important journey. Unlike pharmacotherapy, AIT has the potential to really modify our patients' journeys delivering them long term therapeutic benefit. Now that we have evidence based recommendations, we need to all work to disseminate and implement them for the benefit of all our patients. This will rely on the involvement of healthcare professionals from across health systems. We hope that this EAACI book will serve as a key educational resource for this process. The Taskforces will now focus on dissemination and implementation activities with additional materials being generated to support these.

Graham Roberts and Antonella Muraro

Editors

Disclaimer

These Guidelines published by the European Academy of Allergy and Clinical Immunology (EAACI) have drawn on data from systematic reviews of the literature, more recent published studies and multi-stakeholder expert clinical opinion. These Guidelines are aimed at healthcare professionals who are encouraged to take their recommendations into account in the context of delivering clinical care. These Guideline are not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

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EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

PREVENTION OF ALLERGY

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Allergic diseases are common and frequently coexist. Allergen immunotherapy (AIT) is a disease-modifying treatment for IgE-mediated allergic disease with effects beyond cessation of AIT that may include important preventive effects. The European Academy of Allergy and Clinical Immunology (EAACI) has developed a clinical practice guideline to provide evidence-based recommendations for AIT for prevention of i) development of allergic comorbidities in those with established allergic diseases, ii) development of first allergic condition and iii) allergic sensitization. This guideline has been developed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) framework, which involved a multi-disciplinary expert working group, a systematic review of the underpinning evidence and external peer-review of draft recommendations. Our key recommendation is that a three year course of subcutaneous or sublingual AIT can be recommended for children and adolescents with moderate to severe allergic rhinitis (AR) triggered by grass/birch pollen allergy to prevent asthma for up to two years post-AIT in addition to its sustained effect on AR symptoms and medication. Some trial data even suggest a preventive effect on asthma symptoms and medication more than two years post-AIT. We need more evidence concerning AIT for prevention in individuals with AR triggered by house dust mites or other allergens and for the prevention of allergic sensitization, the first allergic disease or for prevention of allergic co-morbidities in those with other allergic conditions. Evidence for the preventive potential of AIT as disease modifying treatment exists but there is an urgent need for more high-quality clinical trials.

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INTRODUCTION

Allergic diseases are among the commonest chronic diseases and encompass atopic eczema/dermatitis (AD), asthma, allergic rhinitis and allergic rhinoconjunctivitis (both from here onward referred to as AR), food allergy and venom allergy (1-5). They frequently start in early childhood and continue throughout adulthood. Allergies can cause a considerable burden to individuals leading to impaired quality of life (6). At a societal level, they cause additional costs, particularly in terms of healthcare utilization, reduction in economic productivity and impacting on activities of daily living. The latter may include loss of school days, work absence, presenteeism and early retirement (7, 8). For allergic asthma and AR, many patients respond well to pharmacotherapy, whereas others do not or need treatment with more than one product (9). However, there is good evidence for the clinical efficacy of allergen immunotherapy (AIT) for AR, allergic asthma and moderate to severe venom allergy (10-12) with many patients responding to therapeutic AIT, leading to a sustained reduction in symptoms and requirement for symptomatic treatment.

AIT is considered a disease-modifying intervention in IgE-mediated allergic disease, with both a therapeutic, even beyond cessation of AIT (10-12), and the potential for a preventive effect (13-16). It has been shown that children with AR have a 3-fold increased risk of developing asthma (17, 18) and that childhood AD and AR are strongly associated with the incidence and persistence of adult atopic asthma and with allergic asthma persisting into adulthood (19). Studies assessing the long-term effectiveness of AIT in children with AR indicate that AIT might reduce the risk of developing asthma (20-23). AIT has the potential to induce immunological changes that result in immune modification (14). Therefore, AIT should be considered as a preventive strategy in the treatment of allergic diseases.

This Guideline has been developed by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on AIT for Allergy Prevention and form part of the EAACI Guidelines on Allergen Immunotherapy. The aim is to provide evidence-based recommendations for the use of AIT for prevention of i) further allergic co-morbidities in those with established allergic disease, ii) first allergic disease and iii) development of allergic sensitization. This Guideline does not cover prevention of symptoms, exacerbations or progression of already existing allergic disease since this is included in other guidelines in this series. Likewise it does not cover weaning and dietetic strategies, which are considered in the 'EAACI food allergy and anaphylaxis guidelines: Primary prevention of food allergy' (24). Definition of key terms are described in Box 1.

The primary audience for this Guideline are clinical allergists (specialists and subspecialists). It may also provide guidance for other healthcare professionals e.g., physicians, nurses and pharmacists working across a range of primary, secondary and tertiary care settings managing patients with allergic diseases and healthy individuals at risk of developing allergic diseases.

METHODS

Development of the Guideline has been informed by a formal systematic review (25) and meta-analysis of AIT for prevention of allergy (25) with SR principles being used to identify additional evidence, where necessary.

This Guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (26, 27). This structured method for guideline production is designed to ensure appropriate representation of the full range of stakeholders, an exhaustive 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 began in April 2015 with detailed face-to-face discussions agreeing on the process and the key clinical areas to address, followed by face-to-face and 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 recommendations that assist clinicians in the optimal use of AIT for the prevention of development of allergic disease in the management of individuals with, or at risk for, allergic disease, and identifying gaps for further research. The Guideline

Box 1 Key terms

Allergic asthma	Typical symptoms of asthma (wheezing, cough, dyspnea, chest tightness with evidence of reversibility) induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen
Allergic conjunctivitis	Inflammation of the conjunctiva characterized by watery, itchy, red eyes induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen
Allergic diseases	Atopic dermatitis (eczema) (AD), food allergy (FA), allergic asthma, allergic rhinitis/conjunctivitis (AR) and venom allergy at any age
Allergic rhinitis	Inflammation of the nasal mucosa resulting in at least two nasal symptoms: rhinorrhoea, blockage, sneezing or itching induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen
AIT (Allergen immunotherapy)	Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and need for medication for clinical allergies and to prevent the development of new allergies and asthma (adapted from European Medicines Agency (EMA)). This is also sometimes known as allergen specific immunotherapy, desensitization, hyposensitization and allergy vaccination* • 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 tablets
Healthy individuals	Individuals with or without IgE sensitization, but without any manifestations of current allergic disease
Prevention	Prevention of the development of a new sensitization or new allergic disease in healthy individuals without sensitizations, in healthy individuals with sensitizations and in those who already have an allergic disease **Short-term prevention**: preventive effect assessed within a two year window post-AIT **Long-term prevention**: preventive effect maintained after at least two years post-AIT In this document, specific treatment effects such as effect on exacerbations and progression of the disease, including long-term effects, are not regarded as prevention.
Sensitization	Detectable specific IgE antibodies, either by means of SPT or determination of specific-IgE antibody levels in a serum sample

*** Dietary interventions in infants aimed at the prevention of food allergy** are not covered in this Guideline: they form part of the 'EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy' https://www.ncbi.nlm.nih.gov/pubmed/24697491 (24).

builds on a SR conducted to summarise the evidence base in relation to these aims (Box 2) (25).

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on AIT for Prevention represented a range of countries, with various disciplinary and clinical backgrounds, including allergists, primary care physicians, allied health professionals, public health practitioners, representatives from patient interest organisations and methodologists who took the took the lead in undertaking the underpinning SR. Additionally, producers of immunotherapy products were given the opportunity to review and comment on the draft guidelines as part of the peer review and public comment process. The Taskforce members considered these comments and revised the Guideline, where appropriate.

Box 2 Summary of the aim and outcomes in the supporting systematic review (25)

Aim	To provide the evidence basis for formulating clinical practice guidelines for the use of AIT as preventive therapeutic intervention in allergy. This will be based on a rigorous evaluation of current SR evidence on the effectiveness, safety and cost-effectiveness of AIT for prevention of allergic sensitization(s) and allergic disease(s),
Outcomes of the SR:	***Primary*** • The development of the first allergic manifestation in healthy individuals, or of a new allergic manifestation in those with a previous allergic condition (e.g. development of asthma in patients with atopic eczema/dermatitis (AD) or AR, assessed over the short term (< 2 years) or the longer term (≥ 2 years) post-AIT ***Secondary*** • The development of new allergic sensitization(s), spreading of allergic sensitization(s) from one allergen to other non-related allergen(s), spreading of allergic sensitization(s) at molecular level, from one allergenic molecule to other molecules • The development of previously non-existent oral allergy syndrome (OAS) • Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading systems of local and systemic side-effects (28, 29). • Health economic analysis from the perspective of the health system/payer as reported in studies

Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree on one key overarching question: "What is the effectiveness, safety and cost-effectiveness of AIT for prevention of allergic disease and sensitization in all populations?". This was then pursued through a formal SR of the evidence by independent methodologists as previously published (25, 30). We continued to track evidence published after our SR cut-off date October 31, 2015 and, where relevant, studies were considered by the Taskforce chairs and members.

Formulating recommendations

We graded the strength and consistency of key findings from the SR and meta-analysis, using a random-effects model to take into account the heterogeneity of findings (25) to formulate evidence-based recommendations for clinical care, using an approach that was adapted from that proposed by the Oxford Centre for Evidence-Based Medicine (Oxford Centre for Evidence-based Medicine) (Box 3) (31). 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, formulating clear recommendations and making clear the evidence-base 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 systematic review data and clearly labelled in the recommendation tables. In formulating the recommendations not only possible beneficial effects, but also any possible disadvantages and harms was considered (Table 1).

Identification of evidence gaps

The process of developing this Guideline has identified a number of evidence gaps, which are prioritized in Table 2.

Implementation of the Guideline

The Taskforce members identified the resource implications, barriers and facilitators to the

Box 3 Assigning levels of evidence and grade and strength of recommendations

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analyses, randomized controlled trials
Level II	Two groups, non-randomized studies (e.g. cohort, case-control)
Level III	One-group, non-randomized studies (e.g. before and after, pre-test 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" and negative: "cannot be recommended" or neutral "cannot be recommended in favor of against"

Adapted from Oxford Centre for Evidence-based Medicine - Levels of Evidence and Grades of Recommendations (31)

Table 1 Benefits and harms / disadvantages of AIT as preventive treatment in different populations

Population	Benefits	Harms / disadvantages
Healthy +/- sensitization	Possible preventive effect not documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years Frequency of visits to the clinic (SCIT) Risk for adverse events Costs*
Children with AD	Possible preventive effect not documented	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years Frequency of visits to the clinic (SCIT) Risk of adverse events Costs*
Patients with AR	Documented beneficial effect on symptoms and reduction in medication on short - and long-term Possible preventive effect on development of asthma	Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years Frequency of visits to the clinic (SCIT) Risk for adverse events Costs*

* Costs should be evaluated in relation to potential direct and indirect costs related to the development of an eventual allergic disease and other comorbidities; AIT: Allergen immunotherapy; AD: Atopic dermatitis / eczema; AR: Allergic rhinitis / rhinoconjunctivitis

Table 2 Gaps in the evidence

Gaps	Plan to address	Priority
AIT for prevention of asthma in children with AR due to grass pollen - long term effects	Long-term follow up of RCTs Further evaluation of GAP trial	High
AIT for prevention of asthma in children with AR due to HDM	RCTs*	High
Optimal age for introduction of AIT for prevention	RCTs*	High
Optimal duration of AIT for prevention	RCTs*	High
Optimal product, administration form, dose and schedule of AIT for prevention	RCTs* and high quality real life studies	High
Evaluation of influence of AIT for prevention on QoI in different age groups	QoI as outcome in RCTs*	High
AIT for prevention of AR / asthma in children and adults with AD / food allergy	RCTs*	Medium
Evaluation of health economics of AIT for prevention	Cost-effectiveness analysis of RCT	Medium
Evaluation of adherence in AIT for prevention in different age groups	Adherence measured in RCTs and real life studies	Medium
Evaluation of acceptability of AIT for prevention in different age groups	RCTs*	Medium
AIT for the prevention of new allergic sensitizations • spreading from one allergen to related and unrelated allergen(s) • spreading at molecular level, from one allergenic molecule to other molecules	RCTs*	Medium
AIT for prevention of the Oral Allergy Syndrome	RCTs*	Low
AIT for prevention of first allergic disease	RCTs*	Low

** Apart from new RCTs, published clinical data can be reviewed, raw data can be reanalyzed and blood samples can be analyzed further to provide new data*

AIT: Allergen immunotherapy; AD: Atopic dermatitis / eczema; AR: Allergic rhinitis / rhinoconjunctivitis; HDM: house dust mites; GAP trial: Grazax Asthma Prevention Trial

implementation of each recommendation (Tables 3-5), advised on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (Table 6).

Peer-review and public comment

A draft of this Guideline was externally peer-reviewed by invited external experts in this field from a range of organizations, countries and professional backgrounds: Stephen Durham, Peter Eng, Hans Jørgen Malling, Antonio Nieto, Zsolt Szepfalusi and Erkka Valovirta. Additionally, the draft Guideline were made available on the EAACI website for a three-week period in May 2017 for public review 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.

Editorial independence and managing conflict of interests

The production of 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' conflict of interests were declared at the start of the process and taken into account by the Taskforce Chairs as recommendations were formulated. Methodologists, who had no conflict of interests in this area, checked final decisions about strength of evidence for recommendations.

Updating the guideline

EAACI plans to update this guideline using the AGREE II approach in 2022 unless there are important advances before then.

Table 3 AIT for prevention: recommendations for school-age children, adolescents and adults with allergic rhinitis (AR) or asthma

Recommendations for individuals with manifest allergic disease(s), e.g. allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children and adolescents with AR and grass/ birch pollen allergy, who are sub-optimally controlled despite appropriate treatment with antihistamines / nasal corticosteroids, a 3 year course of AIT (SCIT or SLIT) can be recommended for the short-term (i.e. < 2 years post AIT) prevention of the onset of asthma in addition to the sustained effect on AR symptoms and medication use.	I	A	Moderate recommendation: Based on consistent significant results from 2 moderate (41, 43) and 2 high risk of bias (40, 42) RCTs and some CBA studies	The indication should be discussed with the patients / families including the asthma preventive effect as well as the effect on AR and risk of adverse effects, costs and preferences	Möller1986 (41), Möller2002 (40), Novembre 2004 (43), Marogna 2008 (42), Kristiansen 2017 (25)
In children and adolescents with AR and grass/ birch pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the long-term (≥ 2 years post AIT prevention of the onset of asthma as diagnosed by symptoms combined with demonstrated reversibility	I	B	Weak recommendation: Based on consistent results from 2 high risk of bias RCTs (46) (47), non-significant results from 1 low risk of bias RCT (50), and the meta-analyses being not significant due to the latter study	In the Valovirta 2017 (50) study no effect on the primary asthma outcome using a restrictive defintion of asthma based on demonstration of reversibility. More data is needed	Jacobsen 2007 (46), Song 2014 (47), Valovirta 2017 (50), Kristiansen 2017 (25)
In children and adolescents with AR and grass/ birch pollen allergy, the use of AIT (SCIT or SLIT) may be recommended for the long-term (≥ 2 years post AIT prevention of the onset of asthma symptoms and medication use	I	B	Weak -moderate recommendation: Based on consistent results from 2 high risk of bias RCTs (46) (47) and secondary outcomes in 1 low risk of bias RCT (50),	In the Valovirta 2017 (50) study a significant preventive effect on the secondary outcomes asthma symptoms and medication was found. More data is needed	Jacobsen 2007 (46), Song 2014 (47), Valovirta 2017 (50),
In children and adolescents with AR and allergy to house dust mites or other allergens except for birch/grass pollen, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (i.e. < 2 years post AIT) or long-term (i.e. ≥ 2 years post AIT) prevention of the onset of asthma	I	B	Weak recommendation: Based on inconsistent results from 1 high (42) and 1 low risk of bias RCT (38)	Only HDM, parietaria and mix of these and grass/ birch pollen investigated. More data is needed	Marogna 2008 (42), Crimi 2004 (39), Grembiale 2000 (38), Kristiansen 2017 (25)
In adults with AR and house dust mite or pollen allergy, no recommendation can currently be made in favor of or against the use of AIT (SCIT or SLIT) for the short-term (i.e. < 2 years post AIT) or long-term (i.e. ≥ 2 years post AIT prevention of the onset of asthma	I	B	Weak recommendation: Based on 1 small moderate risk of bias study (39)	Only SCIT with Parietaria Judaica investigated. More data is needed	Crimi 2004 (39)

Table 3 Continued

Recommendations for individuals with manifest allergic disease(s), e.g. allergic rhinitis	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children or adults with AR and/or asthma, AIT cannot currently be recommended for the prevention of new sensitizations,	I	B	Weak recommendation: Based on inconsistent results from 4 high (42, 47, 60, 69), 2 moderate (59, 68) and 3 low risk of bias (55, 57, 58) RCTs		Marogna 2004 (60), Marogna 2008 (42), Dominicus 2012 (69), Song 2016 (47), Pifferi 2002 (59), Limb 2006 (68), Garcia 2010 (57), Szepfalusi 2014 (58), Zolkipli 2015 (55), Kristiansen 2017 (25)

Table 4 AIT for prevention: recommendations for individuals with early life atopic manifestations, e.g. atopic dermatitis/eczema (AD) or food allergy

Recommendations for individuals with early atopic manifestations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In children with AD, AIT no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of later allergic manifestations	I	B	Weak recommendation: Based on 1 small moderate risk of bias study (53)		Holt 2013 (53)
In individuals at all ages with other early atopic manifestations e.g. food allergy, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of other allergic manifestations	V	D	Expert opinion. No studies		

Table 5 AIT for prevention: recommendations for healthy individuals

Recommendations for healthy individuals all ages	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adult allergic patients, no recommendations can currently be made in favor of or against the use of AIT for the prevention of onset of allergic diseases in their offspring	IV-V	D	Weak recommendation: Based on results from 1 high risk of bias study (54)		Bozek, 2016 (54)
In healthy individuals with or without sensitization, AIT cannot currently be recommended for prevention of onset of allergic diseases	I	A	Weak recommendation: Based on 1 low (55) and 1 high risk of bias RCTs (56)	One RCT with infant and one with adult population	Zolkipli 2015 (55), Yamanaka 2015 (56)
In healthy children, AIT cannot currently be recommended for the prevention of new sensitizations	I	B	Weak to moderate recommendation: Based on results from 2 low risk of bias RCTs (55) (58)	One RCT with infant and one with preschool population	Zolkipli 2015 (55), Szepfalusi 2014 (58)
In healthy adults, no recommendations can currently be made in favor of or against the use of AIT for the prevention of new sensitizations	V	D	Expert opinion. No studies		

Table 6 Recommendations for individuals with allergic rhinitis: Implementation

Prevention of development of asthma in patients with AR	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
• In children and adolescents with AR and grass/ birch pollen allergy who are sub-optimally controlled despite appropriate treatment with antihistamines / nasal corticosteroids, a 3 year course of AIT (SCIT or SLIT) can be recommended for short-term (i.e. < 2 years post AIT) prevention of the onset of asthma in children with daily symptoms and need for medication	• Lack of recognized policy in Europe about allergies and their treatment • Failure to recognize manifestations in primary care • Lack of knowledge amongst patients, caregivers and primary care professionals about the benefits of AIT • Lack of communication specialists / primary care interface or specific referral criteria primary care • Lack of agreed clinical pathways • Lack of access to AIT • Unavailability of AIT • No reimbursement • Costs of travel and time of work for patients and caregivers • Concerns about side-effects and safety of especially SCIT • Lack of health economics data	• Government and European policy on allergy • Reimbursement of AIT • Accessible education and training in allergy primary care • Agreed competencies in allergy for primary care and allied health workers for shared care protocols • Information amongst patients, caregivers and healthcare professionals about the benefits of AIT • Integrated multidisciplinary working and service delivery • Timely advice and continuous guidance by specialists • Workforce remodeling • Agreed pathways of care with cross boundary working	• Proportion of potentially eligible patients referred from primary care for a specialist assessment • Proportion of potentially eligible patients formally considered for AIT	• Identification of patients who may benefit from AIT. Thorough investigation of the patient including proper assessment of relevant allergies. • AIT need to be prescribed, made available and administered to patients • Evaluation of effect and eventual AEs

AIT FOR PREVENTION: EVIDENCE AND CLINICAL RECOMMENDATIONS

Overarching considerations

This Guideline is based on a comprehensive SR evaluating the evidence according to predefined well-established methods (25). As in other SRs, heterogeneity in the populations under study, methods employed and outcomes studied made it challenging to interpret the evidence. Factors related to the population, such as atopic heredity play a role in the risk of development of allergic disease. In addition, children with sensitization and/or early manifestations of atopic diseases e.g. AD and food allergy or later manifestations such as AR have a higher risk for development of other allergic manifestations such as asthma (17, 32). The age of the population is important as the phenotypic expression may change with age and some manifestations may even disappear spontaneously (33). The results of individual studies are difficult to compare because studies have used different populations, outcome measures, diagnostic criteria (if any, e.g. the exact definition of asthma, intermittent versus persistent asthma), methods and cut-off values for measuring sensitization. Furthermore, the mode of administration and the products used for AIT differ as regards allergens, formulation, strength, (34, 35) schedules, dose, route of administration and duration of the intervention (36). Additionally, many studies are small without sufficient power and adjustment for confounders. Where possible, these factors are taken into consideration in the risk of bias assessment in the SR on which this Guideline is based.

The significant heterogeneity seen in meta-analysis can be explained by differences in the study design, study population, products and schedules evaluated. Therefore, an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated (16, 37). But, caution is recommended as not all AIT products used currently provide sufficient data to support their efficacy in clinical practice. We might consider that a limited class effect can be assumed when the same clinical outcomes were used to evaluate clinical efficacy (and safety) of different products only if the same route of application, similar dosing schemes and demonstrable comparable amounts of relevant allergens and potency were used. However, it should be noted that such comparability is also dependent on standardized and validated assays and that a limited class effect does not neglect the necessity for product specific clinical studies.

Using AIT for prevention of development of new allergic disease or sensitization requires use of products with a high level of safety, especially in healthy individuals. However, if AIT is indicated due to treatment of an already existing allergic disease, and the preventive effect is regarded as an additional effect, then the safety profile should be considered in that context.

Strategies to prevent development of a new sensitization or of a new allergic disease by AIT may vary for different populations at different stages in life. Strategies need to be pursued for different scenarios, e.g. for those planning pregnancy to take measures such as AIT to reduce the likelihood of their child becoming allergic, healthy infants and young children with early manifestations such as AD, older children with manifest allergic disease such as AR, healthy adolescents/adults and adolescents/adults with established allergic disease.

In order to recommend AIT for the prevention of allergic diseases, evidence is required that there is a relevant and substantial beneficial effect on clinical outcomes for the individual. Furthermore, safety aspects of the treatment and of the disease to be avoided, quality of life and evaluation of health economics should be taken into consideration. Thus, an optimal balance between benefits, harms, costs and other possible disadvantages should be achieved (Table 1).

AIT in individuals with AR: Short- and long-term prevention of development of new asthma

Short-term prevention: The SR (25) identified six RCTs investigating the preventive effect up to two years post-AIT on the development of asthma in individuals with AR. These RCTs included three SCIT studies (one of low (38), one of moderate (39) and one of high risk of bias (40)), one of moderate risk of bias on oral AIT (41) plus one of high (42) and one moderate risk of bias SLIT study (34). Three of these (38, 39, 41) were small studies with a trend towards

less development of asthma in the AIT group but no significant differences. The remaining three studies (40, 42, 43) showed a significant reduction of the development of asthma in the AIT groups as compared to the control groups. The SR and meta-analysis (25) demonstrated a significant preventive effect of AIT on the development of asthma up to two years post-AIT in patients with AR. Subgroup analyses showed that AIT with either SLIT or SCIT was beneficial for those aged <18 years but not ≥18 years and for pollen AIT. For HDM AIT the groups were so small that there was a non-statistically significant impact despite an OR of 0.20. There was a high degree of heterogeneity, and therefore the meta-analysis should be interpreted with caution although three RCTs demonstrated a statistically significant preventive effect. Also the results were supported by two large-scale, real-life, retrospective, non-randomized CBAs (44, 45), based on German longitudinal prescription databases; both reporting a short-term preventive effect of AIT on the progression from AR to asthma.

Long-term prevention: For the long-term preventive effect, i.e. two or more years post-AIT, the SR (25) identified two high risk of bias SCIT RCTs (46, 47) in patients with AR. Both showed a significantly lower risk for developing asthma in the SCIT groups as compared to the controls, up to seven years post-AIT (40, 46, 48), and two years post-AIT (47). A large recently published low risk of bias RCT (GAP) (49, 50) explored the effect of a three-year course of SLIT tablets on the prevention of asthma in 812 children with AR and grass pollen allergy. This study (50) failed to demonstrate the preventive effect of AIT on the development of asthma as defined by very strict a priori criteria including reversibility to beta-2-agonists (OR=0.91; 95% CI [0.58 to 1.41])(49, 50) two years post-AIT. However, the number of subjects with asthma symptoms or asthma medication usage (secondary efficacy parameter) was significantly lower in the SLIT group compared to the placebo group at the end of the five-year trial period (OR 0.66; 95% CI 0.45 to 0.97; P<0.036), during the two-year post-AIT follow-up and during the entire five-year trial period. Also AR symptoms were significantly reduced during the entire 5 year trial period. In addition, it appeared that this preventive effect was strongest for the youngest children (50). Two high risk of bias non-randomized studies including one with grass pollen SCIT (22, 23) and one with HDM SCIT (51) in children with AR also suggested a long-term effect. As published in the SR (25), the meta-analysis showed no overall evidence of reduction in the long-term (i.e. at least two years post-AIT) risk of developing asthma, but there was a high degree of heterogeneity so the result should be interpreted with caution. Furthermore, the negative result was due to one RCT with very strict diagnostic criteria for primary outcome (GAP) in which there was an effect when asthma symptoms and/or medication was considered (50). However, some suggest that there is a long-term preventive effect on the development of asthma symptoms and the use of asthma medication though further confirmatory studies are needed.

Thus, there is a question about which asthma outcome parameter is most relevant - a diagnosis based on demonstrated reversibility or on symptoms and medication use. There is an urgent need to define and standardise the optimal clinical asthma outcomes that should be used in future clinical trials.

Indication for AIT for treatment and prevention in patients with AR

The RCTs included in the above evaluation of asthma prevention in subjects with AR (40, 42, 43, 46, 48-50) included patients with a history of AR and the need for medication combined with documented pollen allergy for at least one previous season. Yet, there is no description on AR severity (mild/moderate/severe) or stratification (intermittent/persistent) in these prevention trials, and thus these subjects may have had a milder disease than those included in studies on efficacy of AIT. However, based on baseline descriptions of the populations in these studies (40, 42, 43, 46, 48-50), it is reasonable to assume that most of the patients included had persistent symptoms.

As discussed in another manuscript on AIT for AR of this EAACI AIT Guideline series (10) (52), many patients with AR and pollen allergy benefit from AIT in reducing AR symptoms and need for medication. Thus, AIT is recommended for treatment of patients with moderate-to-severe pollen induced AR if not optimally controlled on antihistamines and nasal corticosteroids (52).

None of the studies on prevention of development of asthma in AR included preschool children and therefore no recommendations can currently be

made in favor of or against AIT for this age group for prevention.

Based on an objective and clinical evaluation of the current published evidence for AIT preventive effects and considering the potential harmful effects, disadvantages and costs associated with the use of AIT, these seem to be outweighed by the beneficial effects for this group of patients (Table 1) ultimately resulting in a favorable risk benefit profile.

Thus, there is moderate-to-high quality evidence indicating that AIT (SCIT or SLIT) can be recommended for short-term prevention up to two years post-AIT of asthma in children/adolescents with moderate/severe AR and pollen allergy who are sub-optimally controlled despite appropriate pharmacotherapy, and there are data suggesting that this benefit persists after two years post-AIT as regards asthma symptoms and medication use (Table 3). AIT may even be considered in patients with milder AR, as AIT might modify the natural disease history, including the long-term effect in AR and the preventive effect regarding the development of asthma, qualities which could never be attributed to current pharmacotherapy.

The indication and initiation of AIT should always be preceded by a discussion with the patient / family considering the possible benefits, harms, disadvantages, costs, preferential route of AIT (SCIT vs SLIT) based on the individual patient's profile, preferences and considerations for future AIT adherence. Using AIT for preventive purposes should include all normal safety recommendations as for treatment of AR as indicated in the corresponding Guideline on AIT for AR in this EAACI AIT Guideline series (52).

Which products and schedules for AIT asthma prevention in individuals with AR should be used?

The products, doses and AIT schedules used in the AIT prevention trials vary. According to the subgroup analysis in the SR (25) it appears that SCIT and SLIT are both effective, and that a three-year AIT course is preferable to a shorter course. The studies that have demonstrated a preventive effect used three-year courses of continuous AIT.

The SR (25) did not compare different AIT products, SLIT drops versus tablets or pre/co-seasonal versus perennial AIT. However, according to the results from two lower quality, real-life non-randomized, controlled before-after AIT treatment studies based on large German longitudinal prescription databases (44, 45), it seems that SCIT (45) and grass pollen SLIT tablets (44) with natural allergen extracts have a preventive effect on the progression from AR to asthma, and that AIT for three or more years tended to have a stronger preventive effect than AIT for less than three years. Further high-quality RCTs and real-life studies are recommended to objectively confirm this.

Since the indication for AIT for prevention of asthma is linked to the indication for treatment of AR, the products, schedules and doses used should be proven effective for AR with the relevant allergen product. Therefore, only those products registered and with the indication for AR (e.g. pollen allergy at present and maybe HDM in the future) should be considered for use in allergy prevention.

AIT in individuals with AD: Short- and long-term preventive effects

The SR (25) identified one moderate risk of bias RCT investigating the effects of 12 months of daily SLIT with a mixture of HDM, cat and Timothy grass allergens on the prevention of asthma and new sensitizations in children with AD and sensitization to one or more food allergens (53). The investigators included the absence of a difference between active/placebo groups in early immunological changes, i.e. specific IgE/IgG antibodies and associated TH-cell responses, as a stopping rule, since this was regarded an indication of whether the treatment was delivering sufficient allergen transmucosally to trigger immunological recognition by the infant mucosal system. As these a priori immunological changes were not met, recruitment was interrupted and the trial reduced to a pilot study status. After 48 months of follow-up, there were no differences in asthma prevalence between the two groups (53).

Based on this study, we cannot currently make any recommendations in favour of or against AIT for the prevention of the development of a first allergic disease in individuals with AD at present (Table 4) and more studies are needed.

AIT for prevention of allergy in the offspring of allergic individuals

This topic was not included in the protocol or in the SR. However, we found one recent case-control study of high risk of bias comparing 194 children of parents

completing AIT at least nine months before birth with 195 controls (54). This study found that the odds ratios of developing any allergic disease and asthma was significantly lower in children with at least one allergic parent after AIT compared with those having allergic parents who did not receive AIT (odds ratio: 0.73, 95% confidence interval 0.59-0.86). The authors hypothesized that AIT in allergic parents might reduce the risk of allergies in their offspring, but this requires further investigation.

Based on the very scarce and very low quality evidence, we cannot currently make any recommendations in favour of or against AIT for allergic adults for prevention of allergic disease in their offspring (Table 5).

AIT in healthy individuals: Short- and long-term prevention of development of new allergic disease

Two RCTs, one of low (55) and one of high risk of bias (56), investigated the possible effect of AIT in healthy individuals on the risk for development of their first allergic disease. The large low risk of bias study (55) found no preventive effect of oral HDM AIT on AD, wheeze and food allergy among infants with a family history of allergic diseases, whereas the small high risk of bias study (56) reported a reduced risk of developing pollinosis among asymptomatic adults sensitized to Japanese cedar pollen in the SLIT group. Data from these two trials (55, 56) are not comparable. No data on a long-term preventive effect were identified. Based on these results from the SR (25) there is currently no good evidence to recommend use of AIT for the prevention of a first allergic disease in healthy individuals (Table 5).

AIT for the prevention of the development of new allergic sensitization

Short-term effects: The SR identified three low risk of bias RCTs (55, 57, 58), one moderate (59) and two high risk of bias (42, 60) RCTs investigating the short-term effects of AIT on the risk of developing new sensitizations. One low risk of bias RCT (55) on oral HDM AIT for healthy infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen (e.g. HDM, grass pollen, cat, peanut, milk and egg) in the active group compared with the placebo group at the end of the trial, but no difference in HDM sensitization (55). The other two low risk of bias RCTs found no effect of SLIT in adult patients allergic to peach (57) post-AIT and after SLIT with grass pollen or HDM extract in mono-sensitized children (58). Three additional RCTs of moderate to high risk of bias (42, 59, 60) found a significantly lower incidence of new sensitizations among children and adults with AR treated with SLIT (42, 60) and SCIT (59) as compared to controls.

Thus, these RCTs of varying quality with varying allergens and formulations showed inconsistent results. Meta-analysis showed an overall reduction in the risk of allergic sensitization but the sensitivity analyses, excluding the two high risk of bias studies by Marogna (42, 60), failed to confirm this risk reduction (25). Due to the high degree of heterogeneity, the results from the meta-analysis should be interpreted with caution.

The inconsistent evidence found in RCTs was also reflected in the included high risk of bias CBA studies with three finding a lower occurrence of new sensitizations among AIT treated subjects compared with controls (61-63), one reporting higher occurrence in the AIT group compared with controls (64) and three studies reporting no differences between groups (65, 66) (67).

Long-term effects: As regards the long-term (i.e. at least two years post-AIT) effects on prevention of new sensitivities the SR identified one moderate (68) and one high risk of bias RCT (69) showing no preventive effect of SCIT among children with moderate-to-severe asthma followed into adulthood (68) and SCIT in adults with AR three years post-AIT (69). Another high risk of bias RCT (47) found that patients with AR treated with HDM SCIT less frequently developed new sensitizations compared with controls two years post-AIT (47).

Thus, there is no good evidence for a reduction in the long-term risk of allergic sensitization.

The seven high risk of bias CBAs investigating long-term preventive effects of AIT produced inconsistent results, one found no difference (70), four showed reduced onset (22, 62, 71-73) and one found a significantly higher occurrence of new sensitization among AIT treated compared with controls (74).

The development of new sensitizations may impose a higher risk for the development of further symptomatic allergies suggesting that it might be relevant to prevent the development of new sensitizations. However, this has not been investigated sufficiently. A subgroup analysis in the SR (25) showed a tendency

towards an effect in children and adolescents after three years of AIT, supporting the rationale of the clinical effect.

Thus, there is currently no good evidence to recommend the use of AIT for either short- or long-term prevention of development of new sensitizations in healthy individuals, children with atopic predisposition (Table 5), children with AD / food allergy (Table 4) or in children and adults with AR / asthma (Table 3). Some positive data though suggests that this may be a good focus for future high quality trials.

Safety

The safety issues are fully covered by the SR and guideline for AR in this AIT guideline series (10, 52). SCIT is occasionally associated with allergic side effects and should therefore be administered in a specialist setting. Fatalities are very rare and have not been reported with the use of SLIT. In a recent meta-analysis about the efficacy of grass-pollen SLIT tablet by Di Bona *et al.* (75) seven treatment related adverse events requiring adrenaline were reported in the SLIT RCTs, however no episode of anaphylaxis was reported. In recent real-life clinical studies of AIT, less severe systemic reactions were reported with SLIT than with SCIT, although the overall rate of adverse reactions is similar in SCIT and SCIT (76, 77). The safety profile for the present purpose is not regarded as being different from AIT for treatment of AR. Due to its better safety profile SLIT might be a better choice for prevention than SCIT.

SUMMARY, GAPS IN THE EVIDENCE, FUTURE PERSPECTIVES AND IMPLEMENTATION

This Guideline on AIT for prevention of allergy has been developed as part of the EAACI Guidelines on Allergen Immunotherapy project. The recommendations in this Guideline are based on a thorough SR performed by a group of experienced and independent methodologists and have been developed by a multidisciplinary EAACI Task Force representing a range of countries and disciplines and clinical backgrounds.

The Guideline provides evidence-based recommendations for the use of AIT for prevention of new allergic disease(s) and new allergic sensitization(s) in all populations. The guideline should assist all healthcare professionals as regards evaluation of AIT for prevention of allergic disease / sensitization, and when to refer which individuals to further evaluation. The main results are summarized in Box 4.

The key limitation of this guideline is the heterogeneity and gaps in the underpinning literature. There are many areas for which there is no evidence or no high quality evidence; these represent gaps in the current evidence (Table 2). Thus, for the preventive effect of AIT in healthy individuals or in children with early atopic manifestations such as AD or food allergy as well as for the possible long-term effect in children with AR, more high quality data are needed. Also, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring the development of new OAS or health economic analyses of AIT used for prevention.

In addition, there is a lack of evidence as regards patient selection (e.g. optimal age and characteristics) for preventive AIT and for the optimal allergen preparation, mode and duration of AIT administration; there is a need to define standardized relevant outcomes including asthma and quality of life (Qol) for future studies.

The current evidence does not allow to identify superiority between SCIT and SLIT; therefore, this choice depends on availability, patients / family's' preferences, safety, costs, routes, schedules and patients adherence to the AIT treatment. Only products and regimens proven effective for treatment of AR should be used. Currently only products with the indication for treatment of AR can be recommended for prevention of asthma in children and adolescents with AR and pollen allergy.

Based on current evidence, AIT can be recommended for up to two years post-AIT prevention of development of asthma in children and adolescents with AR and pollen allergy primarily birch and grass. Some studies suggest a long-term asthma preventive effect as regards asthma symptoms and medication use, though it has to be further demonstrated if this effect can be extended to asthma as diagnosed by

Box 4 Summary

- A three year course of AIT (SCIT or SLIT) can be considered in children with moderate to severe AR and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for
  - Treatment of AR with a sustained effect on symptoms and use of medication beyond cessation of AIT
  - Short-term (i.e. up to 2 years post-treatment) prevention of the onset of asthma in addition to improving the control of AR. Moreover, some studies indicate that this asthma preventive effect is maintained over a longer period as evaluated by symptoms and medication use
- Only AIT products with documented effect in patients with the relevant pollen allergy should be used and a product specific evaluation of clinical efficacy and preventive effects is recommended
- Before initiating AIT the possible benefits including the beneficial effects on controlling AR symptoms and the asthma preventive effect, disadvantages, potential harms, patients' preferences (SCIT or SLIT-tablets/ SLIT-drops), patients' adherence to treatment and costs should be discussed with the patient / family on an individual basis
- There is an urgent need for more high-quality clinical trials on prevention in AIT and more high quality evidence.

Box 5 Key messages for primary care about referral to allergy services

- AIT have a role in delaying/preventing progression from seasonal AR/ARC to asthma
  - Primary care teams should consider early referral of children with troublesome AR in spite of pharmacotherapy with antihistamine and or nasal corticosteroids for a specialist assessment with a view to considering AIT to improve control of AR and also simultaneously delay/prevent asthma
  - Patients should be considered as "individuals" during the assessment to prescribe AIT, they all have to be aware of the potential benefits, risks and costs of AIT
- AIT may be indicated in those individuals with perennial AR on clinical grounds but not only for delaying/preventing progression to asthma (this preventive effect needs to have high quality evidence)
- Recommendations cannot currently be made for AIT to prevent: (i) allergic parents who would be interested in receiving AIT to prevent allergy in their offspring; (ii) healthy infants/children; (iii) infants/children with AD and/or food allergy

stricter diagnostic criteria. Such a disease-modifying effect after cessation of AIT is not achievable with pharmacotherapy. AIT should in particular be considered for those with moderate-severe AR as it has been shown to be effective in controlling this condition in addition to the preventive effect on the development of asthma (10, 52). Furthermore, some patients with less severe AR may prefer AIT to reduce medication use and avoid side effects of other treatments, to obtain long-term efficacy and/or to obtain the asthma preventive effect.

Considerations should be taken when making recommendations for AIT as preventive treatment in allergy, as children and adolescents included in the prevention studies did not necessarily fulfil the criteria for proper endorsement of AIT for treatment of AR as well as they did not necessarily meet the "Allergic Rhinitis and its Impact of Asthma" (ARIA)(9) criteria for moderate/severe AR.

At present, the indications for AIT for prevention of allergic disease are the same as for treatment of AR (i.e. documented IgE-mediated disease caused by the relevant allergens and not sufficiently controlled by antihistamines and nasal corticosteroids) (52). Contraindications are the same as for treatment of AR (52). The asthma preventive effect may in the future downgrade the level of severity of AR required before initiation of AIT in children and adolescents with AR and pollen allergy, especially grass pollen allergy. Therefore, AIT as a relevant treatment option for

children and adolescents up to 18 years of age with less severe AR due to pollen allergy should be further investigated and discussed. Currently, there is no high quality evidence to support AIT for prevention in HDM allergic patients with AR, but further high quality studies are warranted.

The products available, and registered for different indications, have varied over time and across countries. Therefore, at present we cannot make homogeneous product specific recommendations at a European level. In the context of the implementation of this guideline series, we plan to provide such recommendations based on the on each national country availability of the products.

For the implementation of this Guideline (described in Table 6) there is a need to ensure that primary care healthcare professionals recognise AIT as a treatment option for some allergic diseases and have clear guidelines to aid patient selection for early referral to specialist care (78). Patients and patient organizations need to be aware of AIT as a treatment option. Political awareness should be increased to ensure sufficient availability, knowledge, competences, skills and resources in the health care system by demonstrating the economic benefits of AIT by proper assessment of its positive impact on economic productivity. In addition, methods to overcome problems with adherence should be further considered and evaluated. Finally, a plan for monitoring the audit criteria should be part of the dissemination and implementation plan, and as new evidence is published these guidelines will be updated with appropriate revision of specific recommendations.

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Authors' contribution

S Halken chaired the EAACI Guideline AIT for Allergy Prevention Taskforce. D Larenas-Linnemann, G Roberts, MA Calderón, M Penagos, S Bonini, G Du Toit, IJ Ansotegui, J Kleine-Tebbe, S Lau, P Maria Matricardi, G Pajno, NG Papadopoulos, O Pfaar, D Ryan, AF Santos, F Timmermans, U Wahn, M Kristiansen, S Dhami, A Sheikh and A Muraro were all members of the Taskforce and were involved in conceptualizing the guideline, drafting of the guideline and critically reviewed the guidelines draft and I Agache, S Arasi, M Fernandez-Rivas, M Jutel, GJ Sturm, EM Varga, R van Ree, R Gerth van Wijk, and Antonella Muraro were members of the Chairs Steering group who also critically discussed and reviewed the guideline draft. F Timmermans was also the patient group representative. All the authors satisfied the international Vancouver authorship criteria. This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro and coordinated by Graham Roberts. All authors' job titles and role in the guideline development is in Table S1 in the online supplement.

Conflicts of interest

S. Halken reports personal fees from ALK-Abelló, personal fees from Different companies e.g. MEDA, Stallergenes, Allergopharma and ALK-Abelló, outside the submitted work; D. Larenas-Linnemann reports personal fees from MSD, Grunenthal, Amstrong and DBV; grants and personal fees from Astrazeneca, MEDA, GSK, Pfizer, Novartis, Boehringer-ingelheim, Sanofi, UCB; grants from Chiesi and TEVA; other from Stallergenes and from ALK-Abelló, outside the submitted work; she is the Chair of the immunotherapy committee CMICA, member of the immunotherapy committee or interest groups of EAACI, WAO, SLAAI and member and Program Chair of the Board of Directors CMICA 2018-2019; 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; M. A. Calderón has received honorarium in advisory boards for ALK and Hal-Allergy and served as a speaker for ALK, Merck,

Hal-Allergy, Allergopharma and Stallergenes Greer; E. Angier reports being Secretary of Primary Care Interest Group EAACI. ALK conference SOSA meeting 2015. Previous paid advisory board one each for MEDA 2012, Stallergenes, 2012, Schering Plough 2009 and one paid lecture by MEDA; I. Agache has nothing to disclose; I.J. Ansotegui has nothing to disclose; S. Arasi has nothing to disclose; George Du Toit reports income from grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and grants from UK Food Standards Agency (FSA); these grants part funded salary. Prof. Du Toit is; scientific advisor for the Anaphylaxis Campaign, advisor to - and holds stock in - FoodMaestro and is site investigator for Aimmune-sponsored Peanut Desensitisation Trials and is Scientific advisor to Aimmune. He was Chairperson of the EAACI Paediatric Section over the period when this document was formulated; Montserrat Fernandez-Rivas reports grants from European Union, grants from Instituto de Salud Carlos III, Ministerio de Ciencia, España, grants from Ministerio de Economia, España, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, Schreiber foods, personal fees from ALK Abello, Merck, GSK, Allergy Therapeutics, non-financial support from EAACI, personal fees and non-financial support from Fundación SEAIC, other from Hospital Clínico San Carlos, and Universidad Complutense de Madrid. España, outside the submitted work; In addition, Dr. Fernandez Rivas has a patent PT0042/2013 issued; R. Gerth van Wijk reports personal fees from ALK-Abello, Circassia, and Allergopharma, during the conduct of this work; M. Jutel reports personal fees from Allergopharma, Anergis, Stallergen, ALK and Leti outside the submitted work; J. Kleine-Tebbe reports personal fees for 1. Advisory Board membership (ALK-Abelló, Bencard, Leti, Novartis), personal fees for 2. Consultancy (Circassia, UK; MERCK, US), institutional grants from 3. Circassia, UK, LETI, Lofarma, Stallergenes, personal fees from for 4. Lectures including service on speakers bureaus (Allergopharma, Allergy Therapeutics, ALK-Abelló, AstraZeneca, Bencard, HAL Allergy, LETI, Lofarma, Novartis, Sanofi, Stallergenes Greer, ThermoFisher) outside the submitted work; S. Lau reports grants from Allergopharma, personal fees from Merck, during the conduct of the study; grants from Symbiopharm Herborn, grants from Boehringer, outside the submitted work; P.M. Matricardi has nothing to disclose; G. Pajno reports grants from Stallergenes during the conduct of this work; N.G. Papadopoulos reports grants from Menarini, personal fees from Novartis, personal fees from Faes Farma, personal fees from BIOMAY, personal fees from HAL, personal fees from Nutricia Research, personal fees from Menarini, personal fees from Novartis, personal fees from MEDA, personal fees from Abbvie, personal fees from Novartis, personal fees from MEDA, personal fees from MSD, personal fees from MEDA, personal fees from Omega Pharma, personal fees from Danone, outside the submitted work; M. Penagos reports personal fees from Stallergenes and ALK, outside this work; O. Pfaar reports grants and personal fees from ALK-Abello, Allergopharma, Stallergenes Greer, HAL-Allergy Holding B.V./HAL-Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, Biotech Tools S.A., Laboratorios LETI/LETI Pharma, and Anergis S.A.; grants from Biomay, Nuvo, and Circassia; and personal fees from MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA2LEN Partner), Novartis Pharma and PohlBoskamp, outside this work; D. Ryan reports personal fees from MEDA, personal fees from Stallergenes, personal fees from Thermo Fisher, from null, outside the submitted work; and 1. Consulantt Strategic Clinical Advisor, Optimum Patient Care. Director, Respiratory Effectiveness Group. Chair, Primary Care Interest Group, EAACI; A.F. Santos reports grants from Medical Research Council, grants from Immune Tolerance Network/NIAID, personal fees and other from Thermo Fisher Scientific, Nutricia, Infomed, outside the submitted work; G.J. Sturm reports grants from ALK Abello, personal fees from Novartis, personal fees from Bencard, personal fees from Stallergens, outside the submitted work; F. Timmermans has nothing to disclose; R. van Ree: Consultancy and speaker fees for HAL Allergy BV, consultancy for Citeq BV and speaker fees for ThermoFisher Scientific. Funding from EU FP7, Dutch Science Foundation and HESI-ILSI; E-M Varga reports lecture fees from ALK-Abello, Stallergenes-Greer, Allergopharma, Bencard, MEDA and Nutricia outside the submitted work; U. Wahn reports personal fees from Allergopharma, personal fees from ALK-Abello, personal fees from Stallergenes-Greer, personal fees from Biomay, outside the submitted work; M.

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EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

HYMENOPTERA VENOM ALLERGY

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Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a honeybee, vespid or ant sting. Systemic allergic sting reactions have been reported in up to 7.5% of adults and up to 3.4% of children. They can be mild and restricted to the skin or moderate-to-severe with a risk of life-threatening anaphylaxis. Patients should carry an emergency kit containing an adrenaline autoinjector, H1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment to prevent further systemic sting reactions is venom immunotherapy. This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Venom Immunotherapy as part of the EAACI Guidelines on Allergen Immunotherapy initiative. The guideline aims to provide evidence-based recommendations for the use of venom immunotherapy, has been informed by a formal systematic review and meta-analysis and produced using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included representation from a range of stakeholders. Venom immunotherapy is indicated in venom allergic children and adults to prevent further moderate to severe systemic sting reactions. Venom immunotherapy is also recommended in adults with only generalized skin reactions as it results in significant improvements in quality of life compared to carrying an adrenaline auto-injector. This guideline aims to give practical advice on performing venom immunotherapy. Key sections cover general considerations before initiating venom immunotherapy, evidence-based clinical recommendations, risk factors for adverse events and for relapse of systemic sting reaction, and a summary of gaps in the evidence.

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INTRODUCTION

This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Venom Immunotherapy (VIT) and are part of the EAACI Guidelines on Allergen Immunotherapy (AIT) (Box 1). This guideline aims to provide evidence-based recommendations for the use of VIT in children and adults. The primary audience is clinical allergists although these are also likely to be of relevance to all other healthcare professionals (e.g. primary care practitioners, emergency departments and other specialist doctors, nurses and pharmacists working across a range of clinical settings) who may dealing with insect venom allergic patients. Development of this guideline has been informed by a formal systematic review and meta-analysis of AIT for Hymenoptera venom allergy (HVA) with systematic review principles being used to identify additional evidence where necessary (1).

Insects stings by Hymenoptera species are very common with data indicating that 56.6-94.5% of the general population has been stung at least once in their lifetime (2). The most frequent clinical presentations of HVA are large local reactions (LLR) at the sting site and systemic sting reactions (SSR). A large local reaction has been defined as a swelling exceeding a diameter of 10 cm that lasts for longer than 24 hours (3). In SSR, mild symptoms usually manifest as generalized skin symptoms including flushing, urticaria and angioedema. Typically, dizziness, dyspnea and nausea are examples of moderate reactions, while shock and loss of consciousness, or even cardiac or respiratory arrest all define a SSR. The rate of self-reported SSR in European epidemiological studies ranges from 0.3 to 7.5% in adults (4) and up to 3.4% in children (4, 5). LLRs occur in 2.4% to 26.4% (6) of the general population. Severe reactions are life-threatening and have been attributed to fatatlities. Although only 0.03 to 0.48 fatalities/1 000 000 inhabitants/year are reported (2), Hymenoptera sting mortality may have been underestimated due to unrecognized stings in unexplained causes of death. Patients with HVA are advised to carry an emergency kit comprising of an adrenaline autoinjector (AAI), H1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment that can potentially prevent further systemic sting reactions is venom immunotherapy (VIT), which is reported to be effective in 77-84% of patients treated with honeybee venom (7, 8), in 91-96% of patients receiving vespid venom (7, 8), and in 97-98% of patients treated with ant venom (9, 10).

The systematic review suggested that VIT is effective in reducing subsequent SSRs reactions in both children and adults and that this treatment modality can have a significant beneficial impact on disease specific quality of life (QoL) (1). VIT proved to be safe and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established.

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. This is also sometimes known as allergen specific immunotherapy, desensitization, hyposensitization, or allergy vaccination
Aqueous venom preparations	Lyophilized venom, which is reconstituted in (albumin-containing) saline diluent.
Depot venom preparations	Venom preparation adsorbed onto aluminium hydroxide or L-tyrosine.
Purified venom preparations	Venom preparations where irritant low-molecular components < 1000 Dalton are removed.
Venom immunotherapy (VIT)	AIT where insect venom preparations are administered as a series of subcutaneous injections to eliminate systemic allergic reactions after insect stings.

Modelling cost-effectiveness suggested that VIT was likely to be cost-effective in those at high risk of repeated systemic sting reactions and/or impaired quality of life. However, primary studies assessing the cost-effectiveness of VIT could not be identified.

METHODOLOGY

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (11, 12), an internationally recognized and accepted 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 in April 2015 beginning with detailed face-to-face discussions agreeing 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. The present guideline is based on the systematic review and they follow the methods and criteria applied (1).

Clarifying the scope and purpose of the guideline

The scope of this EAACI guideline is multifaceted, providing statements that assist clinicians in the optimal use of use of VIT in the management of patients with Hymenoptera venom allergy and identifying gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on VIT represented a range of 16 European countries and disciplinary and clinical backgrounds, including allergists, pediatricians, primary care practitioners, ophthalmologists, ear nose and throat (ENT) specialists, pharmacists, immunologists, nurses and patient representatives. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guideline as part of the peer review and public comment process. These comments were considered by the taskforce 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 VIT in patients. This was then pursued through a formal systematic review and meta-analysis of the evidence (1). We continued to track evidence published after our systematic review and meta-analysis with a cut-off date of July 1, 2017 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, which is scheduled for publication in 2022.

Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews (1) to formulate evidence-based recommendations for clinical care by applying the GRADE process (13). 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) randomized controlled trials (RCTs) within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach using an expert panel. Recommendations apply to all ages unless otherwise indicated in the tables. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice 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 this guideline was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds. Additionally, the draft guideline was made available on the EAACI website for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the taskforce and, where appropriate, final revisions were made in the light of the feedback received. We will be pleased to continue

Box 2 Assigning levels of evidence and recommendations (13)

LEVEL OF EVIDENCE	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, nonrandomized studies (e.g., cohort, case-control)
Level III	One group nonrandomized (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 studies
Moderate	Evidence from studies at moderate risk of bias studies
Weak	Evidence from studies at high risk of bias studies

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 (13). 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.

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.

Editorial independence and managing conflict of interests

The production of 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' conflict of interests were declared at the start of the process and taken into account by the taskforce chairs as recommendations were formulated. Final decisions about the strength of evidence for recommendations were checked by the methodologists who had no conflict of interests in this area.

Updating the guideline

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

GENERAL CONSIDERATIONS BEFORE INITIATING VENOM IMMUNOTHERAPY

General indications

VIT is indicated in children and adults following a systemic allergic reaction exceeding generalized skin

Table 1 Recommendations: indications for VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
VIT is recommended in adults and children with detectable sensitization and systemic sting reactions exceeding generalized skin symptoms	I (III for children)	A (B for children)	Strong-to-moderate for adults based on two low risk of bias SR (1, 131). Weak for children based on one high risk of bias CBA (15) and one high risk of bias RCT study that included children (87)	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhami 2017 (1), Boyle 2012 (131), Golden 2004 (15), Hunt 1978 (87)
VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired	I	A	Strong-to-moderate based on one low risk of bias SR (1) and two adult RCTs of moderate risk of bias (50, 52)	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhami 2017 (1), Oude Elberink 2002 and 2009 (50, 52)
VIT can be recommended in adults with recurrent, troublesome LLR to reduce the duration and size of future LLR	II	B	Moderate/low based on one open, controlled trial of venom allergic adults with LLR (19)	Cost/benefit profile should be considered for this indication. No pediatric data	Golden 2009 (19)
VIT is not recommended in individuals with incidentally detected sensitization to insect venom and no clinical symptoms	IV	C	Weak based on one case series and expert consensus (18)	Asymptomatic sensitization is very common	Sturm 2014 (18)
VIT is not recommended in patients with unusual reactions that do not represent immediate type systemic reactions	V	D	Weak, as no studies have focused on this. Expert consensus	Reactions of non-allergic nature following Hymenoptera stings require neither diagnostic testing nor administration of VIT	Expert consensus

symptoms with a documented sensitization to the venom of the culprit insect with either skin prick tests and/or specific serum IgE tests and/or the basophil activation test (BAT). VIT should also be considered for adults with skin symptoms only but at high risk of re-exposure and/or impairment in QoL. VIT is not indicated if no sensitization to insect venom can be verified. Also, an incidental finding of sensitization to insect venom (e.g. using a multiplex system) in patients who have not had a SSR is not an indication for VIT. Furthermore it is not indicated in patients with unusual reactions that cannot be attributed to Type I immediate reactions such as thrombocytopenic purpura and vasculitis, rhabdomyolysis or renal failure after multiple stings. The risk for future systemic reactions is low in patients with LLR, in whom only 0.8-7% are expected to develop SSR in the future (14-16). As patients with repeated LLRs have been reported to have a minimal risk for SSR (17, 18), VIT is generally not recommended in these patients. However, subcutaneous VIT has been shown to reduce the size and duration of LLR (19). Therefore, VIT could be considered a treatment option in patients with recurrent, troublesome LLRs. Additional precautions should be taken to avoid insect stings during the build-up phase of VIT by following preventive measures such as not going barefoot, not eating outdoors and avoiding gardening. Beekeepers should stop beekeeping until the maintenance dose is reached because of the increased risk of stings and consecutive SSR (Table 1).

Absolute and relative contraindications and VIT in patients with special conditions

An European position paper on clinical contraindications has been published in 2015 tackling all relevant contraindications in detail (20). In a recently published survey among 520 mainly European allergists, up to 47% had experience with administration of AIT in patients with risk conditions such as cardiovascular disease, taking ACEI or

Table 2 Recommendations: VIT in patients with special conditions

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
VIT can be recommended in patients with cardiovascular disease but the underlying disease should be stabilized before initiation	V	D	Weak based on reviews of expert opinions (20) and one case series study (23)		Pitsios 2015 (20)
Beta-blocker therapy may be continued during VIT but the patient should be informed about possible risks	IV	C	Weak based on two case series studies (26, 24) and expert consensus	Stopping beta-blocker may even harmful for some patients	Ruëff 2009 (26), Ruëff 2010 (24)
ACE inhibitor therapy may be continued during VIT but the patient should be informed about possible risks	IV	C	Weak based on two case series studies (25, 24) and expert consensus		Stoevesandt 2014 (25), Ruëff 2010 (24)
VIT can be recommended in high risk venom allergic patients when malignant disease is stable or in remission	IV	C	Weak based on one case series study (34) and expert consensus		Wöhrl 2011 (34)
VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease is stabilized	V	D	Weak based on expert consensus	Immune-suppressive medication may negatively influence effectiveness of VIT	Expert consensus
VIT cannot be recommended in patients with active, multi-system autoimmune disorders	V	D	Weak based on expert consensus		Expert consensus
Treatment with MAOIs is not a contraindication for VIT but caution is recommended with the use of adrenaline	V	D	Weak based on case reports and expert consensus	MAOIs are nowadays rarely prescribed	Expert consensus
VIT in children below 5 years of age should only be considered in the event of severe sting reactions and when the child is likely to be co-operative	IV	C	Weak based on one case series (38) and expert consensus		Stritzke 2013 (38)
VIT should not be initiated during pregnancy, but well-tolerated ongoing VIT can be continued during pregnancy	IV	C	Weak based on case series studies (39, 40)		Metzger 1978 (39), Schwartz 1990 (40)
VIT may be recommended in patients with underlying systemic mastocytosis as it is safe and effective	IV	C	Weak based on two case series (45, 47)	In few patients, side effects can be more frequent and severe	Bonadonna 2008 (45), 2013 (47)

beta-blockers, malignant disease in remission, and autoimmune disease which previously had been considered as contraindications (21). Problems were uncommon and mostly minor so we have reconsidered contraindications in VIT. Below contraindications are briefly described, and recommendations are given in Table 2.

Cardiovascular disease

Fatality studies have shown that particularly elderly patients with HVA and pre-existing cardiovascular disease have an increased risk of dying from a sting (22). Therefore, in contrast to respiratory allergies, VIT is commonly performed in elderly patients. Based on the risk / benefit profile, cardiovascular diseases per se are not a contraindication for VIT (20).

Beta-blockers

There is good evidence that anaphylaxis does not occur more frequently in patients receiving beta-blockers, as recently summarized in an EAACI position paper (20). However, these patients may theoretically be at increased risk of more SSRs, and emergency treatment with adrenaline may be less effective. Elderly patients with HVA and cardiovascular disease treated with beta-blockers are considered to be

particularly at high risk of severe SSR in the case of an insect sting (23). Based on the risk/benefit profile, there is no contraindication for VIT in patients treated with beta-blockers (20).

Angiotensin-converting enzyme inhibitors (ACEI)

Studies with large number of patient participants conclude that treatment with ACEI does not affect the safety of VIT (24, 25). One study reported a higher risk for more severe SSR (26), however there is a growing base of evidence that indicates that ACEI do not increase the risk for severe SSR in untreated patients (27-29). In univariate analyses, results are often confounded by patient's older age which has been shown to be a strong risk factor for more severe SSR (27, 29, 30). One multicenter study reported that all patients on ACEI tolerated a sting challenge or field sting during VIT (31), whereas in another study patients taking ACEI had a higher risk for relapse (32). However, the risk of ACEI may have been overestimated in certain studies due to the very small patients' group and highly selected patients with suggested cardiovascular comorbidity (33). Therefore, ACE inhibitor therapy may be continued during VIT, but the patient should be informed about possible risks

Malignant neoplasia

AIT was safely administered in patients suffering concomitantly from vespid venom allergy and less advanced stage cancer in one small case series of four patients (34). No controlled studies are available relating to the risk or effectiveness of AIT in malignant neoplasias (20). Therefore, acute malignant neoplasias are considered a relative contraindication, even if there is no evidence on any unfavourable effects of VIT on tumor growth or the efficacy of chemotherapy. The benefits of VIT should be weighed against the possible burdens of the treatment and the activity of the tumour disease. To conclude, VIT can be recommended in high risk venom allergic patients when malignant disease is stable or in remission.

Autoimmune disorders

Caution should be exercised when prescribing VIT to patients with multi-organ autoimmune disorders. Due to a lack of available data, there is a relative contraindication in autoimmune disorders in remission and an absolute contraindication in active forms (20). Organ-specific autoimmune disorders, such as e.g. diabetes mellitus, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, and rheumatoid arthritis are not considered a contraindication when the disease is stabilized, but concerns were raised that immune-suppressive medication could theoretically negatively influence the effectiveness of VIT (35). Therefore, VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease is stabilized

Monoamine oxidase inhibitors (MAOI)

The prescribing of MAOIs is now extremely limited, due to their wide range of dangerous drug-drug interactions (36). The major concern with their use in the context of AIT is that they prevent the breakdown of sympathomimetic drugs; therefore, in the event of adverse events emergency treatment with adrenaline could result in severe hypertension and/or tachycardia (20, 36). To conclude, treatment with MAOIs is not a contraindication for VIT but caution is recommended with the use of adrenaline

Children below five years of age

Generally, severe SSR are less frequent in children, and appear to be rare in children of preschool age (<5 years) (37). In the rare event of a SSR, decisions should be made on an individual basis considering the risk of future severe systemic reactions. Successful VIT in children under four years have been reported (38); as the age limit of five years is arbitrary, there are no specific concerns regarding children younger than five years and the same recommendations as in adults apply.

Pregnancy

The incidence of prematurity, toxemia, abortion, neonatal death and congenital malformation appears to be similar in patients on AIT during pregnancy compared to the general population (39). During VIT only two mild adverse events were observed in 43 pregnancies (40). VIT appears to be safe in pregnant women, but data are scarce. Therefore, initiation of VIT is not recommended. Due to the high risk of relapse after early termination of VIT (41, 42) and the low risk of adverse events (24, 43), a well-tolerated ongoing VIT regime during pregnancy should be continued, using the tolerated VIT maintenance dose administered before pregnancy.

Mastocytosis

Mastocytosis is a risk factor for both the development of HVA and for more severe SSR (44). VIT is usually well tolerated by the majority of patients with

underlying systemic mastocytosis (45), although adverse events can occur more frequently (46). In a recent large study on patients with confirmed systemic mastocytosis and severe initial sting reactions (63% suffered from loss of consciousness), it could be shown that VIT was safe and effective (47). Whether elevated serum tryptase levels alone increase the risk for adverse events is still a debated issue and robust data are scarce. One study showed a slightly elevated risk for adverse events (24), whereas others did not identify a higher risk (25) which may be related to a very low overall rate in objective side effects in all patients. Generally, there is no evidence from the literature that VIT should be performed indefinitely in patients with mastocytosis (48). However, VIT may be less protective in patients with severe initial SSR and mastocytosis and/or elevated serum tryptase (>11.4 µg/L). Therefore, for safety reasons, it should be prolonged in those patients; it remains unclear whether it should be given life-long or after which duration of treatment it should be stopped.

Quality of life

For most patients, and their families, any allergic reaction (regardless of severity) is a frightening experience. Given the effort required to avoid accidental exposures and the inherent uncertainty of success, living with HVA negatively influences QoL. This is particularly due to emotional distress of being alert during activities of daily living (49). VIT improves QoL in vespid venom allergic patients even when they do not experience a re-sting (50). In a study where patients were offered a sting challenge after VIT, 80% of patients reported a significantly increased QoL after tolerating a sting challenge (51). In contrast, therapy with the AAI alone was shown to negatively impact on health related QoL (50, 52), a significantly increased burden for patients (53) and a higher level of anxiety and depression (54). In contrast, more than 90% of patients perceived VIT as (extremely) positive (53), with health and allergy-related QoL improving significantly during treatment (50, 52, 55), dysfunctional beliefs decreasing (55) and anxiety and depression levels were the lowest among VIT treated subjects (54). In a randomized study evaluating dermal reactors, QoL was also impaired in these systemic reactors and VIT was also able to improve their QoL in contrast to the AAIs (52).

VENOM IMMUNOTHERAPY: EVIDENCE BASED CLINICAL RECOMMENDATIONS

Available venoms

Venom of *Apis mellifera* and Vespula species is available throughout Europe, whereas venom of Polistes is accessible in those countries where allergy to Polistes species (e.g. *Polistes dominula* in Spain and Italy) most often occurs. The use of bumblebee venom would be preferable if the primary sensitization was induced by bumblebee stings (56, 57). Bumblebee venom for VIT is currently only available in some countries, e.g. in Italy. Worldwide, also ant venoms are available, such as venom of *Myrmecia pilosula* (Jack Jumper Ant) in Australia.

Preparation of venom

Throughout Europe, non-purified aqueous, purified aqueous preparations and purified aluminium hydroxide adsorbed preparations (so-called “depot” preparations) are used to perform subcutaneous VIT (58) (Box 1). The efficacy is supported by studies using both sting challenge and ‘in-field’ stings (58). The aqueous preparations can be used for build-up protocols including ultra-rush, rush, clustered and conventional, as well as for maintenance phase. Purified aluminium hydroxide adsorbed preparations are typically used for the conventional or clustered build-up and maintenance schedule. Treatment can be switched from aqueous to depot preparations following the rapid up-dosing phase (59). Depot preparations seem to be associated with fewer local side effects than aqueous preparations, but results may have been biased by the slower build-up phase with depot preparations (60). Purified aqueous preparations cause smaller local reactions compared with non-purified aqueous preparations (61). A systematic literature review has documented a similar rate of systemic adverse events when depot and aqueous venom allergen preparations were used, but the difference between purified and non-purified aqueous preparations was not taken into account (62). A comparative study in honeybee venom allergic patients indicates the superiority of the purified aqueous preparations over the corresponding non-purified aqueous preparation under the same rush protocol in terms of systemic reactions during the build-up phase (63) (Table 3).

Table 3 Recommendations: preparation and venom dose, pre-treatment with antihistamines, duration of treatment, carriage of adrenaline autoinjectors during/after VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Key reference
Purified venom preparations can be recommended as they have a lower frequency of local and systemic adverse events than non-purified aqueous preparations	I	B	Weak to moderate based on one RCT of moderate to high risk of bias (63)	Bilo 2012 (63)
For the majority of patients, VIT with one venom may be recommended as sufficient for protection. In patients with a history of systemic sting reactions to different insects or with severe initial reactions and clearly double positive tests, VIT with two venoms (i.e Apis mellifera and Vespula or Vespula and Polistes) is recommended.	IV	C	Weak based on one case series study (64) and expert consensus	Stoevesandt 2013 (64)
Two venoms can be administered simultaneously in the left and right arm, respectively. However, in the case of systemic adverse events, VIT should be continued with 30 minute intervals between injections	V	D	Weak based on expert consensus	Expert consensus
Pre-treatment with H1 antihistamines is recommended as it reduces large local reactions and to some extent also systemic adverse events	I	A	Strong to moderate based on four RCTs, two of them were of low risk of bias (67, 68), two of moderate risk of bias (65, 66)	Müller 2008 (68), Reimers 2000 (67), Brockow 1997 (66), Berchtold 1992 (65)
It is recommended to administer a standard maintenance dose of 100 µg venom	II	B	Weak to moderate based on one CCT of moderate/high risk of bias (88)	Golden 1981 (88)
If patients still react to field stings or sting challenges, a dose increase to 200 µg of venom can be recommended	IV	C	Weak based on one case series study (91)	Ruëff 2001 (91)
It may be recommended to give injections every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a 5 year treatment every 8 weeks from year 3-5	V	D	Weak based on expert consensus (93)	Bonifazi 2005 (93)
In the case of life-long therapy, 12 week intervals may be still safe and effective	II	C	Moderate based one CCT (94) and one CBA (95) study	Simioni 2013 (94), Goldberg 2001 (95)
It can be recommended to perform VIT for at least 3 years. In patients with severe initial sting reactions, at least a 5-year treatment is recommended	IV	C	Weak based on case series studies (98, 99, 101)	Reisman 1993 (98), Lerch 1998 (99), Golden 1996 (101)
Life-long VIT may be recommended in highly exposed patients with bee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grade III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse.	IV	C	Weak based on case series studies (31, 8, 98)	Ruëff 2013 (31); 2014 (8), Reismann 1993 (98)
During and after VIT, AAI cannot be recommended in patients with mild to moderate initial sting reactions without risk factors for relapse	V	D	Weak based on expert consensus	Expert consensus
During and after VIT, AAI may be recommended in patients at risk of multiple stings or with risk factors for relapse	V	D	Weak based on expert consensus	Expert consensus

Treatment with more than one venom

Selection of the correct venom preparation(s) is important to ensure optimal efficacy of VIT. Sensitization to venom of more than one Hymenoptera species is common in insect venom allergic patients (64) and it can be difficult to determine whether this reflects double sensitization due to cross-reactivity of shared allergenic determinants or genuine multiple sensitization to more than one venom. However, in most of these cases treatment with only one venom appears to be sufficient (64). A major diagnostic problem is that currently available tests, such as skin testing, IgE determination including component-resolved diagnosis or the BAT are not able to distinguish between asymptomatic sensitization and clinically relevant allergy with LLR and SSR (18). However, if the initial sting reaction was severe and all allergy tests are almost equally positive to vespid and to honeybee venom, VIT with both venoms should be considered. As there is only limited cross-reactivity between honeybee and vespid venom and Vespula and Polistes venom, simultaneous injections with both venoms should be safe. This approach is common in the United States (US) and partly in Europe, however, no studies have examined this question (Table 3).

Preventive pre-treatment

In several double-blind, placebo-controlled trials, it has been shown that pretreatment with H1 antihistamines improves the tolerability of VIT (65-68). In detail, it was reported that levocetirizine decreased the rate of SSR (68) and fexofenadine decreased the rate of LLR and cutaneous SSR (67) (Table 3). Importantly, effectiveness of VIT was not negatively influenced (68, 69). Antihistamines were usually administered 1-2 hours before the injections or sometimes twice daily. In case of repeated adverse events during up-dosing, pre-treatment with Omalizumab may be recommended (70-72).

Treatment protocols

VIT is performed by subcutaneous injections. VIT consists of an up-dosing phase and a maintenance phase, which is necessary to ensure a sustained effect of VIT. Conventional protocols, where the maintenance dose is reached in several weeks to months, can be administered in outpatient clinics (73). In an effort to reach the maintenance dose faster, rush (73-77) and ultra-rush protocols (78-81) with several injections per day on consecutive days are performed in hospitals. Maintenance dose is reached either within a few hours or within a few days, respectively. Cluster protocols, with several injections per day usually 1-2 weeks apart, are also a quick alternative to conventional protocols (82, 83). Importantly, the risk of adverse events is not associated with the severity of initial reactions (24, 25, 84), high venom-specific IgE levels, or skin test reactivity at low venom concentrations (84, 85). Conventional regimes appear to be best tolerated while rush and ultra-rush protocols are more frequently associated with adverse events (24).

Up-dosing

The recommended starting dose in up-dosing protocols lies between 0.001 and 0.1 µg, but it has also been shown that a starting dose of 1 µg is usually safe and not associated with a higher rate of side effects in adults or in children (86). A maximum dose of 100 µg venom allergen dose usually offers adequate protection against systemic allergic sting reactions in the majority of venom allergic individuals (87-89).

Maintenance dosing

A maintenance dose of 100 µg venom is significantly more effective than 50 µg (88). This dose is equivalent to the dry weight of approximately two honeybee stings or five wasp stings (90) and has been adhered to as the recommended maintenance dose since the first controlled trial (87). A further increased dose gives a better protection when needed (91). A dose of 200 µg is recommended in patients who develop systemic allergic reactions following a field sting or sting challenge while on 100 µg maintenance VIT (91). An increased maintenance dose should also be considered in allergic populations at high risk of multiple stings, such as beekeepers (92) and in exceptional cases where patients have accumulated risk factors for treatment failure.

Although the European Medicines Agency (EMA) had no safety concerns regarding aluminium toxicity from their pharmacovigilance review of aluminium hydroxide in standard AIT, high dose VIT and life-long therapy has not been specifically evaluated. As a precaution, where life-long therapy is planned is can be undertaken with aqueous preparations. If a 200 µg

dose is required for maintenance, half can be given as an aqueous preparation.

The interval for maintenance VIT with 100 µg venom recommended by the manufacturers has been 4-6 weeks for aqueous preparations and 6-8 weeks for purified aluminium hydroxide adsorbed preparations (depot preparations). According to expert consensus, injections are usually given every four weeks in the first year of treatment, every six weeks in the second year, and in case of a five year treatment every eight weeks from year 3-593. Extending the maintenance interval to three months does not seem to reduce effectiveness or increase adverse events (94-96), which could be relevant in terms of convenience and economic savings if life-long treatment is necessary. As there is no specific study available for mastocytosis patients with severe initial SSR, caution should be used in extending the intervals to three months in those patients. A dose interval of six months did not provide suitable protection in honeybee venom allergic patients (97) and is therefore not recommended for standard practice (Table 3).

Duration of VIT

Termination after approximately one or two years leads to a relapse rate of 22-27% (41, 42). Some studies have concluded that VIT for three years may be sufficient (98), particularly in patients with only mild to moderate initial sting reactions (98). Nevertheless, most of the studies concluded that a minimum of a five-year treatment is superior for long-term effectiveness (99-102). Life-long therapy should be considered in patients with severe initial SSR, systemic adverse events during VIT, and honeybee venom allergic patients with high risk of future honeybee stings (Table 3, 4).

Adherence

Adherence to VIT is high, possibly because of patients' perception of an unpredictable risk of life threating sting reactions. In a recent study 95% and 84% of patients still continued VIT after three and five years, respectively (103).

Effectiveness

Treatment with ant venom is very effective as 97 to 98% are protected after VIT (9, 10). The effectiveness of honeybee and vespid VIT is different and ranges from 77 to 84% for honeybee venom compared to 91 to 96% for vespid venom (7, 8). The underlying reasons are still unclear. It has been speculated that the amount of venom delivered by a honeybee sting is much larger and more consistent (90). This may also explain the difference in the reaction rate to sting challenges, which has also been observed in untreated patients (104-106). It also appears that the broad sensitization pattern in honeybee venom allergic patients may play a role in the lower effectiveness of honeybee VIT (107). For example, some patients are predominantly sensitized to Api m 10, which may be underrepresented in certain available honeybee venom preparations (108, 109). However, none of these studies included a patient analysis of molecular sIgE binding patterns to honeybee venom allergens before the start of VIT. Without such a specific IgE stratification aligned with the clinical outcome, the conclusions are of limited value. The specific preparation does not seem to have an impact on the effectiveness. The effectiveness of aqueous and purified aluminium hydroxide adsorbed preparations has been shown to be similar (60, 110).

Effectiveness of VIT after up-dosing phase

Only one recent study has looked at how rapidly protection occurs. In honeybee VIT, 89% tolerated the sting challenge one week after reaching the maintenance dose in a 3-5 day rush protocol or a 3-4 month conventional protocol. Those patients who were not protected with 100 µg venom, tolerated the sting challenge immediately after reaching the dose of 200 µg (89).

Effectiveness during/after maintenance VIT

Most effectiveness data are obtained during VIT. Re-sting reaction rates of 0-10% 1-5 years after discontinuation of vespid VIT have been reported (100, 101, 111). Relapses after honeybee VIT are more frequent as 17% are reported to relapse one year after stopping VIT (112). There are only few reports on the outcome following VIT withdrawal for more than five years, and there are no data for more than 10 years after discontinuing VIT. In two studies 7-7.5% of patients treated with vespid venom relapsed after 7 to 10 years (98, 99), while 15.8% after stopping honeybee VIT had re-sting reactions (99). Another study compared relapse rates after four and approximately 10 years and reported relapse

Table 4 Recommendations: risk factors and management of side effects, duration of treatment

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
It may be recommended that patients treated with bee venom and those on rapid up-dosing protocols should be closely observed for side effects as they are at a higher risk of experiencing adverse events	IV	C	Weak based on case series studies (24, 43)	The intake of beta-blockers or ACE inhibitors are not risk factors for adverse events during VIT. Also most of the mastocytosis patients tolerate VIT well	Ruëff 2010 (24), Mosbech 2000 (43)
It may be recommended that patients with severe initial sting reactions, high skin test reactivity, and high venom specific IgE levels do not require special precautions during VIT, as they are not associated with a higher risk of adverse events	IV	C	Weak based on case series studies (25, 24, 84)		Stoevesandt 2014 (25), Ruëff 2010 (24), Lockey 1990 (84)
In case of VIT- related systemic adverse events during build-up phase, a temporary reduction of the venom dose (e.g. going one to two steps back in the protocol) may be recommended to avoid further adverse events	V	D	Weak based on expert consensus		Expert consensus
In case of repeated systemic adverse events during up-dosing, pre-treatment with Omalizumab may be recommended	V	D	Weak based on case reports (70, 71) and one case series (72)		Stretz 2017 (72), Kontou-Fili 2008 (70), Schulze 2007 (71)
In case of VIT related LLR, it may be recommended to split dose in 2 injections or change injection site but not necessarily to reduce venom dose	V	D	Weak based on expert consensus		Expert consensus
Life-long VIT may be recommended in patients who relapsed after stopping VIT	V	D	Weak based on expert consensus		Expert consensus
It may be recommended to avoid insect stings during build-up phase by abiding by preventive measures (eg stop beekeeping) until maintenance dose is reached	V	D	Weak based on expert consensus		Expert consensus

rates of 10.2% and 16.2%, respectively (113). In children, the long term outcome is superior compared to adults as only 5% with moderate-to-severe reactions relapsed after up to 20 years after stopping VIT (15).

Carriage of adrenaline auto-injectors during and after VIT

It is still a debated issue whether AAI should be carried during and after VIT, and it has also been difficult to reach a consensus on this topic. Most patients are protected after reaching the maintenance dose (89). Therefore, patients usually do not need to carry AAIs at this point, particularly if their sting reaction had been mild or they had tolerated a sting challenge or field sting during VIT. It should also be considered that carrying an AAI can negatively impact on health-related QoL (50, 52) (Table 3). According to the EAACI position paper "Self-medication of anaphylactic reactions due to Hymenoptera stings", 13% of experts/authors would still prescribe an AAI to patients who initially only had generalized skin symptoms after discontinuation of VIT; and 100% considered recommending carrying an AAI in patients who initially suffered from moderate-to-severe reactions after terminating VIT if risk factors for treatment failure were present (114).

RISK FACTORS FOR SYSTEMIC ADVERSE EVENTS WITH VIT AND RELAPSE OF SSR

Risk factors for systemic adverse events with VIT

The frequency of systemic adverse events with VIT in large multi-center studies ranges from 8-20% (24, 43, 84). Several risk factors for the occurrence of systemic adverse events have been described. Most of the studies include only small numbers of patients and provide conflicting data. The most important risk factor is treatment with honeybee venom. It has been consistently reported that there is a 3.1 to 6.0-fold higher risk for systemic adverse events due to treatment with honeybee venom (24, 77, 86). Rapid dose increase during the build-up phase is a weaker, but nonetheless established risk factor (24, 43). Mastocytosis and/or elevated serum tryptase was initially considered as risk factor for adverse events. An EAACI multicenter study found a slightly elevated risk when tryptase was elevated in vespid venom allergic patients (OR 1.56; CI 1.15-2.10) (24), whereas another study performed in honeybee venom allergic patients did not (85). A study performed in patients with mastocytosis concluded that VIT is safe and efficacious (47), confirming previous data (45). Although still a debated issue, ACE inhibitors and beta-blockers are not considered to be independent risk factors for adverse events (23-25). Importantly, severe initial sting reactions (24, 25, 84), positive skin tests at low test concentrations and high specific-IgE levels (25, 84, 85) are not regarded as risk factors for adverse events (Table 4).

Management of adverse events during build-up phase of VIT

Adverse events are generally mild and adequately respond to standard anti-allergic treatment (20, 36). In the case of systemic adverse events, a common procedure during build-up phase is reducing the allergen dose (going one to two steps back in the protocol) and then continuing with the second last well tolerated dose of VIT. If not yet considered, premedication with H1 antihistamines should be established. When systemic adverse events prevent reaching the maintenance dose, premedication with Omalizumab may be an option. Currently, case reports and a case series have documented the usefulness of Omalizumab (70-72, 115) but there is also one negative report (116) (Table 4).

Risk factors for relapse of SSR (Table 4)

Age and type of venom

As already mentioned above, children generally have a more favorable prognosis than adults (15), and patients who were treated with honeybee venom had a higher risk for relapse compared to those who were treated with vespid venom (98, 99, 113).

Severity of reaction prior to VIT

Two studies reported a higher relapse rate in patients who have had a severe SSR before VIT (98, 100). In the larger study, relapses were observed in 4% with mild but 14% with severe pretreatment reactions (98). Other studies concluded that the grade of the SSR prior to VIT was not relevant to the probability of a relapse (112, 117). Although it is still controversial whether severe initial SSR are a risk factor for relapse, it has been agreed that those patients are at greater risk for severe SSR when they relapse (118).

Systemic adverse events during VIT

Patients who developed systemic adverse events during VIT showed a relapse risk of 38%, while those who did not, only had a 7% risk (112). Two more studies reported similar results (46% vs. 8% and 16.4 vs. 5.4%, respectively) (32, 102).

Mastocytosis/elevated serum tryptase levels

A large multicenter study could not detect an association between higher baseline tryptase and therapy failure (31), and 86% of 50 mastocytosis patients were protected after initiation of VIT (47). However, one study indicated that patients with tryptase >20 µg/L and/or mastocytosis in the skin had a 2.7-fold higher risk for therapy failure (32). Available data are scarce and heterogeneous but it appears that mastocytosis is not a strong general risk factor for relapse but should be considered as risk factor in individuals with severe initial SSR.

ACEI

While in one multi-center study all patients on ACEI tolerated a sting challenge or field sting during VIT (31), another study reported a higher risk for relapse in patients taking ACEI (32). However, the risk of ACEI might have been overestimated due to the very small

Table 5 Recommendations: monitoring of VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Key references
In adults, a sting challenge can be recommended as the most reliable method to evaluate effectiveness of VIT	IV	C	Weak based on case series studies (117, 101)	Van Halteren 1997 (117), Golden 1996 (101)
If no sting challenge can be performed, it may be recommended to record outcomes of field stings to evaluate effectiveness of VIT	V	D	Weak based on expert consensus	Expert consensus
It may not be recommended to determine venom specific IgE, IgG levels, BAT response and allergen-blocking capacity to estimate the individual risk for relapse	IV	C	Weak based on case series studies (99, 112, 100)	Lerch 1998 (99), Müller 1991 (112), Keating 1991 (100)

patients' group and highly selected patients with suggested cardiovascular comorbidity (33).

PROCEDURES TO MONITOR VIT

Many attempts have been made to identify biomarkers to monitor AIT. In peripheral venous blood samples of treated patients, there are significant changes of venom-specific T cell populations, secreted cytokine patterns and immunoglobulin levels but these are not appropriate to estimate the individual risk for relapse of SSR. The sting challenge remains the gold standard in identifying unprotected patients (Table 5).

Sting challenges / field stings

Performing sting challenges is still the most reliable method and gold standard to monitor the effectiveness of VIT. VIT is effective immediately after reaching the first maintenance dose (89). Therefore, if feasible, sting challenges should be performed as early as possible to identify those who are not protected with the maintenance dose of 100 µg. If sting challenges cannot be performed, information about field stings may be helpful. However, the risk of misidentification of the stinging insect and the non-standardized sting procedure reduce reliability (112).

The reproducibility of sting challenges, at least for diagnostic purposes, is a debated issue. A study on 129 patients revealed that in 95% of patients a diagnostic sting challenge provided a good prediction of tolerance for subsequent field stings (119). On the other hand, it has been shown that 21% of patients not treated with VIT, who initially tolerated a sting challenge, had systemic symptoms after a second challenge (120). The reliability of early sting challenges to monitor effectiveness of VIT appears to be high (121), although repeated sting challenges during three to five years after treatment identified 8-10% of patients who relapsed (101, 117). Importantly, tolerated sting challenges can improve health related QoL, especially in patients reporting high impairment of health related QoL before the sting challenge (51). Thus, sting challenges should not only be seen in the context of evaluating effectiveness but also in terms of fostering individual belief in disease-specific safety.

Specific-IgE and IgG4 levels

It has been repeatedly shown that specific-IgE levels to the respective venom decrease during VIT after an initial rise during the first months of treatment (60, 121); they usually remain low even after stopping VIT (117). VIT is associated with a significant increase in specific IgG antibodies that has initially been suggested as a marker of effectiveness (122); these immunological changes induced by VIT were also reported in honeybee venom allergic children (123). The sub-class of IgG antibodies is usually restricted to IgG1 and IgG4 (121). However, after stopping VIT, specific IgG starts to decrease (99, 124, 125) and patients appear to be protected by a mechanism independent from venom-specific IgG (122). Taken together, available data do not support the use of specific IgE, specific IgG or specific IgG subclasses or even ratios can be used as predictors for protection during and after VIT in the individual patient.

Intradermal testing

Similar to the decline of specific IgE levels during VIT, intradermal test endpoint concentrations usually decrease from before to after VIT (99, 101). No study

Table 6 Gaps in evidence

Gaps	Plan to address	Priority
Optimal duration of VIT in children and adults (for example, 3 versus 5 years or longer)	RCTs	High
Evaluation of biomarkers such as sting challenges, component-resolved diagnosis, and BAT (inhibition) in assessing the clinical efficacy of VIT	Prospective studies	High
Identification of biomarkers for the risk assessment for side effects and relapse	Prospective studies	High
Comparison of different VIT up-dosing schedules, maintenance doses, and maintenance intervals in adults/children in terms of efficacy both short and long-term	RCTs	High
Safety and efficacy of VIT in patients taking antihypertensive drugs (beta-blockers, ACEI)	Observational studies	High
Safety and efficacy of VIT in patients with elevated serum tryptase/mastocytosis verified by sting challenges	RCTs	High
Comparison of purified and non-purified bee venom preparations in respect of safety and efficacy verified by sting challenges	RCTs	High
Safety of the simultaneous application of two or more venoms during up-dosing and maintenance phase	RCTs	High
Value of VIT on health-related quality of life compared to AAI in children and their parents	RCTs	Medium
Assessing the cost-effectiveness of VIT	Cost-effectiveness analysis of RCT	Medium
Safety of VIT in adults and children with concomitant disease such as cardiovascular disease	Observational trials	Medium

has been able to identify a relevant difference in skin test reactivity between tolerant subjects and patients with relapses (99, 100, 112). Moreover, patients with negative intradermal tests have been reported to have significant relapse, a few with near fatal reactions (102, 113).

Basophil activation test (BAT)

Allergen-specific basophil response remains positive (126) or even unchanged (125) during VIT. However, basophil responses at submaximal allergen concentrations are markedly decreased after VIT in tolerant subjects and this decline seemed to be associated with the induction of tolerance (125, 127). Also the measurement of basophil threshold sensitivity to anti-FcεRI stimulation has been proposed to monitor an early protective effect of VIT (128). BAT inhibition with sera of treated subjects correlated well with effectiveness of AIT in grass pollen allergic patients (129) but this has not yet been shown in patients with HVA.

Enzyme-linked immunosorbent facilitated antigen binding (ELIFAB)

The ELIFAB is a cell-free assay which is used to demonstrate inhibition of allergen-specific IgE binding by blocking antibodies (130). One study measured the serum inhibitory activity of VIT-treated vespid-venom patients (124). During VIT, patients displayed an increased ability to inhibit Ves v 5 binding by IgE antibodies. This allergen-blocking capacity correlated with serum concentrations of Ves v 5-specific IgG4. However, both the inhibitory activity and specific IgG4 levels were again reduced in patients who stopped VIT several years ago (124).

Despite of the availability of new methods such as the BAT and the ELIFAB, most of the parameters cannot precisely distinguish between patients who are protected from future SSR and those who are at risk. Currently, it is not possible to estimate the individual risk for relapse of SSR with any of the currently available parameters (Table 5).

SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

The EAACI Taskforce on VIT has developed this guideline as part of the EAACI AIT Guidelines initiative. The guideline have been informed by a formal systematic review and meta-analysis of VIT (1). The

Table 7 Barriers and facilitators to implementation, audit criteria and resource implications of recommendations

First-line intervention: VIT for venom allergic individuals	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Venom immunotherapy is highly clinically effective in adults and children with moderate to severe allergic reactions to hymenoptera stings	Failure to recognize severe allergic reactions (anaphylaxis) following hymenoptera stings Lack of knowledge amongst patients, caregivers and professionals about the availability of venom immunotherapy Concerns about side-effects The hope that allergic reactions will subside with time or symptomatic treatments only (e.g. AAI, antihistamines/ glucocorticosteroids)	Education and training of emergency care doctors, general practitioners and other physicians on venom allergy and its grades of severity Information about need of follow-up visits with clinical allergists for diagnosis and management of venom allergy Information sheets for patients and caregivers	Proportion of adults and children with moderate to severe SSR who are treated with VIT Proportion of adults and children who experience relapses and/or side effects while on VIT	Venom allergen immunotherapy (VIT) needs to be prescribed by clinical allergists and made available to patients. Patient education about self-treatment with adrenaline (AAI) before starting VIT is important and requires availability of trainer devices
VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired	Lack of knowledge amongst physicians, including clinical allergists about the indication of venom immunotherapy in these circumstances	Education and training of physicians, and allergy specialists Information sheets for patients	Proportion of patients experiencing impairment of QoL when venom allergy is confined to skin only who are treated with VIT	Education and training of both physicians and patients Cost /benefit profile needs to be established
Life-long VIT can be recommended in highly exposed patients with bee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grade III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse.	Lack of resources (professional and financial) Adherence to life-long VIT unrealistic	Provision of insurance cover for life-long VIT within Europe Education and training of clinical allergists Education of patients in terms of sting exposure risk behavior; patient leaflets, smartphone "shot" reminder apps etc.	Proportion of patients who adhere to life-long (or prolonged, i.e. > 5 years) VIT and proportion of patients consecutively tolerate hymenoptera stings	Equipment of specialized allergy centers with skilled staff for successful administration of VIT Safety measures in place to minimize side effects in high risk patients
Pre-treatment with H1 antihistamines is recommended as it reduces large local reactions and to some extent also systemic adverse events	Lack of knowledge amongst health care professionals regarding pre-treatment Reluctance of patients Additional costs for health care system	Education of healthcare professionals, and patients	Proportion of patients with VIT who have antihistamine pre-treatment	Prescription of antihistamines to be taken by patients prior to VIT
AAI during and after VIT is recommended only in patients at risk of multiple stings or with risk factors for relapse	Lack of knowledge amongst health care professionals in terms of (non) prescribing AAI Risk behavior and misconception of patients	Education of healthcare professionals, and patients	Proportion of high risk patients carrying and administering intramuscular (AAI) during or after VIT	Time to educate and train physicians and patients

guideline provides evidence-based recommendations for the use of VIT for patients with LLR and SSR. A summary of the guideline is provided in Box 3 and key messages for primary care practitioners are given in Box 4. The recommendations should be of value to all healthcare professionals involved in the management of patients with HVA.

There are a number of areas in this guideline where high-quality evidence is not available. The primary gaps are highlighted here and in Table 6. There is a major gap in the evidence for the clinical effectiveness of VIT in children and adolescents with recommendations at least one grade lower than for adults in most areas. Contrary to anecdotal findings, an important number of children do not outgrow allergic reactions to insect stings (15). Additionally, the effect of VIT in children and their parents on health-related QoL should be investigated further. In adults, there is need for studies with sufficient power to evaluate risk factors for adverse effects during VIT or for treatment failure. There is also minimal data in the elderly population particularly for patients with cardiovascular disease. Additionally, we need cost-effectiveness and cost utility studies to use in discussions with healthcare funders. Biomarkers to predict effectiveness of VIT and to identify treatment failure are also urgently needed.

Despite all these gaps, we have clear evidence for the clinical effectiveness of VIT for patients with SSR. Potential barriers and facilitators for the implementation of these recommendations are described in Table 7. There is now a need to ensure that primary care healthcare professionals know which patients might benefit from VIT, that national healthcare providers understand that VIT is highly effective and is likely to be cost-effective, and that patients and patient support groups are aware of this approach.

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Contributorship

GJ Sturm and EM Varga jointly chaired the EAACI Guideline on VIT and initially drafted the manuscript. H Mosbech, MB Bilò, CA Akdis, D Antolín-Amérigo, E Cichocka-Jarosz, R Gawlik, T Jakob, M Kosnik, J Lange, E Mingomataj, DI Mitsias, M Ollert, JNG Oude Elberink, O Pfaar, C Pitsios, V Pravettoni, F Ruëff, BA Sin, I Agache, E Angier, S Arasi, MA Calderón, M Fernandez-Rivas, S Halken, M Jutel, S Lau, A Muraro, GB Pajno, R van Ree, G Roberts, D Ryan, R Gerth van Wijk were members of the taskforce who were involved in conceptualizing the guidelines and critically reviewed guideline drafts. S Dhami, H Zaman and A Sheikh provided methodological support to the taskforce. O Spranger was the patient group representative. All the authors satisfied the international authorship criteria with further details in table S1 of the online supplement. This Guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro and coordinated by Graham Roberts.

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3

EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

IgE-MEDIATED FOOD ALLERGY

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Food allergy can result in considerable morbidity, impairment of quality of life and healthcare expenditure. There is therefore interest in novel strategies for its treatment, particularly food allergy allergen immunotherapy (FA-AIT) through the oral (OIT), sublingual (SLIT) or epicutaneous (EPIT) routes. This Guideline, prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE-mediated Food Allergy, aims to provide evidence-based recommendations for active treatment of IgE-mediated food allergy with FA-AIT. Immunotherapy relies on the delivery of gradually increasing doses of specific allergen to increase the threshold of reaction while on therapy (also known as desensitization) and ultimately to achieve post-discontinuation effectiveness (also known as tolerance or sustained unresponsiveness). Oral AIT has most frequently been assessed: here the allergen is either immediately swallowed (OIT) or held under the tongue for a period of time (SLIT). Overall, trials have found substantial benefit for patients undergoing either OIT or SLIT with respect to efficacy during treatment, particularly for cow's milk, hen's egg and peanut allergies. A benefit post-discontinuation is also suggested, but not confirmed. Adverse events during AIT have been frequently reported, but few subjects discontinue FA-AIT as a result of these. Taking into account the current evidence, AIT should only be performed in research centers or in clinical centers with an extensive experience in food allergy AIT. Patients and their families should be provided with information about the use of AIT for IgE-mediated food allergy to allow them to make an informed decision about the therapy.

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INTRODUCTION

Food allergy (FA) has emerged as a significant medical problem in recent decades. With FA now affecting up to 8% of children and 5% of adults in westernised countries, development of therapies for this potentially life-threatening condition has become a public health priority (1-3). The key terms and clinical presentation of FA are summarised in Boxes 1 and 2.

The current approach in managing FA focuses on avoidance of trigger foods and the availability of and training in the use of rescue medication in the event of an allergic reaction. Allergen immunotherapy (AIT) is potentially a curative therapy. AIT may increase the amount of food that the patient can tolerate, preventing allergic symptoms and reducing the risk of potentially life-threatening allergic reactions. The first case of immunotherapy for food allergy (FA-AIT) was described in 1908 to hen's egg (HE) (4); the principles underlying the therapy have remained the same, i.e. therapy consists of the administration of gradually increasing doses of food allergens via the oral, sublingual or subcutaneous routes (2). A fixed dose of allergen can be administered through the epicutaneous route (2).

The ultimate goal of FA-AIT is to achieve post-discontinuation effectiveness so that a patient can eat a normal serving of the trigger food without symptoms. This is also known as "tolerance" or "sustained unresponsiveness". These terms all imply that the food allergen can be ingested without the appearance of allergic symptoms despite a period of absence of exposure. The time period required to establish true post-discontinuation effectiveness is not yet defined. Based on current evidence, a more attainable target is effectiveness during treatment (typically referred to as "desensitisation") which refers to a reversible or partially reversible clinical response that is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity may return (5).

The primary outcome of FA-AIT is a change in the threshold of allergen required to trigger an allergic reaction determined by an oral food challenge (OFC) - where possible, this is preferably a double-blind,

Box 1 Key terms

Allergen immunotherapy	Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and the need for medication for clinical allergies and to prevent the development of new allergies. This is also known as allergen specific immunotherapy.
Effectiveness during treatment	The ability to safely consume foods containing the culprit allergen while on allergen immunotherapy. This clinical response is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity may return. This is also referred to as "desensitization".
Food	Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation, or treatment of 'food' but does not include cosmetics or tobacco or substances used only as drugs [*Codex Alimentarius*]. Food is eaten, drunk or otherwise taken to the body to provide energy and nutritional support, maintain life, or stimulate growth.
Food allergy	An adverse reaction to food mediated by an immunologic mechanism, involving specific-IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) [from EAACI Food Allergy and Anaphylaxis Guidelines (3)].
Post-discontinuation effectiveness	The ability to safely consume a normal serving of food containing the trigger allergen despite a period of absence of exposure. This is also known as "tolerance" or "sustained unresponsiveness".
Sensitization	Detectable IgE antibodies, either by means of skin prick test or determination of serum specific-IgE antibodies.

Box 2 Clinical presentations of IgE-mediated food allergy

Systems	Symptoms
Cutaneous	pruritus, erythema/flushing, urticaria, angioedema, contact urticaria
Ocular	itching, redness, tearing, periorbital edema
Oropharynx	itching, dryness/discomfort, swelling of the oral cavity, lips, tongue and/or pharynx
Respiratory tract	nasal congestion, nasal pruritus, rhinorrhea, sneezing hoarseness, laryngeal edema, dysphonia, shortness of breath, cough, wheezing, chest tightness/pain
Gastrointestinal	abdominal pain, nausea, emesis, diarrhea
Cardiovascular/Neurological	tachycardia, hypotension, dizziness, loss of consciousness/fainting, seizures, incontinence
Multi-organ	anaphylaxis
Miscellaneous	sense of impending doom, uterine cramping/contractions

placebo-controlled, food challenge (DBPCFC). There is great variability in the threshold of exposure between different studies and for different foods (6, 7). Additional parameters have been studied in the monitoring of FA-AIT, including: skin prick tests (SPT) (8), specific-IgE (sIgE), IgG and IgG4 levels in serum (9). Some studies have also looked at basophil activation tests (BAT) (10), cytokines (e.g. IL-10, IL-5 and IFN-γ) (11,12), and regulatory T-cells (13).

The most frequent route of administration of FA-AIT is the oral route where the allergen is either immediately swallowed (oral immunotherapy, OIT) or held under the tongue for a period of time (sublingual immunotherapy, SLIT). There are currently ongoing studies using the subcutaneous route (subcutaneous immunotherapy, SCIT) for peanut and fish allergies (14-16). Epicutaneous immunotherapy (EPIT) is also under investigation for peanut and cow's milk (CM); it involves application of patches containing food allergen onto the skin (17). In general, there has been no consistent formulation of food in FA-AIT studies conducted to date (18). Dilutions of unprocessed products, crude extracts and flours have been used. Some studies have been carried out with powdered or lyophilized products. Only a few have used food extracts with a quantification of major allergens prepared by pharmaceutical companies or hospital pharmacies (11, 19).

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE-mediated Food Allergy. It is part of the EAACI Guidelines on Allergen Immunotherapy. This Guideline aims to provide evidence-based recommendations for the use of AIT in patients with diagnosed IgE-mediated FA. The primary audience are clinical allergists. This Guideline is also likely to be of relevance to other healthcare professionals (e.g. other doctors, nurses, dieticians, psychologists and paramedics) who are involved in the management of patients with food allergy and their families in any setting.

The development of this Guideline has been informed by a formal systematic review (SR) and meta-analysis on FA-AIT that included 31 trials studying 1259 patients. There were 25 randomised clinical trials (RCT) and 6 non-randomised controlled clinical trials (CCT). OIT was covered by 25 studies, SLIT was used in 5, and EPIT in 1. The food allergies most frequently studied were CM (16 studies), HE (11 studies), and peanut (7 studies) (18).

METHODOLOGY

This Guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) framework (20, 21), which is 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 minimised

Box 3 Summary of the aims and outcomes of the supporting systematic review (18)

Aim	To provide a systematic review of the evidence on the effectiveness, safety and cost-effectiveness of AIT for IgE-mediated food allergy.
Outcomes of the SR:	***Primary*** • Effectiveness during the treatment (i.e. the ability to safely consume foods containing the allergen in question while on AIT) or post-discontinuation effectiveness (the ability to consume foods containing the allergen in question after discontinuing AIT) at food challenge. • Assessment of changes in disease specific quality of life (QoL) using a validated instrument. ***Secondary*** • Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the WAO grading system of side-effects • Health economic analysis from the perspective of the health system/payer as reported in studies.

at each step of the process. The process started in 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 web-conferences in which professional and lay representatives participated.

Clarifying the scope and purpose of the Guidelines

This Guideline aims to assist qualified clinicians in the optimal use of AIT in the management of patients with IgE-mediated FA, and highlight gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on FA-AIT represented a range of 16 countries, and different disciplinary and clinical backgrounds, including allergists, paediatricians, primary care physicians, immunologists and patient group representatives. Additionally, producers of AIT products were given the opportunity to review and comment on the draft Guideline.

Systematic review of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree one key question: what is the effectiveness, changes in disease-specific quality of life (QoL), cost-effectiveness and safety of AIT in patients with IgE-mediated FA. This was then pursued through a formal SR of the evidence by independent methodologists as previously published (18) (Box 3). We continued to track evidence published after our SR cut-off date of 31st March 2016 and, where relevant, recent studies were considered by the Taskforce's joint Chairs. This most recent evidence will formally be considered in the SR update that will precede the update of this Guideline.

Formulating recommendations

We assessed the strength, consistency and quality of evidence in relation to key findings from the SR and meta-analyses (18) (which were undertaken using random-effects models to take into account the heterogeneity of findings) to formulate evidence-based recommendations for clinical care (Box 4) (22). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. Where the SR did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, i.e. (i) other SRs 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) an expert consensus-based approach. This evidence was also assessed, as described above. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organisational compliance with each recommendation.

Box 4 Assigning levels of evidence and 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, pre-test, 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 (22). 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.

Peer review and public comment

A draft of this Guideline was externally peer-reviewed by invited external experts from a range of organisations, countries, and professional backgrounds. Additionally, the draft Guideline was made available on the EAACI Website for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce and, where appropriate, final revisions were made in 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 we have prioritised.

Editorial independence and managing conflict of interests

The production of 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' conflict of interests were taken into account by the Taskforce Chairs as recommendations were formulated. Final decisions about strength of evidence for recommendations were reviewed by methodologists who had no conflict of interests in this area.

Updating the guidelines

We plan to update this Guideline in 2021 unless there are important advances before then.

GENERAL CONSIDERATIONS BEFORE INITIATING AIT FOR IgE-MEDIATED FOOD ALLERGY

AIT is potentially indicated for patients with evidence of an IgE-mediated FA and in whom avoidance measures are ineffective, undesirable or cause severe limitations to a patient's QoL. Prior to initiating AIT, confirming the diagnosis of IgE-mediated FA is mandatory. This requires a recent, clear clinical history of an acute reaction(s) after consumption of the triggering food. The presence of IgE to the triggering food should be established with SPT and/or sIgE. Where the diagnosis is unclear, an OFC is required. The baseline reaction threshold may be used to establish the efficacy of AIT in individual patients (Box 5).

Studies to date have enrolled patients with heterogeneous ages and clinical presentations (18). Studies have included infants and pre-school children who have tolerated FA-AIT safely (23, 24). However, the limited ability of young children to report early symptoms of allergic reactions should be considered. Furthermore, young children have a high likelihood of developing spontaneous tolerance, particularly to CM, HE, wheat and soy (25-31). Therefore, it might be more appropriate to wait for the natural acquisition of spontaneous tolerance before commencing AIT for these allergens (25-31). The right time to start may be around 4-5 years of age, but this should be decided on an individual basis.

FA-AIT is logistically demanding, time-consuming and most patients are affected by side effects. These are usually mild, but systemic reactions - including life-threatening anaphylaxis - may occur. AIT for FA should therefore only be undertaken in centres with professional training in FA care with the expertise, competencies and full resuscitation facilities to safely deliver this therapy and manage any complications, including anaphylaxis (Box 6). Only patients and families who understand the aim of the intervention and its risks, and are motivated and adherent should be considered for FA-AIT (Boxes S1 and S2 in the online). There are therefore many issues to be considered and discussed with the patient and family before commencing FA AIT (Box 7).

Box 5 Diagnosis of IgE-mediated food allergy before initiating FA-AIT

- Detailed medical history to establish current clinical reactivity to the food (recent reactions)
- Allergy testing (skin prick tests-SPTs, with food allergen extracts or fresh foods) and/or specific IgE (sIgE) to food allergen extract(s) or component(s) (component resolved diagnosis, CRD)
- Oral food challenge (OFC)

Box 6 Personnel and equipment required to perform FA-AIT

Personnel	Medical doctor and nurse trained and experienced in the diagnosis of food allergy including oral challenges, and trained and experienced in the recognition and treatment of allergic reactions including anaphylaxis. Personnel should be able to provide at least 12 hours of observation in case of adverse reactions related to AIT. #Anesthesiology team or intensive care or equivalent team particularly trained in resuscitation on call, at hand within 5 minutes.
Equipment	Stethoscope Sphygmomanometer Pulse oximeter Oxygen Spirometer, peak flow meter Laryngoscope(s), intubation tube(s), ventilation bag(s) Heart defibrillator (knowledge and experience how to use it) #Crash trolley
Medication	Adrenaline (epinephrine), antihistamine (oral and parenteral), inhaled beta2-agonist, corticosteroids (oral, parenteral). IV lines and IV fluids

According to the local facilities and organization of assistance to patients experiencing severe anaphylaxis.

Box 7 General considerations before initiating FA-AIT

Confirmed, persistent, systemic IgE- mediated FA.
Consider the likelihood of spontaneous resolution of the specific FA (e.g. CM and HE allergies)
Patients and their families should be motivated, adherent and capable of administering emergency treatment (including intramuscular adrenaline) in case of adverse effects
Clinical centres undertaking FA-AIT should have the expertise and facilities to safely deliver this therapy.

Box 8 General contraindications to FA-AIT

Absolute	• Poor adherence • Uncontrolled or severe asthma • Active malignant neoplasia(s) • Active systemic, autoimmune disorders • Active EoE or other gastrointestinal eosinophilic disorders • Initiation during pregnancy
Relative	FA-AIT should only be used with caution in an individual patient when benefits outweigh potential risks • Severe systemic illness or severe medical conditions such as cardiovascular diseases • Systemic autoimmune disorders in remission/organ specific (i.e. thyroiditis) • Uncontrolled active atopic dermatitis/ eczema • Chronic urticaria • Beta-blockers • ACE inhibitors • Mastocytosis

GENERAL CONTRAINDICATIONS

Given the long-treatment duration and common adverse reactions, any medical or social condition that might prevent patients attending frequent clinical visits, being aware of side effects or adhering to treatment represents an absolute contraindication. Uncontrolled asthma is also an absolute contraindication as it is associated with an increased risk of life-threatening systemic reactions (32). Well-controlled asthma is however not a contraindication for FA-AIT. Although a history of moderate to severe anaphylaxis to a food may be associated with more side effects, it is not a contraindication; these patients require appropriate evaluation before starting FA-AIT and close supervision particularly during the build-up phase. Uncontrolled, severe atopic dermatitis/eczema and chronic urticaria are relative contraindications given the risk of acute exacerbation while on AIT and because they can confound safety assessment of AIT. Therefore, both disorders should be controlled before AIT is initiated. The presence of eosinophilic esophagitis (EoE) or any other eosinophilic gastrointestinal disease is a contraindication for FA-AIT because of the risk these worsen whilst on FA-AIT (33, 34).

There is a lack of available data on the risks associated with FA-AIT in autoimmune disorders, severe medical conditions such as cardiovascular diseases, mastocytosis, or with the concomitant use of medications such as beta-blockers or angiotensin-converting enzyme (ACE) inhibitors. However, the risk in other types of AIT has been assessed (35-39): these conditions can be considered relative contraindications, and FA-AIT should only be used with caution when likely benefits outweigh risks (Box 8). The final decision about starting AIT should be established on an individual basis in discussion with the patient and/or family.

EFFECTIVENESS OF DIFFERENT APPROACHES TO AIT FOR IgE-MEDIATED FOOD ALLERGY

The effectiveness of FA-AIT has to be assessed in relation to the culprit food and route of administration.

Effectiveness of oral immunotherapy

A recently performed SR identified 23 trials: 18 RCTs and 5 CCTs (18). A meta-analysis of 22 of these trials involving 982 subjects revealed a substantial benefit for the patients (children and mixed population) undergoing OIT with CM, HE and peanut with respect to efficacy during treatment (RR 0.14, 95% CI 0.08, 0.24) (18).

There were 7 studies included in the SR (18) that assessed post-discontinuation effectiveness, but only 4 studies could be included in the meta-analysis (8, 40-42). This analysis suggested but did not confirm the longer-term benefits of OIT (RR 0.29, 95% CI 0.08, 1.13) (18). These 4 trials covered HE (8, 40-42) (169 subjects) and CM (40) (25 subjects), and assessed effectiveness by an oral challenge performed after 1 to 3 months of discontinuation of OIT. No subgroup analysis on the type of food or period of discontinuation could be performed. In an egg OIT trial, published after our SR (43), post-discontinuation effectiveness of egg OIT was enhanced with duration of OIT; however, there was no control group in the follow-up period to compare with natural resolution of the egg allergy. In this trial children were treated for up to 4 years, whereas those included in the meta-analysis were treated for a shorter period of time.

Regimens for OIT varied widely from rush protocols to slow up-dosing regimens with or without an initial dose escalation day (18). There was no apparent difference regarding effectiveness during treatment between CM, HE and peanut, and between the different protocols with all showing substantial effectiveness during treatment (18). The data published to date do not allow the ideal treatment regimen, including doses and intervals, to be determined. Additionally, the definition of effectiveness (i.e. increment of threshold) and its assessment varied among studies, and so the overall magnitude of the effect cannot be established.

In conclusion, FA-OIT is recommended for persistent CM, HE or peanut allergy for children from around 4 to 5 years of age on the basis of its ability to increase the threshold for clinical reactions while on OIT (Grade A) (Table 1-3). At present, there are insufficient data to be able to recommend AIT for other foods (Table 4) and for adults outside clinical trials (Table 5).

Effectiveness of sublingual immunotherapy

There are few published studies which have assessed the effectiveness of SLIT. A recent meta-analysis identified four placebo-controlled RCTs and one CCT for the assessment of efficacy of SLIT while on therapy (18). The total number of patients treated was limited (n=189), and the food allergies covered included peanut (12, 52), hazelnut (11), and peach (53) in RCTs, and different foods in a CCT (50) (RR=0.26, 95% CI 0.10, 0.64). Overall, SLIT revealed substantial benefits for the patients in regard to desensitization (18),

Table 1 Recommendations on efficacy of OIT in children with persistent cow´s milk allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase threshold of reaction while on treatment in children with persistent cow´s milk allergy, from around 4 - 5 years of age.	I	A	Strong recommendation based on convincing evidence from SR and meta-analysis (18) including RCTs at low (7, 9) or unclear risk of bias (44)	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion.	Nurmatov 2017 (18); Longo 2008 (7); Pajno 2010 (9); Skripak 2008 (44)
A recommendation cannot currently be made for OIT as a treatment option in children with persistent cow's milk allergy with the goal of post discontinuation effectiveness.	I	B	Weak as only one small RCT at high risk of bias (40)	Further studies needed	Staden 2007 (40)

*OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 2 Recommendations on efficacy of OIT in children with hen's egg allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT can be recommended as a treatment option to increase the threshold of reaction while on OIT in children with persistent hen´s egg allergy, from around 4 - 5 years of age.	I	B	Moderate recommendation based on evidence for effect from SR and meta-analysis (18) including low risk of bias RCTs (8, 42). Studies are all small with some heterogeneity in results.	Risk of adverse reactions needs to be considered. Age recommendation is based on expert opinion. Additional large studies required.	Nurmatov, 2017 (18); Burks, 2012 (8); Caminiti 2015 (42)
A recommendation cannot currently be made for OIT as a treatment option to achieve post-discontinuation effectiveness in children with persistent hen´s egg allergy	I	B	Strong recommendation based on only one RCT with low risk of bias (43)	After 4 years of OIT 50% of subjects achieved sustained unresponsiveness 4-6 weeks after stopping OIT (43). Further studies needed.	Jones 2016 (43)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 3 Recommendations on efficacy of OIT in children with persistent peanut allergy

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase the threshold of reaction while on treatment in children with peanut allergy from around 4-5 years of age	I	A	Strong recommendation based on consistent evidence from SR and meta-analysis (18) with low risk of bias RCTs (45-47)	Risk of adverse reactions to be considered. Age recommendation is based on expert opinion.	Nurmatov 2017 (18); Narisety 2015 (45); Tang, 2015 (46); Varshney 2011 (47)
A recommendation cannot currently be made for OIT as a treatment option to achieve post discontinuation effectiveness in children with peanut allergy	I	B	Strong recommendation based on two RCTs at low risk of bias (23, 45)	Inconsistent study results. Further studies needed.	Vickery 2017 (23), Narisety 2014 (45)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 4 Recommendations on efficacy of OIT in children with persistent allergies to other foods

Recommendations*	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
A recommendation cannot currently be made for OIT as a treatment option to increase the threshold of reaction while on treatment in children allergic to other foods (e.g. fish, wheat, peach)	II	B	Weak recommendation based on a few cases reported in one RCT at high risk of bias (48) and two CCTs at moderate risk of bias (49, 50)	Risk of adverse reactions to be considered	Patriarca, 1998 (48), Patriarca, 2003 (49); Patriarca, 2007 (50)

* OIT for food allergy should only be undertaken in highly specialised clinical centres with expertise and facilities to safely deliver this therapy.

Table 5 Recommendation on efficacy of OIT in adults with persistent food allergy

Food	Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Cow´s milk	No recommendation can be made about OIT as a treatment option in adults with persistent cow´s milk allergy	V	D	No recommendation due to lack of evidence		
Hen's egg	No recommendation can be made about OIT as a treatment option in adults with persistent hen´s egg allergy	V	D	No recommendation due to lack of evidence		
Peanut	No recommendation can be made about OIT as a treatment option in adults with peanut allergy	II	B	Weak as only one CCT including mixed populations (51). No recommendation due to lack of evidence.		Syed 2014 (51)
Others	No recommendation can be made about OIT as a treatment option in adults allergic to other foods (e.g. fish, wheat, peach)	V	D	No recommendation due to lack of evidence.		

but none of the studies included in the SR assessed post-discontinuation effectiveness. However, an open follow-up of a peanut SLIT trial in children and adults found only 11% of patients achieving tolerance after three years on SLIT and post-discontinuation of the AIT for 4-6 weeks (54).

Head-to-head trials of OIT versus SLIT

Two trials directly compared the efficacy of OIT and SLIT: the first focused on CM (55) and the second on peanut allergy (45). The first trial randomized 30 children with CM allergy to SLIT alone or SLIT followed by OIT. This trial clearly showed that OIT after SLIT was more efficacious for desensitization and sustained unresponsiveness after six weeks off therapy to CM than SLIT alone (55). The second trial was a double-blind study involving 21 children with peanut allergy who were randomized to receive either active SLIT/placebo OIT or active OIT/placebo SLIT. As in the CM trial, OIT was far more effective than SLIT for the treatment of peanut allergy as the increased threshold was significantly greater in the active OIT group while on therapy (45). OIT would seem to be a better therapeutic option than SLIT, but it is associated with significantly more adverse reactions. Currently, we cannot recommend SLIT for FA due to the limited effectiveness.

Other routes of AIT under investigation

EPIT with unmodified allergens is currently under investigation for peanut and CM. Efficacy results of one placebo controlled RCT with peanut EPIT in 74 subjects aged 4-25 years have shown an increase in the threshold of reaction while on therapy. This effect was higher in patients younger than 11 years of age (17). Moreover, SCIT with modified allergens is also under development (14-16). Two SCIT trials are currently ongoing: one using a chemically modified peanut extract (14) and another one using hypoallergenic recombinant parvalbumin for fish allergy (16). And finally, a phase 1 trial with modified peanut allergens administered by the rectal route has been conducted, but showed significant side effects, which led to early termination of the trial (56). At present, we cannot recommend EPIT or SCIT for FA-AIT.

SAFETY OF AIT

Alongside efficacy, safety is pivotal to any treatment. In AIT, safety is particularly important, as potential adverse events are mostly immediate onset, food-induced IgE-mediated reactions, which can lead to anaphylaxis. Events related to safety have been highlighted in the studies addressed by the SR (18). The heterogeneity in the reporting formats reduced the number of studies that could be pooled in the meta-analysis. Despite this, it was shown that patients receiving the active preparation experienced significantly more reactions, both systemic and local, than those who received placebo (18). Recommendations on safety of AIT are shown in Table 6.

Oral immunotherapy

OIT to foods is associated with a large number of local reactions. These are mainly itching of the oropharynx, perioral rash, and mild abdominal pain and can be bothersome when they occur repeatedly. Local reactions may evolve into more severe systemic reactions, but only a minority of patients experiences these. Results for systemic reactions from five OIT studies and for local reactions from 7 studies were pooled in the meta-analysis. Patients receiving active treatment had a higher risk of systemic reactions than those in the placebo group (RR of not experiencing a systemic reaction in controls: 1.16, 95% CI 1.03, 1.30) (18). OIT was also associated with a higher risk of local reactions (RR of not experiencing a local reaction in controls: 2.14, 95% CI 1.47, 3.12) (18). No deaths have been reported in the meta-analysis (18). It is therefore recommended that patients are carefully monitored for local and systemic allergic reactions in FA-AIT, particularly during the up-dosing phase of FA-OIT (Grade A).

Dosing with an empty stomach, irregular intake, exercise, infection, medication use, menses, and suboptimal control of asthma or of allergic rhinitis may increase the risk of reactions (59-63) especially during the maintenance phase(s) of OIT, when patients continue treatment at home. Although adverse reactions have been reported in the absence of these co-factors, patients should be informed and instructed on how to manage AIT in these situations (Boxes 9 and 10). It is recommended that a careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is undertaken before starting AIT (Grade C) (Table 6).

Table 6 Recommendations on safety of FA-AIT

Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
It is recommended to carefully monitor patients for local and systemic allergic reactions in FA-AIT particularly during the up-dosing phase of FA-OIT	I	A	Strong recommendation based on SR and meta-analysis (18) including RCTs at low risk of bias (9, 42)		Nurmatov, 2017 (18); Pajno 2010 (9); Caminiti 2015 (42)
It is recommended to monitor patients for symptoms of new onset eosinophilic esophagitis which may appear in the course of FA-OIT	I	B	Moderate recommendation based on SR (33) including one RCT and case reports.		Lucendo 2014 (33)
A careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is recommended before starting AIT	V	D	Moderate recommendation based on the risks identified by experts in RCTs at low (7) and unclear risk of bias (40)		Longo 2008 (7); Skripak 2008 (44)
A careful evaluation of levels of sIgE, SPT and concomitant asthma control is recommended before starting FA-AIT as high levels of sIgE and skin reactivity, and asthma have been found as risk factors for adverse events.	IV	C	Weak as based on expert review of consistent observational data (57-61)	Individual predictors of severe reactions still need to be identified	Vazquez-Ortiz, 2013 (57); Vazquez-Ortiz, 2014 (58); Martínez-Botas (59); Varshney 2009 (60); Narisety 2009 (61)

Box 9 Summary of the management

- Provision of individualized schedule, clearly written in simple non-medical language. It should include personal identification data (name, address, contact details of the parents, guardian, a next of kin, and family doctor).
- Copy of schedule should be kept by the patients or his/her caregiver(s), and their family doctor.
- Clear identification of food allergen to be administered during FA-AIT.
- Clear explanation that FA-AIT escalation dose(s) has to be administered in clinical specialized setting under strict medical supervision properly equipped for treatment of potentially severe allergic reactions.
- The risk of reaction caused by FA-AIT should be explained to the patient and his/her caregiver before starting FA-AIT.
- Provision of emergency kit with copy of emergency action plan and adrenaline auto-injector for treatment of anaphylaxis.

Box 10 Practical recommendations for patients

- Take dose daily
- Do not take dose on an empty stomach
- Do not go to the bed in the hour following a dose
- Do not do exercise in the 2-3 hours following a dose
- Reduce or withhold the dose during infections, asthma exacerbations, gastrointestinal diseases or menses.

Additionally, a careful evaluation of levels of sIgE, SPT and concomitant asthma control is recommended before starting FA-AIT as high levels of sIgE and skin reactivity, and asthma have been found as risk factors for adverse events (Grade B) (Table 6).

Dose adaptations are made according to the severity of allergic reactions. In mild reactions, doses can remain the same according to the protocol. With repeated mild reactions, particularly when bothersome to the patient, dose increments may be stopped, or doses may even be reduced. With systemic reactions, doses are usually reduced, although it is not established if a reduction is necessary in all patients, particularly when reactions only develop in the presence of co-factors. In patients with systemic reactions, individualized schedules with a longer and slower up-dosing phase, and premedication (antihistamines, or omalizumab) may be considered (58). We suggest a case-by-case evaluation of dose adaptation, and a thorough review of any underlying condition. The control of any concomitant allergic disease, and especially asthma, has to be optimal. Safety should remain the priority.

Sublingual immunotherapy

SLIT is associated with a lower risk of significant adverse events than OIT. In RCTs of SLIT (11, 12, 52-54), systemic reactions have been uncommon (<0.5-2.3% of doses) and generally mild, and appeared not to differ from those observed in the placebo treated patients. Meta-analysis of 2 SLIT studies (11, 53) did not show a significantly higher risk of systemic reactions in the active group (RR of not experiencing a systemic reaction in controls: 0.98, 95% CI 0.85, 1.14) (18). The most common adverse events in SLIT trials were mild local reactions in the oropharynx (7-40% of patients), which can be observed during both the up-dosing and maintenance phases. A meta-analysis of local reactions with SLIT could not be undertaken due to different formats in reporting reactions between trials.

SCIT and EPIT

The experience with SCIT using whole peanut aqueous allergen extracts is limited, mostly due to the high number of severe adverse events (including severe anaphylaxis) (64, 65). SCIT studies are currently underway with hypoallergenic recombinant parvalbumin and chemically modified peanut extract. These modified allergens have reduced allergenicity, but their safety profiles have not been yet reported (14-16).

One phase II RCT of EPIT with peanut suggests a favorable safety profile (17). Although patch-site reactions were observed in more than 90% of active treated patients, most were mild. Non-patch-site reactions were observed in less than 20% of patients, were also mild and responded to oral antihistamines or topical corticosteroids. No reactions required adrenaline.

The clinical setting for food allergy AIT

FA-AIT should only be undertaken in a setting where the full spectrum of food allergy reactions - including life-threatening anaphylaxis - can be managed (Boxes 6 and table 6). In particular, administration of initial doses and regular increments requires the presence of staff trained to manage anaphylaxis. Doses tolerated in the clinical setting are subsequently taken at home. Patients need clear instructions on how to detect an allergic reaction and its appropriate self-management. They also need to have on-hand appropriate medications including adrenaline auto-injectors. All dose increments have to be performed in a clinically specialized setting, and if no reactions are observed the same dose can be subsequently taken at home.

When to stop AIT after adverse reactions?

With repeated local adverse reactions and/or systemic adverse events, discontinuation of AIT should be discussed with the patient and/or family.

Long-term safety

Long-term safety is not addressed in trials; these predominantly focus on efficacy and short term safety. The development of EoE after OIT has been reported (33, 34, 62, 66). In a SR, new onset EoE was found in 2.7% (95% CI 1.7, 4.0). All the studies analyzed were retrospective with significant publication bias suggested by funnel plot analysis (33). It is therefore recommended to monitor patients for symptoms of new onset EoE which may appear in the course of FA-OIT (Grade A).

ALLERGEN FACTORS THAT AFFECT THE EFFECTIVENESS AND SAFETY OF AIT

In the SR on FA-AIT, the majority of trials were on CM (n=16), HE (n=11) and peanut (n=7), with only 1-3 studies for each of the other foods (18). AIT for CM, HE and peanut had similar efficacies in terms of desensitization with RR of 0.12 (95% CI 0.06, 0.25), 0.22 (0.11, 0.45) and 0.11 (0.04, 0.31), respectively. Of note, in these pooled analyses, the majority of studies were OIT with just a few SLIT ones and the products differed (e.g. peanut flour for OIT versus a peanut extract for SLIT).

Seven trials on different foods (3 CM, 1 HE, 1 peanut, 1 peach and 1 hazelnut; the latter two dealing with SLIT, and the remaining 5 with OIT) could be pooled for analysis regarding occurrence of systemic reactions. An increased risk of systemic reactions was observed with OIT, but a comparative subgroup analysis on the type of allergen could not be undertaken (18). For local reactions, milk seems more prone to cause side effects than egg although no statistically significant differences were found between them (milk 2.70, 1.33, 5.47; egg 1.55, 1.09, 2.22) (18). In conclusion, there is no evidence that the efficacy and safety are affected by the type and nature of the food allergen used in AIT.

PATIENT FACTORS THAT AFFECT THE EFFICACY AND SAFETY OF AIT

Different patient factors have been suspected to affect the outcomes of FA-AIT, both in terms of efficacy and safety. Concerning patient age, the SR and meta-analysis found that FA-AIT is effective in reducing FA in children and a population of mixed ages with IgE-mediated FA to a range of foods. It is still unclear if AIT is effective for adults. There are no studies of OIT performed exclusively in adults and in those performed with mixed (i.e. children and adult) populations, efficacy could not be analyzed separately according to age (18). The only studies focused on adults used SLIT with hazelnut and peach, and showed an increase in threshold of reaction while on therapy (11, 53).

In the SR and meta-analysis on FA-AIT, there were insufficient data to analyze the role of other patient factors such as the number of culprit foods of clinical relevance, co-existence of asthma or other severe allergic disorders, on FA-AIT outcomes (18). Some studies have shown that patients with greater IgE-sensitisation, lower threshold/higher severity and associated asthma are those with a higher frequency of adverse events (57, 58, 62). In a similar vein, some studies found that smaller SPT wheal size and lower sIgE levels have been associated with an increased likelihood of achieving desensitization and tolerance (67, 68). However, other studies did not find a significant correlation between pre-FA-AIT SPT/ sIgE

results and treatment success (45, 52), and some FA-AIT studies have included children with severe FAs or anaphylaxis with elevated sIgE who were successfully treated with FA-AIT (7, 9). Two studies performed in children allergic to CM have shown that IgE recognition of peptides of CM proteins are biomarkers that predict safety and efficacy of CM-AIT (54, 61).

ADHERENCE TO AIT

Adherence to treatment is a crucial consideration both to ensure efficacy and safety of FA-AIT. Given that FA-AIT is time-consuming and burdened by potential side effects, patients and their families must be extremely adherent, reliable and committed to a treatment regimen that may cover a long period of time. Given these premises, poor adherence to the treatment is an absolute contraindication (Box 8). A clear and detailed explanation about the FA-AIT procedure (i.e. up-dosing schedules, setting), the related outcomes and risk of side effects, together with getting information on patients' and/or families' opinions and expectations are pre-requisites to the inclusion in the treatment protocol. Patients and their families need to be supported during the entire treatment. Informed consent should be signed by patients (where appropriate) and their parents.

SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

FA-AIT represents the active treatment of IgE-mediated FA instead of avoidance and rescue drug management. The usual management of FA demands changes in eating habits with serious repercussions on QoL, potential risk of nutritional deficiencies, especially in young children, and severe adverse reaction in case of accidental exposure to the culprit food.

The recent SR and meta-analysis on FA-AIT (18) clearly demonstrated that FA-AIT is effective in reducing the likelihood of reacting to foods while receiving the therapy. In pediatric patients with FA to CM and peanut, data suggest that OIT is more effective than SLIT (45, 55). There is an increased risk of local (the most frequent) reactions with both OIT and SLIT but only OIT showed a significantly higher risk of systemic reactions. Due to the length of the protocol and safety issues, patients and their families must be extremely adherent, reliable and committed to the treatment. FA-AIT may improve QoL scores, particularly with regard to social limitations, accidental exposure and anxiety, although further studies are needed (5).

Many children with CM allergy or HE allergy develop tolerance spontaneously. For this reason, for many patients and families, allergen avoidance whilst awaiting spontaneous resolution may represent a better option than FA-AIT. Therefore, FA-AIT cannot be recommended as routine practice, but must be limited only to carefully selected patients managed in specialized clinical settings, by trained personnel (Boxes 9 & 10).

There are still many gaps that need to be addressed (Table 7). The duration of FA-AIT may be burdensome for patients and their families. After completion of therapy, patients frequently need to continue to consume the allergen to maintain tolerance. It may be easier to achieve post-discontinuation effectiveness (e.g. tolerance or sustained unresponsiveness) for allergens that are typically outgrown in childhood (e.g. CM and HE) compared to other allergens (such as peanut), where probably lifelong ingestion may be required after therapy. In addition, efficacy during the treatment with CM can be maintained with a twice-weekly regimen. We await maintenance follow-up studies to assess whether more flexible regimens are possible with other foods (69).

The quality of allergen preparations is critical for both diagnosis and treatment. Standardized allergen preparations of known potency and shelf-life should be used. Currently, the allergens containing food protein and those prepared by pharmaceutical companies or hospital pharmacies are not available as standardized products. The allergens in such products should be well characterized as it is known that different formulations of a product may have significant variations in allergen load. Both the bacteriological load and biological activity of these products are still undetermined. Therefore, the use of fresh material or native foods for FA-AIT is advisable to achieve the goal of desensitization. Different disciplinary and clinical backgrounds including medical care, patient groups, allergen manufacturers and regulators should be involved in the process of producing new data on standardized allergen preparations for the active treatment of FA.

Table 7 Gaps in the evidence for FA-AIT

Gaps in the evidence of FA AIT	Plan to address	Priority
Standardized products	Collaboration between clinical investigators, regulators.	High
Establish validated protocols with optimal dosing and duration of therapy	Analysis of existing data New observation and controlled trials Consensus discussion	High
Treatment of patient suffering from persistent allergies to multiple foods	Analysis of existing data New observation and controlled trials Consensus discussion	High
Definition of clinically relevant outcomes of effectiveness	Analysis of existing data New observation and controlled trials Consensus discussion with patients, clinicians and regulators Development and validation of relevant outcomes	High
Continued effectiveness after FA-AIT discontinuation	Analysis of existing data New observation and controlled trials Development and validation of relevant outcomes	High
Safety of FA-AIT during up-dosing and maintenance phases	Analysis of existing data Establish a standardized European registry of systemic adverse events New observation and controlled trials	High
Impact on QoL (patient-related outcomes)	Development and validation of relevant outcomes New observation and controlled trials	High
Cost-effectiveness	New observation and controlled trials	High
Advanced insight in the mechanisms of action	Collaborative research using biological samples (biobanks) of patients already treated. New observation and controlled trials	High
Identification markers of response	Analysis of existing data and biological samples New controlled trials	High
Identification the most suitable candidates (personalized care)	Analysis of existing data and biological samples New controlled trials	High
"Precision medicine" algorithms for patient tailored (individual) treatments	Analysis of existing data Consensus discussion	Medium
Standardized nomenclature according to clinical needs, newly developing treatments and mechanisms	Consensus discussion	Medium
Role of the different routes of administration	Randomised controlled trials	Medium
Effect of concomitant administration of anti-IgE on safety, efficacy and length of therapy	Analysis of existing data New controlled trials	Medium
Effect of concomitant administration of probiotics on safety, efficacy, and length of therapy	Controlled trials	Low

Novel therapeutic approaches are being developed to improve FA-AIT, most of them in pre-clinical or early clinical trials. In particular, co-administration of humanized monoclonal anti-IgE (omalizumab) seems to markedly reduce adverse reactions due to OIT compared to placebo (70-72). Furthermore, as bacteria are potent stimulants of Th1 immune responses, modified bacterial products are under investigation as adjuvants for FA-AIT (46).

Clinical studies carried out with FA-AIT have some limitations, a key one is the heterogeneity in protocols between centers. It is yet unclear which duration and frequency of ingestion of the allergic food(s) is required to maintain desensitization. Furthermore,

Box 11 Key messages

- FA- AIT should be considered for children from around 4 - 5 years of age with symptoms suggestive of persistent IgE-mediated food allergy to cow's milk (Grade A), hen's egg (Grade B) or peanut (Grade A) plus evidence of IgE sensitization to the triggering allergen.
- The majority of children allergic to milk and egg develops tolerance spontaneously. For these patients, waiting to see if they outgrow their allergies, before initiating FA- AIT, represents a sensible option.
- Among FA-AIT routes, OIT affords better efficacy than SLIT; however OIT is associated with higher frequency of adverse events compared with SLIT; adverse events may occur either during build - up phase and with maintenance phase but most of them are not severe.
- Currently, for OIT FA-AIT the use of fresh material or native foods is advisable.
- Key contraindications are: poor adherence; uncontrolled or severe asthma, active systemic autoimmune disorders; active malignant neoplasia; eosinophilic esophagitis. Careful review of benefits and risks are required with active severe atopic dermatitis, chronic urticaria, cardiovascular diseases, beta-blocker or ACE inhibitor therapy.
- FA-AIT should be administered by competent personnel with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.
- The initial FA-AIT dosage and each increased dosage during the build-up phase should be performed in clinical setting.

we are lacking criteria with which to evaluate and diagnose permanent tolerance. In AIT trials and in clinical practice, safety is of the paramount importance: strategies for improving safety during either up-dosing protocol or maintenance regimen need to be standardized. Managing these pivotal issues is mandatory for use of OIT/SLIT outside research settings or specialized clinical centers for FA-AIT.

FA-AIT should be utilized for patients with persistent food allergy (Box 11). In many patients, the downside of the adverse events associated with treatment is outweighed by both the achievement of desensitization and the reduced risk of a serious allergic reaction by accidental exposure at home or in the community. Considering the current evidence, there are still considerable knowledge gaps about how best to perform FA-AIT and more well-designed AIT trials are required.

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Contributorship

GB Pajno and M. Fernandez-Rivas jointly chaired the EAACI Guideline: AIT for IgE-mediated Food Allergy Taskforce. S Arasi, C Akdis, M Alvaro-Lozano, K Beyer, C Bindslev-Jensen, W Burks, M Ebisawa, P Eigenmann, EF Knol, KC Nadeau, A Muraro, LK Poulsen, R van Ree, G Roberts, A Santos, G du Toit, were members of the Taskforce involved in conceptualizing the guidelines, writing and critical revision of drafts. S Arasi, S Dhami, U Nurmatov and A Sheikh provided methodological support to the Taskforce. Y Boloh was the patients' group representative. I Agache, E Angier, S Halken, M Jutel, S Lau, O Pfaar, R van Ree, D Ryan, G Sturm, E-M Varga, R Gerth van Wijk were members of the EAACI Guidelines Steering Committee and contributed in conceptualizing the guidelines and critically reviewed draft versions. All the authors satisfied the international authorship criteria with further details in the online supplement. This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by A Muraro and coordinated by G Roberts.

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EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

ALLERGIC RHINOCONJUNCTIVITIS

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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) route 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 Allergen 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.

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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

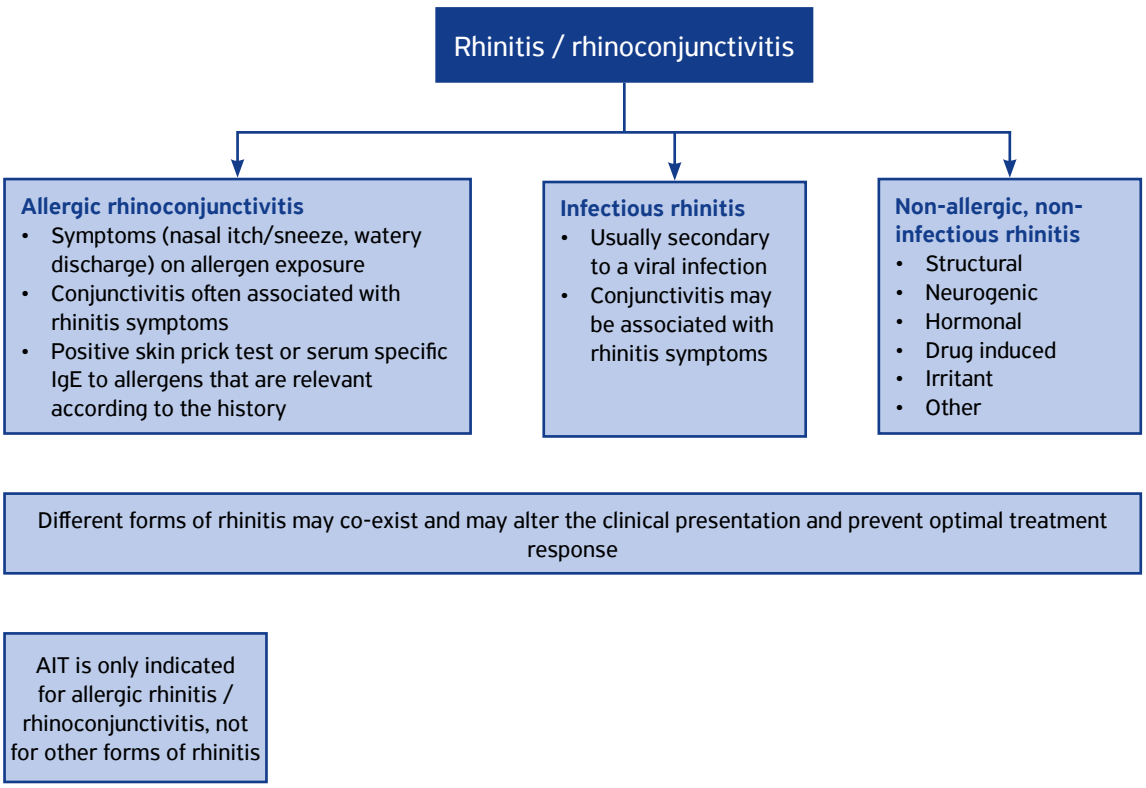

Figure 1 Differential diagnosis of allergic rhinoconjunctivitis. Adapted from Roberts *et al* 2013 (7). Local allergic rhinitis may be seen where there is only evidence of local nasal allergic sensitization (15, 16, 26). There are numerous other causes of non-allergic, non-infectious rhinitis, an example is non-allergic rhinitis with eosinophilia syndrome (NARES). 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.

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 Allergen 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.

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.

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.

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.

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) (8, 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 solution 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

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.

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.

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

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), Pfaar 2014 (11)	

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

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; only standardized AIT products with evidence of efficacy in the clinical documentation should be 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, Grade 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).

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

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 (60-62). 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 (69-72). 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. † Recommendation for children downgraded from B to C due to lack of exclusive pediatric data.	Dhami 2017 (14) SR, e.g. Adult: Dokic 2005 (67), Ewan 1988 (68), Varney 2003 (66)

* 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. The SmPC should also be checked for for product specific recommendations.

Table 3 Continued

Recommendation	Adults		Children and adolescents		Strength of recommendation	Other considerations	Key references
	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation			
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, 69-73, 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 (86-89) 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).

* 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. The SmPC should also be checked for for product specific recommendations.

Table 3 Continued

Recommendation	Adults		Children and adolescents		Strength of recommendation	Other considerations	Key references
	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation			
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 (97-99, 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 just one high risk of bias RCT so only grade C recommendation (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 (50-54) 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)

* 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. The SmPC should also be checked for for product specific recommendations.

Table 3 Continued

Recommendation	Adults		Children and adolescents		Strength of recommendation	Other considerations	Key references
	Evidence level	Grade of recommendation	Evidence level	Grade of recommendation			
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.

* 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. The SmPC should also be checked for for product specific recommendations.

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 tablets 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 (50-55).

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

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) and one with tree pollen (224). 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

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

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 three low risk of bias studies (113, 114, 172). Weak recommendation for children (130).	Consistent randomized controlled data; only one ragweed pollen study, others grass and tree pollen. Only one uncontrolled before and after study pediatric study (130).	Adult: Drachenberg 2001 (113), Drachenberg 2002 (224), DuBuske 2011 (114), Patel 2014 (172) 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)

* 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.

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).

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 (134-136) 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 (52-54) 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 (132), 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;

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

-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 orphan allergens where such studies are uneconomic and have to be regulated as named patient products (47).

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 (25-31).

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, 152-155), 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 demonstrated to be effective in the short term in mixed adult/adolescent 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 (163-169). 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 (163-165, 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). 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.

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 (53) 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).

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, 180-182). 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

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 90-92, 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)

Table 6 Continued

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
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)

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

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	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)

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, studies indicate that modified allergen extracts are associated with less adverse effects (189-192). 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 (193-195). 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 Tables 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 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, 197-199). 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)

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

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	Pfaar (11)
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)

Table 8 Continued

Recommendation	Evidence level	Grade of recommendation	Strength of recommendation	Contextual comments	Key references
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.	IV	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

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% (202-206). 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 (209-212).

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 (213-219). 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).

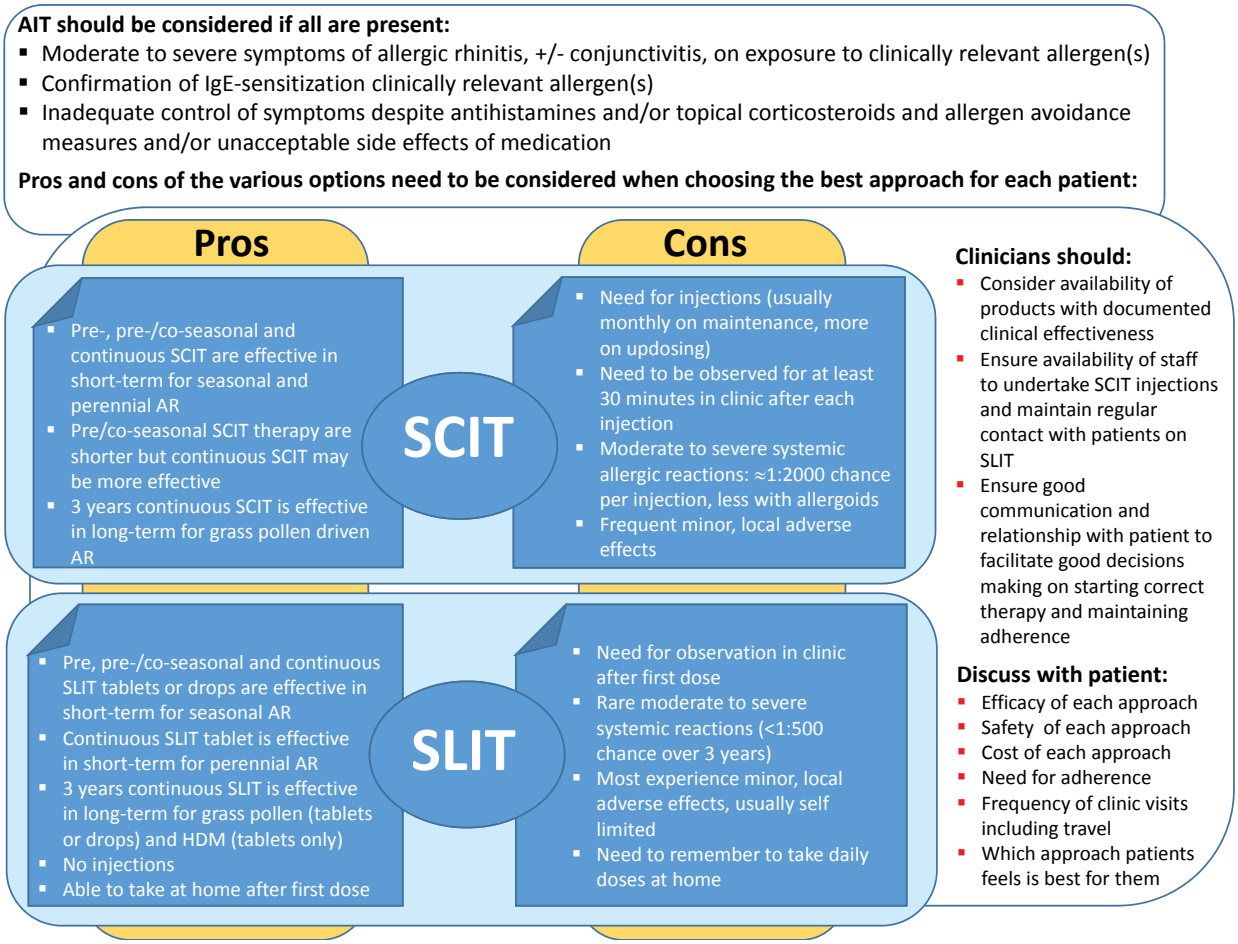

Figure 2 Schematic approach to deciding which approach to AIT is best to use in individual patients. For details to specific recommendations, see table 3. For details about local and systematic adverse reactions, see adverse event section above.

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 the patient's specific presentation, 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 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 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

Box 5 Continued

- 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)

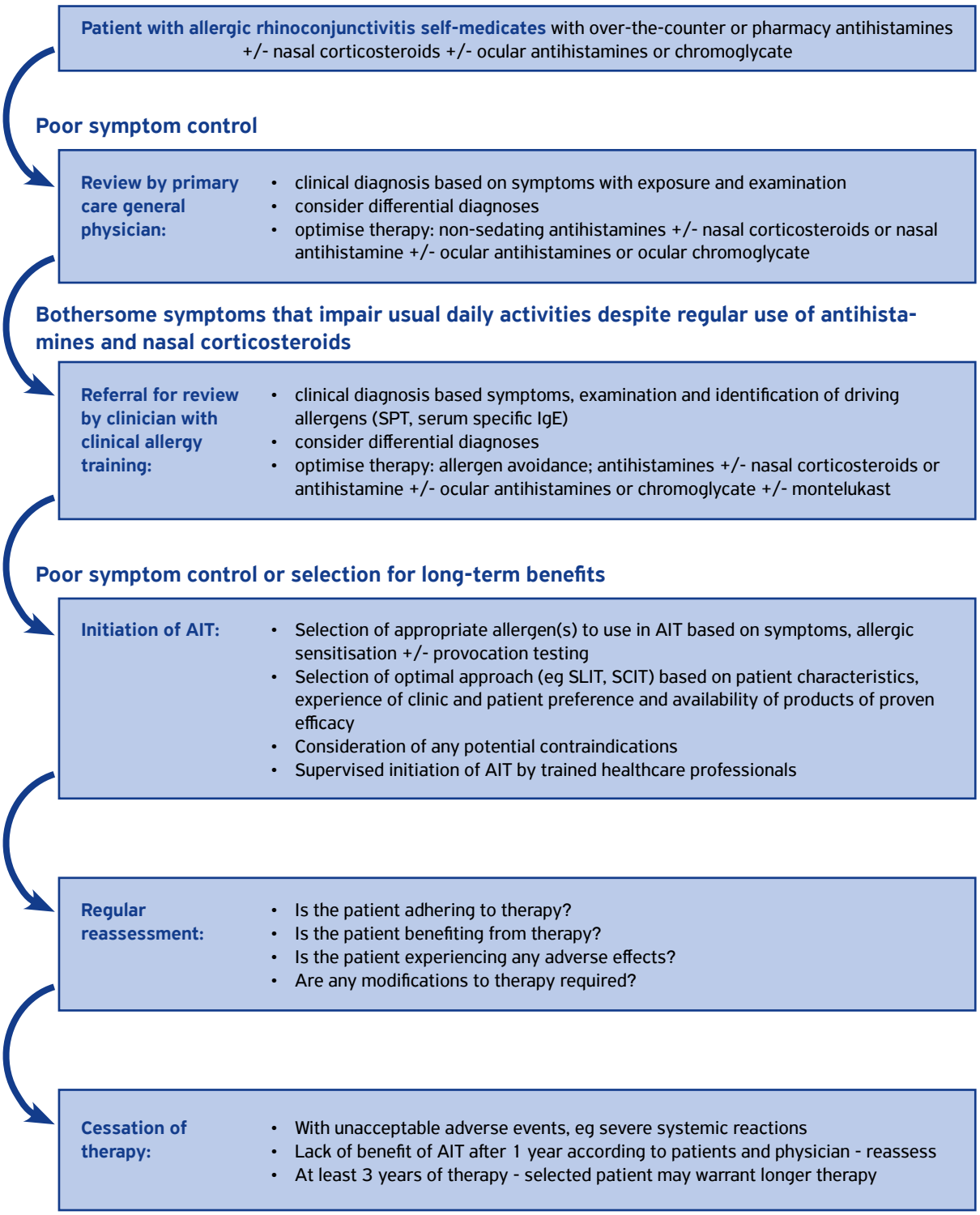

Figure 3 Approach to using AIT for allergic rhinoconjunctivitis. Schematic illustration of the approach to using AIT for AR starting with self-medication and management in primary care moving to assessment by a clinician trained in clinical allergy for consideration and initiation of AIT in suitable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

Table 9 Continued

Recommendation areas	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
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

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

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 local and 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

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.

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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G Roberts and O Pfaar jointly chaired the EAACI Guideline: AIT for rhinoconjunctivitis Taskforce; together with A Muraro and A Sheikh, they conceptualized the manuscript. CA Akdis, IJ Ansotegui, SR Durham, R Gerth van Wijk, S Halken, D Larenas-Linnemann, R Pawankar, C Pitsios, A Sheikh and M Worm all initially drafted sections of the guideline. S Arasi, M Calderon, C Cingi, S Dhami, J-L Fauquert, E Hamelmann, P Hellings, L Jacobsen, EF Knol, SY Lin, P Maggina, R Mösges, JNG Oude Elberink, G Pajno, EA Pastorello, M Penagos, G Rotiroti, CB Schmidt-Weber, F Timmermans, O Tsilochristou, E-M Varga, J Wilkinson, A Williams and L Zhang as members of the Taskforce plus I Agache, E Angier, M Fernandez-Rivas, M Jutel, S Lau, R van Ree, D Ryan and GJ Sturm as chairs of the other AIT Guidelines were all involved in conceptualizing the guidelines and critically reviewed guideline drafts. S Dhami and S Arasi also provided methodological support to the Taskforce. F Timmermans was the patient group representative. All the authors satisfied the international authorship criteria (further details in online supplement Table S4). This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro and coordinated by Graham Roberts.

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

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5

CHALLENGES IN THE IMPLEMENTATION OF THE EAACI AIT GUIDELINES

A SITUATIONAL ANALYSIS OF CURRENT PROVISION OF ALLERGEN IMMUNOTHERAPY

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***Purpose**: The European Academy of Allergy and Clinical Immunology (EAACI) has produced Guidelines on Allergen Immunotherapy (AIT). We sought to gauge the preparedness of primary care to participate in the delivery of AIT in Europe.*

***Methods**: We undertook a mixed-methods, situational analysis. This involved a purposeful literature search, and two surveys: one to primary care clinicians and the other to a wider group of stakeholders across Europe.*

***Results**: The 10 papers identified all pointed out gaps or deficiencies in allergy care provision in primary care. The surveys also highlighted similar concerns, particularly in relation to concerns about lack of knowledge, skills, infrastructural weaknesses, reimbursement policies and communication with specialists as barriers to evidence-based care. Almost all countries (92%) reported the availability of AIT. In spite of that, only 28% and 44% of the countries reported the availability of guidelines for primary care physicians and specialists, respectively. Agreed pathways between specialists and primary care physicians were reported as existing in 32-48% of countries. Reimbursement appeared to be an important barrier as AIT was only fully reimbursed in 32% of countries. Additionally, 44% of respondents considered accessibility to AIT and 36% stating patient costs were barriers.*

***Conclusions**: Successful working with primary care providers is essential to scaling-up AIT provision in Europe, but to achieve this the identified barriers must be overcome. Development of primary care interpretation of guidelines to aid patient selection, establishment of disease management pathways and collaboration with specialist groups are required as a matter of urgency.*

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INTRODUCTION

The march of allergy proceeds relentlessly with up to a third of the general population and half of young people suffering from some manifestation of the disease at some stage in their lives (1). The most prevalent of these conditions are atopic eczema/dermatitis, asthma and allergic rhinitis (2-5). These result in a significant impact at the personal level because of impaired quality of life, a significant impact on family and friends, on the health care system because of increased medical costs and at a societal level because of lost productivity through presenteeism and absenteeism (6, 7). Currently, allergy is often not well recognized and is as a result poorly managed (8). Patients seek assistance from various sources, often involving considerable expense and inappropriate treatment (9-11). Primary care professionals (hereafter referred to as PCPs, these including general practitioners, nurses and pediatricians, in some countries (12), are poorly equipped to deal with the management of allergy, particularly the more complex issues associated with AIT, due to deficiencies in undergraduate and postgraduate training (13). Previous surveys have revealed a low level of PCPs' self-estimated knowledge or confidence in delivering AIT (12). To date, there is no care system which delivers comprehensive allergy care in a systematic fashion (14).

In most cases, the management of allergy comprises allergen avoidance (15) and symptom alleviation by pharmacotherapy. This contrasts with allergen immunotherapy (AIT) which targets the immunological basis of the disease. It can be used as complementary to or in some cases as an alternative to pharmacotherapy in patients for whom pharmacotherapy is not sufficiently effective or for patients who prefer a disease-modifying treatment over chronic, often life-long use of symptom relieving drugs (16). AIT involves the administration of allergen to deviate the immune response from immediate hypersensitivity towards tolerance (17). Typically, either injection (subcutaneous AIT, SCIT), sublingual AIT (SLIT) or oral AIT (OIT) are used (18).

The European Academy of Allergy and Clinical Immunology (EAACI) has embarked on a process of formulating comprehensive guidelines for AIT supported by underpinning systematic reviews on the effectiveness, cost-effectiveness and safety of AIT for allergic rhinitis (19), asthma (20, 21), venom allergy (22), food allergy (23), and the prevention of allergy and allergic disorders (24). The EAACI Guidelines on AIT should help to identify patients who are most likely to benefit from this potentially disease-modifying treatment while also highlighting the current gaps in knowledge and service provision.

For comprehensive AIT services to be implemented, a system-wide approach is needed, commencing and ultimately culminating in primary care. This requires an understanding of primary care (25) taking into account the significant regional and national variation in configuration of health services across Europe (26). AIT needs to be seen in the wider context of overall provision of care for allergic patients, which itself needs to be contextualized within overall healthcare provision.

We have performed a mixed-method, situational analysis of current provision of AIT, comprising of a literature review and surveys, in primary care across Europe. This was done as part of the EAACI AIT Guidelines initiative and aimed to develop a summary of the current deficits in the service delivery of allergy care and AIT across the whole health system. We collected survey data from: (i) GPs; and (ii) allergy stakeholders, including patient and specialist organizations. We focused on asthma, allergic rhinitis and venom allergy; we excluded AIT for food allergy and allergy prevention as these are developing areas. Our aim was to summarize the different perspectives on the current capabilities of primary care in the provision of allergy management, in particular AIT. It will build on our previous EAACI position paper (27) and work performed in the UK (28).

METHODS

We developed a mixed-methods approach to assess the current capabilities of AIT provision in primary care, and used our findings to draw up a list of recommendations.

Literature search

To inform our paper, we (DR, EA) performed a focused PubMed literature search (see online supplement for search strategy). This was supplemented by a (UK) Royal College of General Practitioners Discovery and Medline search. The abstracts were assessed by DR

and EA. Papers not written in English and irrelevant papers were rejected. The remaining papers were read in full. Due to the diversity of papers with few recurring themes, a narrative description of the literature search was undertaken.

Situational analysis

We undertook a situational assessment using an online questionnaire (see online supplement 1) to understand the perspectives of stakeholders: (1) General Practitioners (GPs), and (2) stakeholders (specialist allergy societies and patient organizations) in different European countries. We developed a draft survey, which was piloted and, where necessary, revised. There were 12 questions for GPs and 10 questions for stakeholders (see online supplement 2). A combination of closed and open-ended questions was chosen to elicit additional information regarding perspectives on strategies to improve uptake of AIT in primary care. The survey was administered through the web based SurveyXact system. (SurveyXact, Aarhus, Denmark). Invitations to participate in the survey were distributed to European GPs via the International Primary Care Respiratory Group (IPCRG) and World Organization of National Colleges and Associations, Europe (WONCA); to European specialist allergy societies using a list supplied by EAACI; and to European allergy patient support group via the EAACI patient representative contacts list. Data collection took place between December 2016 and February 2017. Two email reminders were sent. Data were analyzed using descriptive statistics. Answers to open-ended questions were coded using content analysis and illustrative quotes were selected (please see supplement 3 in the online materials). We recorded positive answers thereby focusing on presence of services, education, training, reimbursement and barriers. We pooled negative and missing answers as the questionnaire did not always permit us to make a clear distinction between both categories. We have not presented the responses from non-European sources.

RESULTS

Literature search

A total of 59 references were obtained from the combined searches. Of these, 36 were excluded as they provided results of clinical trials, were guidelines or cost-effectiveness analyses. A further 12 papers were duplicates. Eleven papers were thus included; these are summarized briefly below.

One paper addressed care delivery in a generic fashion. It described critical factors for achieving good care, using efficient primary care systems to translate service delivery into high quality outcomes. The authors described a combination of access, continuity and comprehensiveness (29). A further paper addressed the variability in allergy care provision in primary care (30). Two papers focused on the use of specific-IgE in informing patient management as part of a strategy to improve care (31, 32).

Five papers studied perception, knowledge or practice of AIT across various specialist groups, including primary care, pediatricians and ear, nose and throat (ENT) specialists, delivering services in primary care across a large geographical spread (33-37). These papers also suggested that SCIT was more likely to be prescribed in specialist care and SLIT more commonly prescribed in primary care.

One paper provided an historical description of allergy and how care had progressed over the last 50 years. It highlighted that much still needed to be done to understand the predisposition to atopic disease and identifying the environmental cofactors involved in the 'allergic epidemic' and

therefore targets for effective primary prevention (38). The final paper identified common questions in allergy practice gathered from delegates attending a conference on allergy care (39).

In summary, this literature review described what was already known, namely that there are major gaps in knowledge and skills in the provision of allergy care, and that these are widespread and not limited to primary care. The literature review also laid bare the paucity of relevant research in primary care settings. The details of the search are made available in supplement 1 in the online materials.

Situational analysis

Primary care clinician survey

The GP survey yielded evaluable responses from 132 GPs of which 70 (52%) were from Europe (i.e. Greece, Ireland, Macedonia, Norway, Poland, Portugal Romania Turkey, UK). The majority of these responses were from the UK and Romania (53 respondents). The

paucity of responses coupled with poor geographical spread, led us to create a narrative summary of our findings (supplement 3, online materials).

Ten percent reported awareness of any national primary care guidelines; 13% stated that AIT was part of general practice training and 17% said that formal AIT training for GPs was available. 38% stated that GPs were aware that AIT could be administered by subcutaneous and sublingual routes. However, 55% felt that GPs were competent in taking an allergy history.

The greatest barriers perceived for GPs working with AIT were a lack of knowledge and infrastructure (both 79%), concerns about reimbursement policies (68%), time pressures (67%) and suboptimal communication with specialists (55%). Most (67%) respondents stated they were open to collaboration with allergy specialists. These data strongly resonated with other published data (8, 13).

Stakeholder survey

The stakeholder survey was sent to 173 specialist allergy societies and allergy patient support groups, with 50 responses (29%) covering 25 European countries. Where more than one set of data was received from one country, the most positive result from that country was included. The rationale for this was to present the best-case scenario. Table I gives the positive replies from the 25 European countries to a selected series of questions. From the 36 responses covering the European countries, 18 came from allergy societies, three from patient groups and 15 were from mixed origin (GPs, individuals, GP societies or not stated).

It would seem that AIT is available in most European countries with the exception of Bosnia and Herzegovina, and Malta. The most common location for administration was in specialist care (84%), but in some countries administration took place in primary care (20%) or shared care (16%) settings. In 56% of countries did there appear to be any national policy on AIT. The absence of a national policy did not preclude some form of reimbursement, but countries without a national policy were less likely to attract any form of reimbursement.

Comparing answers given to the number of question items generated, some countries clearly had a more comprehensive approach to allergy care (i.e. Germany, Denmark and the UK) whereas other countries (Malta, Portugal and Ireland appeared to have given less consideration to AIT (Table 1).

With regards to barriers to delivering care as assessed by the stakeholders, accessibility (44%) and costs to the patient (including time missed from work and travel costs, 36%) were viewed as the greatest obstacles whereas safety fears (12%) were very low on the list (Table 2).

DISCUSSION

The literature review and PCP and stakeholder surveys revealed knowledge and skills gaps coupled with non-existent or poorly formulated pathways of training and care. We found that there were more specialist guidelines than primary care ones and more accreditation pathways for specialists than PCPs. Given that specialists would be training primary care colleagues and remain a vital resource, it is important that pathways of care and shared care models are developed. It is to be noted that collaboration between PCPs and specialists was judged to a critical success factor in the Finnish 10 Year Allergy Programme (40). In reality, patients will present anywhere along a pathway of care. Most AIT is delivered by specialists (41) but this might alter with the availability of SLIT which is easier to deliver in the community. Adherence with AIT may be facilitated by the involvement of PCPs and pharmacists and may result in cost savings, with specific reference to minimizing time lost from work by patients (42). Combining shared care pathways with the development of relevant competencies and capacities might increase accessibility to AIT. Tools such as pocket guidelines may also facilitate service delivery (43).

There are three key areas which need to be addressed. The first is the development of education and training of PCPs. The second key area is diagnosis and stratification of patients into those who can be managed exclusively in primary care and those with more problematic disease who need referral to specialist care. The final area is service delivery and the monitoring of treatment effectiveness at the patient level.

Education and training

Our survey and other published data12 suggest that PCPs are not trained to adequately manage allergy

Table 1 Survey. Current situation

		AL	BA	BG	CH	CY	CZ	DE	DK	EE	ES	A	HR	IE	IT	LV	MT	NL	PL	PO	RO	RS	SE	SL	TR	UK	%
Availability of Immunotherapy		x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	92
National Policy					x		x	x	x		x	x	x					x	x	x	x		x		x	x	56
National Guidelines	Primary Care		x		x						x	x						x							x	x	28
	Specialist Care	x			x		x	x	x		x	x									x	x	x			x	44
Is there an accreditation pathway for Specialists		x	x	x				x		x			x								x	x	x			x	40
Is there an accreditation pathway for Primary Care								x					x								x		x				16
Agreed Pathway	Shared Care			x	x		x	x	x	x	x	x									x		x			x	44
	Referral Criteria	x			x			x	x		x	x						x		x	x	x	x			x	48
	Follow up monitoring			x	x			x	x			x	x					x		x	x	x	x			x	48
	Agreed care between professionals			x	x	x	x			x						x							x			x	32
Training Pathways							x	x	x	x	x	x	x								x		x			x	40
The location of administration of SCIT	Specialist	x	x	x	x	x	x	x	x	x	x		x	x		x		x		x	x	x	x	x	x	x	84
	Primary Care				x			x	x									x		x							20
	Shared Care							x	x				x											x			16
Who makes the decision to discontinue treatment?	Specialist	x	x	x		x	x	x	x	x	x	x	x	x		x		x		x	x	x	x	x	x	x	84
	Patient			x		x		x	x	x	x	x															28
	Primary Care				x				x												x						12
Is there reimbursement of the product?	Any			x	x		x	x	x	x	x	x	x									x	x	x	x	x	56
	Full reimbursement				x			x		x			x									x		x	x	x	32
	Partial reimbursement			x			x		x		x	x											x				24
Is there reimbursement for administration of AIT?						x	x	x	x	x			x			x				x	x	x		x	x		48

X represent a positive response. %: percentage of positive responses. Abbreviations: AL Albania, BA Bosnia and Herzegovina, BG Bulgaria, CH Switzerland, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, HR Croatia, IE Ireland, IT Italy, LV Latvia, MT Malta, NL Netherlands, PL Poland, PO Portugal, RO Romania, RS Serbia, SL Slovenia, SE Sweden, TR Turkey, UK United Kingdom

Table 2 Survey. Barriers

	AL	BA	BG	CH	CY	CZ	DE	DK	EE	E S	FI	HR	IE	IT	LV	MT	NL	PL	PD	RD	RS	SE	SL	TR	UK	%
Fees for time			x				x								x					x						16
Reimursement barriers to patients travel costs			x				x													x					x	16
Time off work for patients			x			x	x	x												x					x	24
Accessibility			x		x			x		x			x						x	x		x	x	x	x	44
Beliefs about efficacy		x				x	x	x													x			x	x	28
Beliefs about sa fety				x			x	x																		12
Costs to patients travel time and time off work etc.			x		x		x	x		x			x						x	x					x	36

patients. Allergy hardly features in most undergraduate medical curricula (13). There is little allergy training in primary care postgraduate specialist training (41). There has though been assessment of training needs (44) and identification of core competencies required (45) which should facilitate an education process. We suggest that training in allergy and AIT should be included in all undergraduate medical curricula. Furthermore, we suggest that sufficient training in allergy and AIT is included in primary care postgraduate medical specialist training to allow the development of core competencies in the diagnosis and management of common allergic presentations. This would include the use and interpretation of tests used to confirm the presence of sensitization and whether or not this was relevant to the patients' clinical state (46).

Dialogue between specialist and PCPs should help to improve knowledge and treatment pathways at a local level. The issue of reimbursement of practitioners and patients need to be recognized as these issues may affect the accessibility to AIT, including those related to travel and missing time from work.

Diagnosis and stratification of patients

Prior to any other intervention, a secure diagnosis needs to be made. Further, to optimize allergy management patients need to be stratified, probably by disease severity, into those who can be managed exclusively in primary care and those who need referral into specialist care. Characteristically, patients attending their GP or pharmacist suffer from as yet undiagnosed problems. A thorough history leads to a diagnosis or differential diagnosis. The history should guide the request for investigations (47). To firmly establish a diagnosis, a physical examination, appropriate to the presenting complaint and investigation(s) is likely to be required, although for some allergic disorders there may be no relevant physical finding.

According to our survey (data not shown), many GPs across Europe have access to serum specific-IgE testing; in contrast, very few have access to skin prick testing (48). Small studies confirm that such testing improves the ability to make a diagnosis of allergic and, importantly, of non-allergic diseases (31, 49). There is a clear rationale for using specific-IgE tests in primary care (31, 50). Further work needs to be undertaken around the place and utility of specific-IgE

in primary care and how best to educate practitioners in the interpretation of results in the clinical context (46). This has been identified as a pressing research need by the IPCRG (51).

Service delivery and monitoring

Developing vertically integrated care pathways might be one way of developing a process for service delivery (52). Such a pathway could include community pharmacists to aid in identification of patients; they may also be able to play a role in promoting adherence. The patient journey often commences with the community pharmacist, providing a rationale for including them in any proposed care (53). A further option to be considered, particularly where specialists are scarce, is the development of a network of GPs with specialist interests (GPwSIs) whose remit would include service provision and local educational initiatives working in close collaboration with specialist mentors (54, 55). This would also present an opportunity to develop a network of care to establish clear communication and shared decision making.

Strengths and limitations of the surveys

An exploratory analysis is presented, the first of its kind. The study focuses on the views of primary care clinicians and relevant stakeholders concerning allergy care and AIT and on barriers in this field. The main limitation of this study is the low response rate, particularly in the GP survey. It was difficult to identify appropriate respondents for each country. A substantial number of stakeholder responses came neither from patient groups nor from allergy societies, thus responses may not be completely representative of the situation in specific countries although together they provide a reasonable description of the reality across Europe. Finally, although the surveys give a good impression of available services and barriers for GPs in Europe, pooling negative and missing responses and classifying the latter as negative, limits the accuracy of the outcome.

Looking ahead

Based on our findings, we have made some recommendations (see Table III). Although our findings seem somewhat discouraging, there is room for optimism. Clinical trials in AIT have been successfully carried out in primary care, demonstrating proof of concept (56, 57). It is of further interest that in a real-life study of AIT adherence carried out in the Netherlands, that adherence and persistence was higher amongst patients of GPs than those of allergists or other specialists (58). The development of pathways of care should facilitate the delivery of high quality effective services and improve patient selection. These will vary from health system to health system depending on existing configuration, but are likely to have similar themes. Such pathways would aim to establish a register of those who had received AIT to facilitate identification of type and severity of side-effects as well as permit the assessment of effectiveness of AIT in different patient types which would ultimately aid in patient selection. This would be facilitated by the development of a template which would permit uniformity of coding and clinical parameters entered. This should incorporate a mechanism whereby primary care can report safety issues and adverse effects via a web based registry system. In addition, network of care with specialists and primary care professionals needs to be developed to establish clear communication and shared decision making. If, as is happening in some countries, PCPs commence immunotherapy without specialist referral, they should ensure that the products used have proven safety and efficacy.

CONCLUSIONS

We have undertaken this work to explore how the EAACI Guidelines on Allergen Immunotherapy for the prevention and management of allergic conditions might be implemented in primary care. The findings from this mixed-methods evaluation strongly suggest that European primary care providers are sub-optimally positioned to identify and manage those who are most likely to benefit from AIT. We have identified a number of important barriers - including educational and training, infrastructural and financial - that need to be overcome in order to scale-up AIT delivery across Europe. In order to encourage the successful adoption of AIT as a mainstream therapy, there needs to be wide spread publicity concerning its effectiveness. Health care provision has great heterogeneity across Europe: the generic recommendations made in this paper will therefore need to be interpreted and tailored in line with local health care policies and priorities. Commissioners of health services and politicians need to be made aware

Table 3 Recommendations, barriers and facilitators

Key Recomendations	Barriers	Facilitators	Key References
Teaching in allergy and AIT should be included in all undergraduate medical curricula.	Low priority on educational agenda. Inadequate skills and knowledge in the medical workforce. Inadequate representation of Allergy in general Undergraduate or Postgraduate curricula.	Allergy campaigns to raise awareness to governments and patients. Workforce remodeling with collaborative relationships with specialists. Clinical system wide leadership with investment in education and training.	Potter, 2009 (59), Campbell 2015 (38), Shehata 2006 (13)
There should be sufficient training in allergy and AIT included in primary care postgraduate medical specialist training to allow the development of core competencies in the diagnosis and management of common allergic presentations.	Low priority on political agenda with lack of treatment prioritization. Inadequate health economics data and population based outcomes. Inadequate representation of Allergy in general Undergraduate or Postgraduate curricula.	Workforce remodeling with collaborative relationships with specialists. Clinical system wide leadership with investment in education and training.	Campbell 2015 (38), Tan 2014 (39), Eigenmann 2013 (60), Wallengren 2011 (45)
Primary care workers should have access to specific-IgE testing and, if required, have assistance in interpretation of results.	Inadequate skills and knowledge in the medical workforce. Poor understanding of diagnostic tests in primary care used in the assessment and diagnosis of allergy. Lack of clear care pathways and referral criteria. Heterogeneous reimbursement policies for investigations and their administration. Clinical system wide leadership with investment in education and training.	System wide health care delivery mirroring patient journey from pharmacists through to specialists. Harmonization of reimbursement policies.	Pelone 2013 (29), Hansen 2010 (30), Dranitsaris 2014 (42) Ellis 2012 (44), Bousquet 2015 (61)
There is a need to develop and implement vertically integrated care pathways to improve delivery of allergy care and AIT. This could include clinical decision support systems. It may involve the development of intermediate level GPs with a specialist interest in allergy.	Lack of clear care pathways and referral criteria. Inadequate health economics data and population based outcomes. Heterogeneous reimbursement policies for products and their administration.	Allergy campaign62s to raise awareness to governments and patients. System wide health care delivery mirroring patient journey from pharmacists through to specialists. Practice nurses involved in delivery of care, under supervision, allowing flexibility of approach delivering care closer to home.	Diwakar 2017 (14), Smith 2009 (47), Fromer 2014 (50), Bousquet 2016 (63), Yao 2015 (62), Flokstra - de Blok 2017 (64), Ryan 2005 (54)
Develop specific recommendations to aid identification, stratification and referral criteria to enable effective referrals from primary or specialist care.	Low priority on political agenda with lack of treatment prioritization. Inadequate skills and knowledge in the medical workforce. Lack of clear care pathways and referral criteria.	Workforce remodeling with collaborative relationships with specialists.	Haahtela 2008 (40), Ryan 2017 (12)

of potential benefits and ultimately cost savings in line with the triple aim of health care: better patient experience, improving the health of populations and reducing the cost of health care.

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6

CHALLENGES IN THE IMPLEMENTATION OF EAACI GUIDELINES ON ALLERGEN IMMUNOTHERAPY

A GLOBAL PERSPECTIVE ON THE REGULATION OF ALLERGEN PRODUCTS

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Regulatory approaches for allergen immunotherapy (AIT) products and the availability of high quality AIT products are inherently linked to each other. While allergen products are available in many countries across the globe, their regulation is very heterogeneous. First, we describe the regulatory systems applicable for AIT products in the European Union (EU) and in the United States (US). For Europe, a depiction of the different types of relevant procedures, as well as the committees involved is provided and the fundamental role of national agencies of the EU member states in this complex and unique network is highlighted. Furthermore, the regulatory agencies from Australia, Canada, Japan, Russia, and Switzerland provided information on the system implemented in their countries for the regulation of allergen products. While AIT products are commonly classified as biological medicinal products, they are made available by varying types of procedures, most commonly by either obtaining a marketing authorisation or by being distributed as named patient products. Exemptions from marketing authorisations in exceptional cases, as well as import of allergen products from other countries, are additional tools applied by countries to ensure availability of needed AIT products. Several challenges for AIT products are apparent from this analysis and will require further consideration.

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INTRODUCTION

The availability of medicinal products to provide a reliable diagnosis of clinical allergy and effective treatment(s) is of critical importance for patients with suspected or proven allergy. Products for allergen immunotherapy (AIT) have been approved by national competent authorities in different regions of the world. However, the regulatory landscape governing the approval of these products is enormously heterogeneous - both within the European Union (EU) and even more so when looking globally - thereby rendering it extremely complicated and challenging to develop a harmonized, international approach to regulating these products.

Pharmaceutical companies are increasingly focused on global strategies to develop and market their products. It is therefore very important to understand the current regulatory situation for allergen products from an international perspective, as this will have a direct impact on the availability of these medicinal products to patients throughout the world. Certain regulatory patterns can be observed on a global scale. For example, whereas AIT was previously mainly used and placed on the market on the basis of expert opinions with limited regulatory oversight, the requirements for high quality clinical data for granting market access have greatly increased during the last 20 years. In the EU, legislation applicable for new and existing products (1, 2) has been in force since 1989 demanding that allergen products are registered as medicinal products with corresponding requirements for clinical data. The development of the guidelines on Good Clinical Practice (GCP) in the conduct of clinical trials has been the main driving force for the specific requirements in the legislation. In the EU, the Clinical Trials Directive (3) implemented GCP as a mandatory requirement for the conduct of clinical trials. Since 2004, EU member states have needed to apply the provisions on GCP established by this Directive. For AIT products, this has resulted in the performance of numerous state-of-the-art, randomized, double-blind, placebo-controlled trials in recent years as documented by the US and European databases on clinical trials (4, 5). However, due to the seasonal nature of many allergic diseases and the protracted immunological processes induced by AIT, clinical trials can be very time consuming and costly, particularly if a disease modifying effect is the intended indication as defined by the respective European Medicines Agency (EMA) Guideline (6). In this systematic analysis, we provide an overview on how products for the in vivo diagnosis of allergies, as well as for AIT, are regulated in different regions of the world. Approval of allergen products involves large and complex regulatory networks directing the independent assessment of allergen therapeutics and providing guidance on how to determine whether or not a specific product shows a favorable risk-benefit profile. Moreover the activities by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) displayed formidable achievements in the last decades. While they already led to the harmonization of various aspects related to medicinal products development and authorisation (e.g. Guidelines on quality and (non-)clinical development as well as regulatory guidance on a common format for the submission of marketing authorisation dossiers), other aspects of regulatory procedures remain heterogeneous. Activities and decisions of the responsible regulatory agencies directly influence the availability of products. This analysis has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Regulatory Aspects of Allergen Immunotherapy (AIT) and is part of the EAACI AIT Guidelines. The primary audiences are expected to be clinical allergologists and regulators, but the document is also likely to be of relevance to all other healthcare professionals dealing with AIT. As the focus of this EAACI systematic analysis is to describe the regulatory situation and heterogeneity observed, it is not intended to advise on solutions to the situation described and is not to be seen as a regulatory guidance document.

INTERNATIONAL AND NATIONAL REGULATION OF ALLERGEN PRODUCTS

The regulatory system in the European Union

In the EU, allergen products are defined as medicinal products according to Directive 2001/83/EC (7). As stated in this Directive, therapeutic allergen preparations are considered medicinal products as

they are substances or combination of substances presented as having properties for treating or preventing disease in human beings. Furthermore, any substance or combination of substances that may be used in or administered to human beings to obtain a medical diagnosis are also considered medicinal products. This includes in vivo diagnostic test allergens, including skin prick tests, provocation tests, intradermal tests and epicutaneous tests. Where such products are prepared industrially or manufactured by a method involving an industrial process, these medicinal products fall within the scope of the above mentioned Directive. Generally, these products are required to obtain a marketing authorization in order to be placed on the market. Some exemptions apply, which will be discussed below.

The EU has a unique combination of national regulatory agencies that work together in a network to regulate market access of medicinal products. Each member state of the EU holds its own national competent authority. The EMA (8), is an agency that is responsible for the coordination of several types of procedures related to the marketing authorization of medicinal products, including the centralized procedure. Furthermore, EMA hosts a number of independent scientific committees that are deeply involved in the assessment of specific aspects or types of medicinal products as well as the development of scientific guidelines that are then used for a standardized assessment of the medicinal products.

Procedures and assessment of marketing authorization applications

It should be noted that the scientific assessment of all marketing authorizations, post-marketing authorization procedures (i.e. variations to a marketing authorization) as well as the development of the guidance and opinions in scientific advice procedures is actually performed by the national competent authorities. To this end, for centralized procedures, there is a call for countries that are willing to act as Rapporteur (or Co-Rapporteur) in a procedure. The scientific assessment itself occurs in the national competent authorities of those countries that are acting as Rapporteur or Co-Rapporteur; assessment reports are subsequently presented and discussed within the EMA's respective committees where a collective opinion is adopted by all members.

In the EU, different types of procedures may apply in order to obtain a marketing authorization (see Figure 1A and 1B). For certain products, depending on manufacturing and/or medical indication, the **centralized procedure** is mandatory for marketing authorization (Table 1). This type of procedure is therefore applied when marketing authorization is sought for recombinant allergen products. However, in the EU, there are currently only marketing authorizations for products derived from natural sources and neither products for the diagnosis of allergens nor products for AIT have yet been authorized by the centralized procedure. Most allergen products, for which marketing authorizations exist within the EU, have been authorized via a **National Authorisation Procedure**. In such a case, a pharmaceutical company applies for marketing authorization in one member state only. Consequently, after finalization of the procedure, the product is only authorized in the respective country. In contrast to the agreed timelines for multinational procedures (as described below), the national procedures are executed under national timelines and these vary among countries. If the company then decides to

Table 1 Medicinal products to be authorized by the centralized procedure according to (14)

Human medicines containing a new active substance to treat
• acquired immune deficiency syndrome (AIDS)
• cancer
• diabetes
• neurogenerative diseases
• auto-immune diseases and other immune dysfunctions
• viral diseases
Medicines derived from biotechnology processes
Advanced-therapy medicines
Orphan medicines
Optional for other medicines
• containing new active substances
• that are a significant therapeutic, scientific or technical innovation
• whose authorisation would be in the interest of public health at EU level

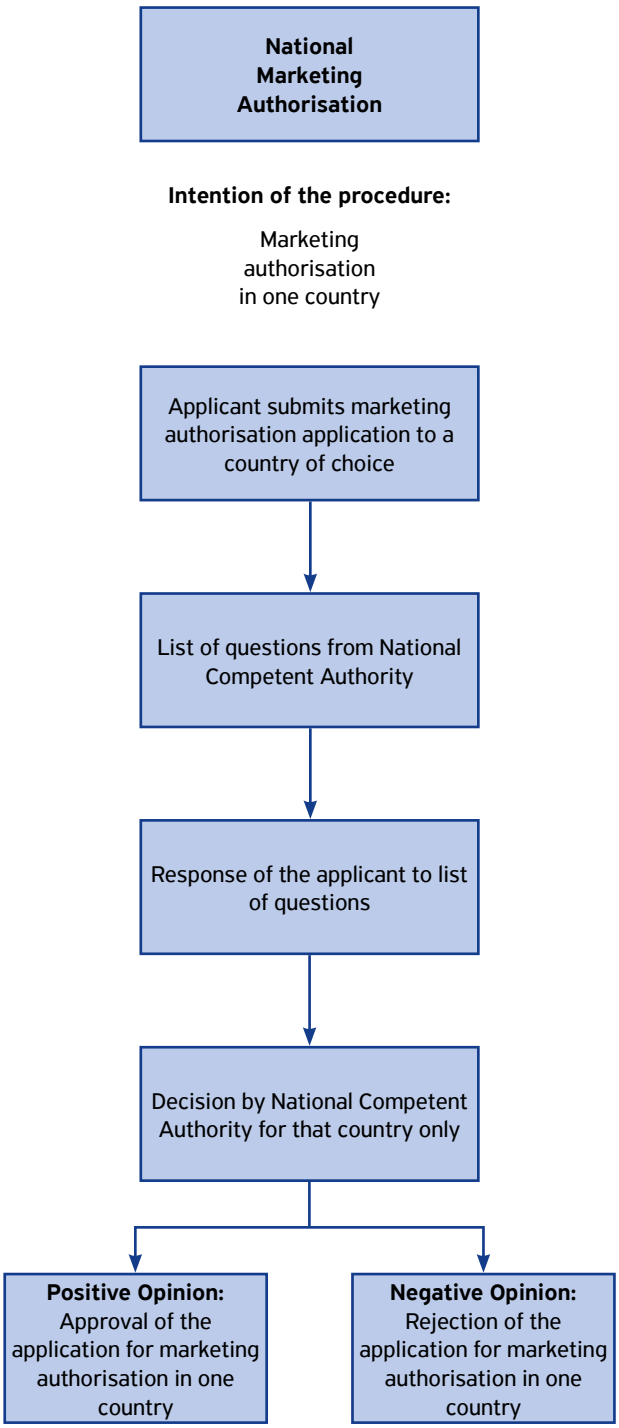

Figure 1A Simplified flowchart of the national marketing authorisation procedure. For reasons of clarity, some details of the procedure have been omitted in the figure, e.g. timetables are differing in each country.

apply for marketing authorizations in additional member states, the **Mutual Recognition Procedure** (MRP) has to be applied. In this procedure, the country in which the marketing authorization has already been granted acts as so-called Reference Member State (RMS) and will provide the assessment report that led to the original authorization of the product to those countries in which an authorization is sought (Concerned Member States, CMS). Often, the original assessment report will need to be updated by the RMS in case that considerable time has passed between the original authorization and the actual start of the MRP to reflect the up-to-date status of the marketing authorization dossier. The procedure itself typically takes 90 days, only where no consensus among member states is reached, the procedure will last 150 days due to arbitration by CMDh. An important drawback of this approach is that two procedures (national authorization followed by MRP) are conducted sequentially in the MRP, thereby prolonging the timeframe from initial submission of a marketing authorization application and eventual market access in intended countries. A speedier alternative is the **Decentralized Procedure** (DCP), which is the preferred route for allergen products without preexisting national marketing authorisation to achieve such authorization in multiple EU Member States (see also (9-11)).

Overall, the DCP allows the decision and potential approval to be reached within a shorter timeframe as there is no requirement for a national authorization to precede the DCP. To initiate a DCP, an applicant will request the national competent authority (NCA) in a country of their choice to act as coordinating authority (RMS), which will then be leading the assessment and coordinating the procedure. If the requested authority agrees to be RMS, the company submits an application for marketing authorization to the RMS and all involved member states, which are selected by the applicant. For DCP, the procedure can be closed by the RMS at different time points as soon as consensus is reached by RMS and CMS. This can happen at Day 105, Day 150, or Day 210 of the procedure. Where necessary, the procedure will be stopped in a so-called *clock-off period* at Day 105 to allow the applicant to respond to issues raised in the procedure. In case arbitration by CMDh is needed, the CMDh adopts its final position by Day 270. The result of both, a MRP and DCP, typically is that after

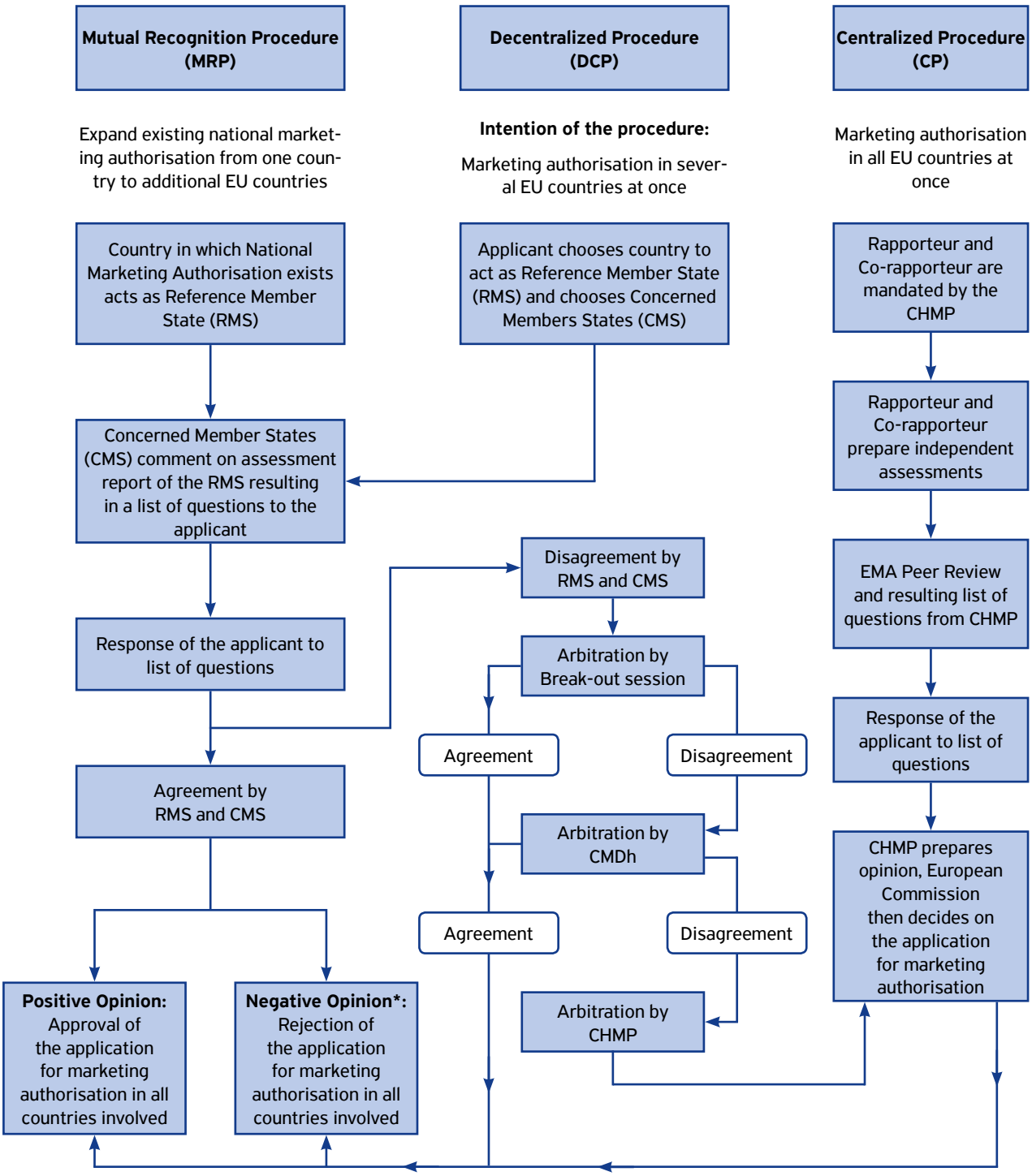

Figure 1B Simplified flowchart of the multinational marketing authorisation procedures in the European Union. For reasons of clarity, some details of the procedures have been omitted in the figure, e.g. timetables for each procedure are differing. * A MRP cannot directly result in a negative opinion. Only where a public health concern is raised by a CMS, the procedure will be referred to the CMDh/CHMP where the outcome may result in a negative opinion.

positive finalization of a procedure, the product might not be authorized in the entire EU, but only in the RMS and respectively involved countries/CMS that the applicant decided to include in the procedure. The RMS prepares an assessment report including a list of questions on issues that need to be resolved before authorization can be granted. For both, MRP and DCP, the CMS comment on the assessment report, which may result in additional issues to be raised. Next, the assessment report as well as the list of outstanding issues is provided to the applicant to allow for resolution of these issues. The RMS then reassesses the updated documentation and, in agreement with the CMS, a decision is made on whether or not the medicinal product can be approved. In case there is disagreement between the RMS and the CMS on issues that may potentially harm the patients ("potential serious risk to public health" (12)), the procedure may be referred to the Co-ordination group for Mutual recognition and Decentralized procedures - human (CMDh) (see below) and possibly to the Committee for Medicinal Products for Human Use (CHMP) for arbitration (see also (10, 11)).

For all marketing authorization procedures, a public assessment report is prepared (either by the CHMP (for CP), the RMS (for MRP and DCP) or the respective national competent authority (for national procedures)) upon granting of a marketing authorization, thereby publicly documenting the assessment for a concerned medicinal product. However, those parts of the dossier that are confidential will not be included in the public assessment report. This is typically the case for specifics of the manufacturing process. Clinical and non-clinical data are typically not considered to be confidential.

For allergen products, several committees and working parties play important roles in the different phases of development, marketing authorization, and post-marketing authorization procedures (online supplementary table S1 and S2).

The networks of institutions and committees involved in procedures resulting in the marketing of a medicinal product in the EU and resultant procedures (variations to an existing marketing authorization, pharmacovigilance monitoring, etc.) are complex. We will therefore give an overview of the major committees playing a role in regulatory procedures for allergen products in Europe.

The Committee for Medicinal Products for Human Use (CHMP) and related committees

The CHMP is the committee at the EMA responsible for preparing opinions on issues with respect to medicines for human use. In centralized procedures, the CHMP assesses the marketing authorization application and gives a recommendation on whether or not a specific product may be approved. The final decision on this will then be made by the European Commission (EC) on the basis of the opinion provided (13, 14). The opinion by the CHMP is prepared within the European regulatory framework and based on scientific criteria allowing a conclusion on the benefit-risk balance using the information provided by the applicant concerning quality, safety and efficacy of the medicinal product. A recommendation for marketing authorization is only made where this balance is favorable. In addition to the initial marketing authorization procedure, the CHMP is also responsible for a number of post-authorization activities, such as changes to an existing marketing authorization (variation) (14).

For Mutual Recognition and Decentralized Procedures, the CHMP plays an important role in situations where the member states involved in a specific procedure (including the RMS as well as the Concerned Member States) do not come to an agreement concerning the marketing authorization of a specific product. This may, for example, be the case where a CMS raises issues of potential serious risk to public health while the RMS does not share this concern. In such circumstances, the CHMP will arbitrate and take a decision on whether or not a concern should be upheld (which results in a recommendation to deny a marketing authorization) or whether the presented issues are not profoundly affecting the benefit-risk balance in a negative way (which would typically result in the approval of a specific product by the RMS and CMS).

Another very important aspect of the CHMP`s responsibilities is the provision of scientific advice during all phases of a products life-cycle, e.g. during clinical development and after marketing authorisation. In addition, CHMP is responsible for the development of scientific guidance for the pharmaceutical industry. These guidelines, although not directly mandatory from a legal perspective, reflect the scientific or regulatory state of the art and are typically applied by the regulatory agencies of the EU Member States. Accordingly, applicants should follow these guidelines

or provide comprehensible justifications in case deviations from these documents are intended. As a part of its mandate, the CHMP has established a number of working parties, which provide expertise in particular scientific fields. These working parties are composed of European experts selected from the national competent authorities. On varying issues, the CHMP will ask these working parties to contribute to the development of specific guidelines or to the assessment of marketing authorisations and EMA scientific advice procedures - for example the Safety Working Party (SWP) for specific non-clinical issues or the Biologics Working Party (BWP) for quality issues concerning biologicals, including allergens from natural and recombinant sources (15).

The Co-ordination group for Mutual recognition and Decentralized procedures - human (CMDh)

The CMDh is not a committee of the EMA but is associated to the Heads of Medicines Agencies (HMA), which is a network of the Heads of the National Competent Authorities in the European Economic Area (EU and the non-EU countries Iceland, Liechtenstein and Norway). The CMDh was set up by Directive 2004/27/EC (16) and plays a fundamental role with respect to procedural issues in Mutual Recognition and Decentralized procedures. Based on its mandate as given in this directive, the committee has developed guidance on all aspects of MRP and DCP and discusses issues that arise in ongoing procedures. As stated previously, these types of procedures have steadily risen in relevance for allergen products in recent years. As described above for CHMP's role in CP, an unresolved potential serious risk to public health issue in a marketing authorization procedure with disagreement between RMS and CMS will first result in discussion of the relevant issues at CMDh. Only if the disagreements remain unresolved in the CMDh, the issue is passed to the CHMP for arbitration. Accordingly, in addition to procedural questions, the CMDh is also involved in scientific issues.

Role of the Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC is responsible for assessing and monitoring safety issues for human medicines. These responsibilities include the detection, assessment, minimization and communication of safety issues such as adverse reactions observed for specific medicinal products (17). For this, the PRAC prepares recommendations and provides these to the CHMP and CMDh as well as to the EC in related procedures. Yet, for allergen products, the role of PRAC is currently limited as most issues relating to pharmacovigilance are presently still handled by the member states.

The Paediatric Committee (PDCO)

As part of a valid marketing authorization application, European legislation (in this case Paediatric Regulation (EC) 1901/2006 (18)) mandates that an applicant for the marketing authorization of a medicinal product and therefore also for allergen products for therapy and in-vivo diagnosis, must provide a paediatric investigation plan (PIP) that has been assessed and approved by the PDCO of the EMA. This plan is provided by the applicant during development of the medicinal product to delineate how data on the clinical efficacy and safety of a specific product will be generated in children to support the authorization and use of this medicine in this population group. For certain classes of medicines, the requirement to submit a PIP is waived due to the fact that these classes of medicines are likely to be ineffective or unsafe in paediatric populations, are intended for conditions that occur only in adults, or will not result in a significant therapeutic benefit compared to existing treatments in paediatric populations. As allergen products typically do not fall in any of these categories, an approved PIP is mandatory for these products and, if missing, will prohibit authorization even at the national level. However, a deferral can be requested where it is appropriate to conduct clinical studies in adults prior to initiating studies in the paediatric population (19). Such deferrals are often granted for allergen products. Yet, the requirement to perform clinical studies in paediatric populations has resulted in varying difficulties in reality as recruiting can be profoundly difficult and ethical issues arise.

National specifics on regulatory issues for allergens in Europe

Allergen products are regulated according to European law since 1989 (1, 2). The implementation of the European Directive 2001/83/EC (7) crucially advanced the legal framework for allergen products so that it is basically harmonized in the EU. Yet, there is still a high level of heterogeneity in how EU member states regulate market access for this type of products. For most parts, this is due to specific regulations such as Article 5 of above mentioned Directive that

allows member states to place specific allergen products, especially named patient products (NPP), on the market without the requirement of a marketing authorization. Furthermore, while implementing the particulars of the European Directive 2001/83/EC into national legislation, many member states adapted or elaborated this legislation by specific national law such as ordinances or decrees. Some examples are provided in the online supplementary section of this document to demonstrate the spectrum of approaches on how allergens are currently regulated in the EU. For reasons of brevity, there are specifics in additional EU member states that are not covered by this review.

Allergen products in the US

Allergen products in the US are regulated as biological medicinal products under the Public Health Service (PHS) Act and as drug products under the Federal Food, Drug and Cosmetics Act (FD&C Act) Additional Acts (laws) contain important provisions for regulation of biological products and drug products, but the PHS Act and FD&C Act and their related amendments are the primary laws under which biological products are regulated. In addition, FDA is authorized or required under these laws to issue Federal Regulations. Federal Regulations, which have the force of law, detail requirements on how to comply with US law. Products administered to man for the diagnosis, prevention, or treatment of allergies, are defined by Federal Regulation as Allergenic products (hereinafter referred to as allergen products). Allergen products licensed in the US include sterile injectable allergen extracts for diagnosis and immunotherapy, allergenic extracts in sublingual tablet formulations for treatment of certain allergies, and allergen patch tests. Generally, there are no differences in the regulation of allergens for diagnosis versus therapy. Allergen products require a marketing authorisation termed a Biologics License Application (BLA).

US-licensed allergen extracts are either "standardized" or "non-standardized", depending on the labeled units. Standardized extracts are labeled in units tied to biological activity and each released lot of a standardized allergen extract meets potency-related specifications. Non-standardized allergen extracts carry labeled units (PNU or w/v) that do not correlate to potency. US-licensed allergen products that are not aqueous extracts do not carry the designation of standardized or non-standardized.

Separate BLAs are assigned for each of the existing standardized allergenic extracts, but non-standardized allergen extracts from each manufacturer are licensed under one BLA. That BLA includes every non-standardized extract manufactured by a specific license holder, regardless of extract type. Therefore, a specific license holder's BLA for non-standardized allergenic extracts could encompass many different products. The model for non-standardized allergen extracts is historical. Entities seeking a BLA for a previously unlicensed allergen product or a licensed allergen product with a new clinical indication must demonstrate that their products are safe and effective for their intended use in accordance with requirements specified under laws and regulations for BLAs. Briefly, in general the allergen product is first assessed for safety and efficacy in clinical trials conducted under an IND Application that a sponsor submits to FDA. FDA may also accept data from foreign studies not performed under IND provided certain requirements are met. After successful completion of clinical trials, the product is submitted for licensure under a BLA. BLAs are submitted electronically using the harmonized eCTD format. The BLA contains all required information on the quality of the medicinal product, as well as all clinical, pharmacological and toxicity data. FDA expects that a BLA will demonstrate that an applicant manufactures a quality product in accordance with current Good Manufacturing Practices (cGMPs) that is safe, pure and potent. After licensure, changes to the manufacturing process are submitted to FDA according to a three-tiered supplement and annual report system, depending on the nature of the proposed changes. FDA regulations and guidance discuss reporting requirement for post-approval changes. NPPs are not marketed in the US, and the marketing of allergen products manufactured in pharmacies is not permitted.

Guidance documents provide FDA's current thinking on implementation of regulations or law. FDA Guidance documents span a wide range of topics including: design, production, labeling, promotion, manufacturing, and testing of regulated products; processing, content, and evaluation or approval of submissions; or inspection and enforcement policies. As in other regions of the world, changes in laws and regulations occur and FDA updates guidance documents as necessary to insure that approaches to compliance with applicable laws and regulations

are current. These changes then apply to a wide range of FDA-regulated products, including allergen products, regardless of their use in therapy or diagnosis. ICH guidance documents are used for the same purpose as FDA guidance and apply to allergen products, depending on the scope of the guidance. Pharmacovigilance monitoring is required in the U.S. for allergen products, and specific regulations for reporting of adverse events exist. Periodic Safety Update Reports are also required for licensed products. During the conduct of clinical trials, adverse events are also reported in the IND annual report.

Allergen products in selected parts of the world

General regulation of allergen products

Allergic diseases affect people all over the world. Hence, allergen products are available in many countries and yet there is little information available on how such products are regulated on a global scale. We therefore developed a questionnaire in which national competent authorities from a selection of countries were asked to provide information on the regulation of allergen products in their countries. Responses were received from the NCAs in Australia, Canada, Japan, Russia and Switzerland as well as feedback on selected questions from China and Indonesia. The responses to the questionnaire received give an impression of such regulation from various areas of the world. Table 2 displays some key findings extracted from the responses to the questionnaire. Some general observations can be made from the responses received. For example, it becomes clear that as in the EU and US, allergens are considered biological medicinal products in most countries (Australia, Canada, China, Indonesia, Japan, Russia) and typically allergen products are not in general exempted from the requirement for a marketing authorization. Such authorizations are issued for the finished product. Furthermore, the basic regulatory frameworks typically do not differentiate between therapy and test allergens. Nevertheless, although allergen products are considered as biological medicinal products, some countries have implemented specific regulations for this type of products. For example, Switzerland has implemented an allergen ordinance in December 2009 allowing for a simplified authorization procedure for test and therapy allergens from natural sources (20). In this ordinance, specifics on the requirement on data to be provided for marketing authorization are laid down individually for test and therapy allergens. Among other addressed issues, there are details provided on the requirements for data from clinical studies for both groups of allergen products. Additionally, Swissmedic published a guidance document on the simplified authorization of allergen products (21).

In Canada, there are currently two regulatory authorization pathways for allergen extracts in place. Firstly, there are so-called 'Grandfathered Products'. These products were approved under a framework that was applicable before 2012. In this framework, there are two main types of allergenic extracts to be considered: non-standardized and standardized extracts. Non-standardized allergenic extracts are further divided into extracts derived from pollen or non-pollen materials. Currently, for these non-standardized products, one authorization is given for all pollen products and one authorization is given for all non-pollen products per company. In contrast, for standardized allergenic extracts, one authorization is given to each product per company. In addition, Health Canada follows the FDA standards for the Standardized Allergenic Extracts.

Secondly, in November 2012, Health Canada published a guidance document entitled Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin used for the Diagnosis or Treatment of Allergic Diseases which introduced a new policy for the regulation of allergen extracts (22). All Allergen Extracts approved after the introduction of the new Framework in 2012 are regulated and authorized under the same regulatory authorization pathway as other Biologic Drugs. Each product requires its own authorization. As stated in the response provided by Health Canada, the agency is currently examining options for aligning these two pathways.

Named patient products

As is the case within the EU, the regulation and acceptance of named patient products differs widely globally. For example, according to the Russian legislation it is allowed to produce medicinal products on the basis of a prescription only in cases where authorized substances are used in the production process. However, according to the NCA in Russia, no authorized allergen drug substances are currently available on the Russian market, only finished products.

Table 2 Overview on responses of NCAs to selected questions of the questionnaire

	Requirement for a MA for allergen products	Stage of the production process to be authorized	Named Patient Products marketed	Import of allergen products
Australia	MA required	Finished Product	No named patient products but practitioners may obtain Authorised Prescriber status for allergens under the Authorised Prescriber program	If a specific allergen product is not approved in Australia, a prescribing physician may request it for use in an individual named patient under the Special Access Scheme.
Switzerland	MA required	Finished Product	*Formula magistralis* Medicinal Products corresponding to NPP	Patients and health professionals are allowed to import medicinal products authorized in a third country by specific rules. This is only possible, when there is no authorized product available in Switzerland. This is not applicable for NPPs.
Canada	MA required	Finished Product	Not allowed	All products sold in Canada must be authorized for sale in Canada by Health Canada.
Russia	MA required	Finished Product	It is allowed to produce medicinal products on the basis of a prescription only if authorized substances are used in the production process. Since currently no authorized allergenic substances are available in the Russian market, no NPPs can be produced based on a prescription for an individual patient.	Only those therapeutic allergens that have been authorized in Russia are allowed to be imported
Japan	MA required	Finished Product	Not allowed	Based on the responsibility of the physician, products may be imported from other countries. Such products are exempt from Relief System for Suffers from Adverse Drug Reactions in Japan.

Therefore no NPPs can be produced based on a prescription for an individual patient. In Switzerland, the Swiss Therapeutic Products Law defines so-called 'formula magistralis' medicinal products which are exempt of a marketing authorization. These medicinal products have to be manufactured upon a specific prescription by a physician which would potentially also be feasible for allergens. The information on the actual availability of such products on the market lies at the regional Cantonal Health Authorities.

Contrasting with the previous examples, Australia, Canada and Japan generally do not allow NPPs to be placed on the market. However, while NPPs are not available as such in Australia, practitioners there may obtain so-called Authorized Prescriber status for allergens under a special program, the Authorized Prescriber program (23). This may be applied in cases where patients require access to medicines or medical devices that have not been approved for supply by the Australian agency. For those countries for which NPPs are allowed on the market, specific information on the number and type of NPPs on the market is often non-available to the NCAs responsible for the marketing authorization and monitoring of the authorized allergen products.

Import of allergen products

Non-availability of authorized allergen products may result in crucial gaps in the provision of needed products to patients. To overcome this, some countries allow alternative routes for such products to

be made available. In addition to the above mentioned Authorized Prescriber program, Australia also applies a so-called special access scheme (24). For this, the import and/or supply of a specified unapproved therapeutic good (or class of unapproved therapeutic goods) to specific patients (or classes of recipients) with a particular medical condition can be granted upon request of a prescribing physician. The decision on such requests is taken on a case-by-case basis, and is based on the clinical information supplied by the doctor. Any approval or rejection is limited to the named patient only for a defined dose and duration of therapy and does not allow supply to another patient and is not tantamount to progression to general marketing. Also, extemporaneous compounding by pharmacies is permitted for individual patients on prescription-based orders of treating physicians but is not an avenue for general marketing to other patients. In Switzerland, patients and health professionals are allowed to import medicinal products authorized in a third country by specific rules (25). This is only possible, when there is no authorized product available in Switzerland. This is not applicable for NPPs. In Japan, based on the responsibility of the physician, allergen products are allowed to be imported from other countries. However, these products are then exempt from Relief System for Suffers from Adverse Drug Reactions. In Russia, the import of therapeutic allergen products is allowed for those products that are also authorized within the Russian Federation. In Canada, all products to be sold must be authorized for sale by Health Canada. China allows the import of certain allergen products from overseas, adding to the domestic products registered there. Apart from the exceptions described above, manufacturing of allergen products in pharmacies without marketing authorization is not allowed in any country replying to the questionnaire.

Post-authorization requirements for allergen products

All countries stated that there are post-authorization requirements such as pharmacovigilance monitoring in place (for example Risk Management Plans and/or Periodic Safety Update Reports) for authorized allergen products. In Canada, in addition, each lot of a biological medicinal product is subject to the Lot Release Program before sale. The risk-based Lot Release Program covers both pre- and post-market stages and derives its legislative authority from section C.04.015 of the Food and Drug Regulations. Products are assigned to one of four evaluation groups, with each group having different levels of regulatory oversight (testing and/or protocol review) based on the degree of risk associated with the product. The graded risk-based approach to testing and oversight allows the Biologics and Genetic Therapies Directorate of Health Canada to focus ongoing testing on products for which enhanced surveillance is indicated such as vaccines and blood products. The criteria used to determine the appropriate Evaluation Group include, but are not limited to, the nature of the product, the target population, the lot testing history in the Directorate, and the manufacturer's production and testing history.

Regulations for specific types of allergen products

As was previously described for the EU and the US, there is no particular regulation or guidance in place in any country that responded to our questions for allergen challenge products, for example for food challenge. Typically they are considered to be diagnostic allergen products and are treated as such.

Moreover, thus far there are no authorizations for recombinant allergen products or for peptides derived from allergen sequences anywhere in the world. Special requirements are applicable in some countries for such products, for example, in Switzerland, an administrative ordinance for human medicines with new active pharmaceutical ingredients (26) must be followed.

CURRENT REGULATORY CHALLENGES FOR ALLERGEN PRODUCTS AND UNMET NEEDS

Recent years have shown tremendous rearrangements in the allergen market and consequently the availability of allergen products. In some countries, many AIT products have disappeared, for example due to novel regulations such as the therapy allergen ordinance in Germany (27) or the enforcement of Directive 89/342/EEC in the Netherlands (2) (see online supplementary for further information) or reimbursement issues. For other products, state-of-the-art clinical and quality data has been generated resulting in the development and even marketing authorization of a new generation of products (28-30).

Although such positive developments are observed, other aspects may be more ambivalent. Several recommendations have been made by academia to improve thoroughly standardized definitions for future trials in AIT and should be consequently followed (31, 32).

It should be noted that this is a dynamic situation and the ongoing developments in this field will continue to reshape the allergen market fundamentally.

Several issues have surfaced in recent years that are thought to be key triggers of the current developments. Overall, the requirements on the data that must be provided to successfully apply for a marketing authorization have risen significantly in the last 20 years. There has been a clear shift towards products with proven quality, safety and efficacy, which has also been evident in some cases for previously authorized products. Randomized, double-blind placebo controlled studies according to current GCP-regulation are required as the current state-of-the-art approach. Products for which such proof is not provided will not be approved for marketing. Furthermore, it has become evident in recent years that the distribution of products as NPP for in vivo diagnosis and AIT for highly prevalent allergies is neither necessary nor desirable. The data to be generated for documentation of clinical efficacy and safety as well as proof of adequate manufacturing of these products should be provided and independently assessed. In contrast, while for highly prevalent allergies it is feasible to conduct randomized double blind placebo controlled studies, for allergens with a lower prevalence this may not be possible due to insufficient recruiting of patients.

In addition, considering the (non-)availability of allergen products, it should be distinguished between a potential lack of newly developed products (e.g. for allergies with low prevalence) and the withdrawal of products from the market due to the decision of companies to cease marketing. Consequently, while certain causes resulting in these two scenarios are overlapping (e.g. economic profit to be expected with respect to reimbursement), they are differing in other aspects. For example, the requirement to provide GCP-compliant clinical data on efficacy and safety as requested by Directive 2001/83/EC will not necessarily affect products for which a marketing authorization has already been issued.

Economic considerations influencing the availability of allergen products

As several factors are influencing the current and future availability of allergen products, pricing and reimbursing are among those most commonly discussed. As with the regulatory framework, reimbursement for allergen products is very heterogeneous with even more differences between countries. Decision making on reimbursement is often based on national procedures for so-called Health Technology Assessments (HTA). However, in many countries, HTA is not performed by the same authorities that are responsible for marketing authorisation and the assessments are based on different criteria. This can result in potentially diverging opinions on one medicinal product between HTA and the assessment in a marketing authorisation procedure. However, it should be noted that regulators involved in scientifically assessing the medicinal products are neither in a position nor are they commissioned to include considerations on reimbursement in their decision making on a marketing authorization application (33). Complicating matters, in addition to the differences in reimbursement, the fees that are to be paid to the respective NCAs involved in a marketing authorization procedure (as well as post-marketing procedures such as variations to an existing marketing authorization) in national procedures, MRP and DCP are defined on a national level, resulting in enormous differences in the magnitude of fees. Furthermore, these national fees may add up to considerable sums, thereby enticing companies to market their product in a selected number of countries, limiting the availability of products in countries not considered for marketing authorization. Adding up to the fees applicable for marketing authorization itself, there are national fees to be paid in each country where a variation to an existing marketing authorization is applicable as well as fees for pharmacovigilance activities. Besides, in many cases fees do not consider the economic attractiveness of a specific product and therefore do not distinguish between, for example, a commonly prescribed therapy allergen and a test allergen for diagnosis of an allergy with low prevalence, thereby likely intensifying the focus of pharmaceutical companies on allergen products for the most prevalent allergies. However, some countries have implemented measures to account for the specific characteristics

of allergen products. For example, in Switzerland, the fees raised for allergen products are differentiated for allergens for therapeutic and diagnostic purpose (the latter ones with a fee reduction of 90%). Variation fees are also reduced by 50% for both therapeutic and diagnostic allergens in comparison to other medicinal products.

Future perspectives

Considering the current position, companies are tending to focus on a core group of allergens. While it is reasonable that products for rare allergies that are of insufficient quality or have no or very little data on clinical efficacy are disappearing from the market, this is problematic for patients who require them and where there is no adequate alternative. This situation is especially evident for allergen products for in vivo diagnosis. Consequently, strategies to counteract this development, for example with regard to the regulatory management of such products may be needed. However, to do sufficient justice to this topic and its significance, it requires separate discussion elsewhere.

Furthermore, the situation concerning the heterogeneity of the regulatory status of allergen products worldwide and in the EU is deeply rooted in their regulatory history, as for decades these products have been managed on a national level only. Resulting diverseness is evident, for example, in the applicability and prevalence of use for NPPs in the EU. In contrast, while NPPs are not marketed as such in the US, it has been reported that products are frequently mixed at the physician's office. Although respective guidance has been developed for this approach (34, 35), there is a lack of evidence to support the efficacy of the individual mixtures used. Moreover, the EU is an evolving structure with the decision of the UK to leave the EU and several countries having joined the EU in the last decades. The latter ones have had the challenge of integrating their own national regulations and medicinal products available on their markets into the regulatory system of the EU. In light of these differences, companies are faced with the challenge to keep their products (and manufacturing processes) standardized during development as well as post-marketing in a global distribution setting.

Some of the issues concerning allergen products and their availability have resulted in activities by responsible European committees. Due to problems resulting from the regulatory disharmony observed in the EU, for example with respect to pharmacovigilance obligations, the CMDh has started an activity to work on proposals for harmonized regulatory approaches for allergen products within the EU (36).

For certain types of medicinal products in life-threatening diseases, considerations for application of a life cycle approach are made where a medicinal product can be authorized based on less comprehensive data than normally required if the public health benefit of their immediate availability to patients outweighs the risk (37). However, this is typically not the case for allergen products. In such lifecycle approaches, a product will be assessed for its benefit-risk balance on an on-going basis post-marketing (38). Similar approaches are being applied in different parts of the world (39), although they are often criticized, especially because products within such a lifecycle approach are made available with insufficient data to fully determine a benefit-risk ratio at the time of market access.

Several projects are in place targeted at supporting manufacturers in developing effective and safe medicinal products, for example the Innovative Medicines Initiative (40). Also, PRIME (41)(derived from priority medicines) has been founded by the EMA to support in the development of medicines aimed at currently unmet needs. With respect to allergies, there are several fields, where medical need can currently not be adequately addressed with authorized medicinal products (e.g. in oral immunotherapy of food allergies) and where such programs may be of benefit for future developments.

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Disclaimer

The views expressed in this review are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authorities, the European Medicines Agency or one of its committees or working parties.

Authors' contributions

This paper was drafted by Bonertz A, Hoefnagel M, Timon M, Slater J, Rabin R, Bridgewater J, Pini C and Vieths S. It was revised following critical review by Roberts G, Pfaar O, Bonini S, Sheikh A and then by all the co-authors. The EAACI task force developing the manuscript was chaired by Vieths S. Coordination of authors' contributions was done by Bonertz A. This study is part of the EAACI AIT guidelines project, chaired by Muraro A and coordinated by Roberts G.

Supporting Information

Additional supporting information can be found online.

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7

HEALTH ECONOMIC ANALYSIS OF ALLERGEN IMMUNOTHERAPY (AIT) FOR THE MANAGEMENT OF ALLERGIC RHINITIS, ASTHMA, FOOD ALLERGY AND VENOM ALLERGY

A SYSTEMATIC OVERVIEW

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***Background**: The European Academy of Allergy and Clinical Immunology (EAACI) is developing guidelines for allergen immunotherapy (AIT) for the management of allergic rhinitis, allergic asthma, IgE-mediated food allergy and venom allergy. To inform the development of clinical recommendations, we undertook systematic reviews to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT for these conditions. This paper focusses on synthesizing data and gaps in the evidence on the cost-effectiveness of AIT for these conditions.*

***Methods**: We produced summaries of evidence in each domain and then synthesized findings on health economic data identified from four recent systematic reviews on allergic rhinitis, asthma, food allergy and venom allergy, respectively. The quality of these studies were independently assessed using the Critical Appraisal Skills Programme (CASP) tool for health economic evaluations.*

***Results**: 23 studies satisfied our inclusion criteria. Of these, 19 studies investigated the cost-effectiveness of AIT in allergic rhinitis, of which seven were based on data from randomized controlled trials with economic evaluations conducted from a health system perspective. This body of evidence suggested that sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) would be considered cost-effective using the (English) National Institute for Health and Clinical Excellence (NICE) cost-effectiveness threshold of £20,000/quality adjusted life year (QALY). However, 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. For asthma, there were three eligible studies, all of which had significant methodological limitations; these suggested that SLIT, when used in patients with both asthma and allergic rhinitis, may be cost-effective with an incremental cost-effectiveness ratio (ICER) of £10,726 per QALY. We found one economic modelling study for venom allergy which, despite being based largely on expert opinion and plausible assumptions, suggested that AIT for bee and wasp venom allergy is only likely to be cost-effective for very high risk groups who may be exposed to multiple exposures to venom/year (e.g., bee keepers). We found no eligible studies investigating the cost-effectiveness of AIT for food allergy.*

***Conclusions**: Overall the evidence to support the cost-effectiveness of AIT is limited and of low methodological quality, but suggests that AIT may be cost-effective for people with allergic rhinitis with or without asthma and in high risk subgroups for venom allergy. We were unable to draw any conclusions on the cost-effectiveness of AIT for food allergy.*

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BACKGROUND

Allergen immunotherapy (AIT) is a potential treatment option in those with severe and/or potentially life-threatening allergic disorders who are inadequately managed with pharmacotherapy. AIT is most relevant in relation to the management of allergic rhinitis, asthma, food allergy and venom allergy and it is for this reason that the European Academy of Allergy and Clinical Immunology (EAACI) is in the process of producing clinical practice guidelines for these conditions.

We have recently completed systematic reviews investigating the role of AIT in the management of allergic rhinitis, asthma, food allergy and venom allergy focusing on the effectiveness, safety and cost-effectiveness of AIT (1-4). During the course of undertaking these reviews, we identified a number of health economic evaluations, which we considered it prudent to synthesize with a view to drawing overarching insights into the state of this evidence-base and in order to guide future evaluations.

Our specific aims were to:

- Synthesize data on the cost-effectiveness of AIT for the clinical management of allergic rhinitis, allergic asthma, IgE-mediated food allergy and venom allergy from the perspective of health payers; and
- Identify research gaps in relation to the cost-effectiveness of AIT for these conditions.

METHODS

A detailed outline of the methods have previously been published in the protocols and papers of each individual review (1-8). We therefore confine ourselves to a synopsis of the methods employed. The review has been conceptualised in figure 1.

Search strategies

Highly sensitive search strategies were developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic rhinitis, asthma, food allergy and venom allergy from electronic bibliographic databases. The search strategies were developed on OVID MEDLINE and then adapted for the other databases (1-4). In all cases, the databases were searched from inception to October 31, 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field. There were no language restrictions employed.

Study selection

All references were uploaded into the systematic review software DistillerSR and duplicate records were removed. Studies were independently checked by two reviewers (SD, MA, AaS) against the inclusion criteria detailed in the reviews (1-4). Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

Quality assessment

Quality assessments were independently carried out on each study by two reviewers (MA and SD). The Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies was used for this purpose (9). Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

Data extraction, analysis and synthesis

A data extraction sheet was developed to capture the pertinent features of the cost-effectiveness analysis based on the Drummond checklist and the National Institute for Health and Clinical Excellence (NICE) reference case for economic evaluations (10, 11). Data were independently extracted onto a customized data extraction sheet developed for the purposes of these reviews by two reviewers (MA, AaS or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). Where studies reported results from multiple perspectives, results from the health systems perspective were presented and where there were multiple outcome measures including quality adjusted life years (QALYs) the focus of the review was to present results in terms of QALYs. Costs were translated to 2014/15 GBP prices using National Health Service Personal Social Services Research Unit (NHS PSSRU) inflation indices (12) and standard exchange rates to aid the comparability of the studies.

A detailed descriptive report was produced on each study to summarize the literature. This data extraction process was used to assess the methodological features of the applied economic evaluations and highlight key methodological gaps in the studies from a

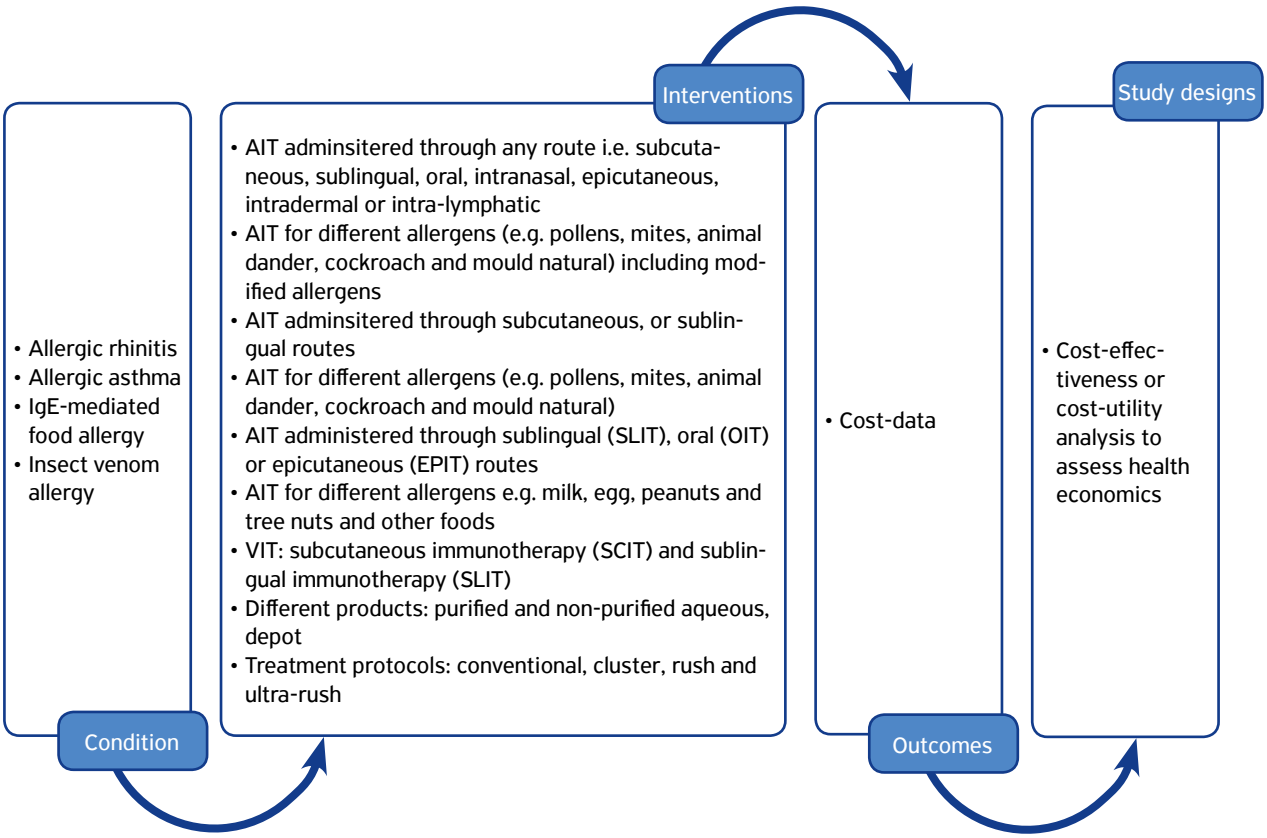

Figure 1 Conceptualization of cost-effectiveness of allergen immunotherapy for allergic rhinoconjunctivitis, allergic asthma, food allergy and venom allergy- a systematic overview

health economics perspective. The summary tables are reproduced in the results section of this article, with full data extraction forms available in online supplement 1.

Registration and reporting

The underpinning reviews have been registered with the International Prospective Register of Systematic Reviews (PROSPERO): Allergic Rhinitis: CRD42016035373; Allergic Asthma: CRD42016035372; Venom: CRD42016035374; Food Allergy: CRD42016039384. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (online supplement 2).

RESULTS

Overall description

Our searches yielded 21 studies assessing the cost-effectiveness of allergic rhinitis, asthma and venom allergy that met our inclusion criteria (see Table 1 and online supplement 1). Two of these studies are included separately in both the asthma and rhinitis analyses. Nineteen studies focussed on allergic rhinitis (13-31), three on asthma (13, 14, 32) and one on venom allergy (33). No studies were identified investigating the cost-effectiveness of food allergy. We identified studies looking at both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT), and which included both children and adults.

Quality assessment

The overall quality of the studies was low. Of the 19 allergic rhinitis studies, nine were assessed to be of low quality (13, 16-19, 22, 24, 28, 29), six medium (15, 20, 21, 23, 25, 30) and four high quality (14, 26, 27, 30). Of the three asthma studies, two were of a low quality (13, 32) and one high quality (14). The one included venom allergy study was assessed to be of medium quality (33). The quality of the studies is summarized in Table 2.

Table 1 Data extraction

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
RHINITIS AND ASTHMA STUDIES															
Ariano, 2009, Italy (13)	CEA	Health system	Patients with dust mite induced allergic asthma and rhinitis	SLIT / Standard Care	5 years	RCT 5 year follow up	70	VAS symptom score	0%	RCT patient diary and unit costs	?/Euros	0%	Overall costs lower in SLIT patients and lower symptom score	NA	Very little detail provided of the analysis performed no real economic analysis or interpretation of the results provided
Nasser, 2008, UK (14)	CUA	Health system	Patients suffering from grass pollen induced RC co-existing with asthma	SLIT (Grazax) / Standard care	9 years	RCT 1 year follow-up	151	EQ5D - QALYs	3.50%	RCT patient diary linked to unit costs	2005/ GBP	3.50%	ICER £8816 per QALY	One way sensitivity analysis to explore impact of changing time horizon	Results based on patients in UK, Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy· Treatment effect assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
RHINITIS WITH OR WITHOUT ASTHMA															
Bachert, 2007, UK, Germany, Netherlands, Sweden, Denmark, Norway, Finland (15)	CUA	Health system	Patients with grass pollen induced rhinoconjunctivitis	SLIT / Standard care	9 years	RCT 1 year follow up	493	EQ5D - QALYs	3 - 5% depending on country	RCT patient diary mapped to country specific unit costs	2005 / Euro	3 - 5% depending on country	Cost per year of treatment must be below 2200 euros for SLIT to be cost effective at NICE threshold of £20000 per QALY	N/A	Price of SLIT not given so ICERs not calculated, rather max price for SLIT to be cost effective calculated Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Berto,2006, Italy (16)	CEA	Health system	Young adults with pollen induced rhinitis with or without allergic asthma	SLIT / Standard care	6 years	Retrospective non-random subset selected from clinical study	2000	Number of patients improved	0%	Clinical records linked to unit costs	2002 / Euro	3%	SLIT is cost saving and more effective than standard care	Deterministic one way exploration of hospital costs	Potential for selection bias as physicians asked to pick subsets of patients from clinical study for economic evaluation
Bruggenjurgen, 2008, Germany (17)	CUA	Health system	Patients with pollen or mite induced allergic rhinitis with or without asthma	SCIT / Standard care	15 years	Published study	N/A	QALYs	3%	Published study	? / Euro	3%	ICER SCIT vs standard care 8308 euros per QALY	One way deterministic exploration od alternative treatment durations and discount rates	Difficult to assess the validity of cost or utility data as very little detail of studies that this analysis is based on given in the paper
Canonica, 2007, Spain, Italy, France, Austria (18)	CUA	Societal	Patients with a 2 year history of grass pollen induced allergic rhinoconjunctivitis with or without asthma	SLIT / Standard care	9 years	RCT 1 year follow up	Unclear subset of 634	EQ5D - QALYs	3 - 5 % depending on country	RCT patient diary linked to unit costs	2004 / Euro	3 - 5 % depending on country	0.134 incremental QALYs in SLIT patients. 29000 euro per QALY in all four countriesif SLIT costs 1400 euro per year then ICER would be less than	Repeated analysis excluding Spanish patients	Results calculated for France even though trial did not cover France.. Unclear exactly what data from the multi country trial was used to calculatethese results. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation.

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Dranitsaris, 2014, Canada (19)	CEA	Health system	Patients with grass induced allergic rhinitis with or without asthma	SCIT / SLIT (GRX) / SLIT (OA) / Standard care	1 year	Meta-analysis of 20 RCTs	N/A	Symptom control	0%	Expert opinion	2012 / CAD	0%%	SCIT, SLIT (GRX) and SLIT (OA) had similar efficacy in terms of symptom control. Cost of SCIT = 946 CAD; Cost of SLIT (GRX) =2122 CAD; Cost of SLIT (OA) = 844 SLIT (OA) is as effective as SLIT (GRX) and SCIT but cheaper over 1 year	N/A	Unclear what the allergic rhinitis symptom score represents and if it was comparable between studies Unclear about how much of the cost data was expert opinion as opposed to data from the meta analysis
Keiding, 2007, UK (20)	CUA	Health system	Adults with clinical history of grass pollen induced seasonal allergic rhinoconjunctivitis	SCIT / Standard treatment	9 years	RCT 1 year follow up	306	RQLQ mapped to EQ5D - QALYs	0%	Resource use collected in trial with national unit costs applied	2005 / Euro	3%%	ICER in Euro per QALY Austria 9716; Denmark 2586; Finland 13683; Germany 10300; Netherlands 24519; Sweden 22675	one way deterministic analysis on costs described but results not reported	Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation. Mapping from RQLQ to EQ5D applied to calculate QALYs not standard or validated
Meadows, 2013, England (21)	CUA	Societal	Patients with pollen induced allergic rhinitis with or without allergic asthma	SLIT / SCIT / Standard care	6 years	Meta-analysis of RCTs	N/A	RQLQ mapped to EQ5D - QALYs	3.5%	Resource use from expert opinion with unit costs applied	2011 / GBP	3.50%	ICER SLIT vs standard care £37537 per QALY ICER SCIT vs standard care £29579 per QALY ICER SCIT vs SLIT £24404 per QALY	N/A	Mapping between RQLQ and EQ5D to calculate QALYs not validated

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Omnes, 2007, France (22)	CEA	Health system	Children over 5 and adults over 16 with dust mite or pollen induced allergic rhinitis	SLIT / SCIT/ Standard care	7 years children; 6 years adults	Expert opinion	N/A	Asthma cases avoided	0%%	Expert opinion	? / Euro	0%%	ICER vs standard care children dust mite SLIT: 3938; SCIT: 583 ICER vs standard care children dust pollen SLIT: 824; SCIT: 597 ICER vs standard care adults dust mite SLIT: 3158; SCIT: 393 ICER vs standard care adults dust pollen SLIT: 1708; SCIT: 1327. All in Euros per asthma case avo	N/A	Entire study seems to be based on expert opinion Does not compare treatment with SLIT against SCIT incrementally
Petersen, 2005, Denmark (23)	CEA	Societal	Patients with grass pollen or mite allergy	SIT / Standard care	5 years	Retrospective questionnaire following trial	253	Patient year of improved well being	5%	Administrative data	2002 / DKK	5%	ICER 2784 DKK per patient year of improved well being	N/A	Selection bias due to partial response rate to questionnaire not controlled for. Recall bias not controlled for. Outcome measure is not validated and does not capture degree of improvement.
Pokladnikova, 2008, Czech Republic (24)	CEA	Health system	Adults with at least 2 years of seasonal allergic rhinoconjuctivitis with or without allergic asthma	SLIT / SCIT / Standard Care	3 years	RCT 5 years follow up	19 SLIT, 23 SCIT, 22 Standard Care	RQLQ	0%	Administrative data linked to unit costs	2002 / Euro	3%	SLIT and SCIT both performed better on RQLQ than standard care	One way deterministic sensitivity analysis performed on costs and discount rates	No incremental cost effectiveness results were provided

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Poulsen, 2008, Denmark (25)	CUA	Health system	Adults with grass pollen induced rhinotconjuctivitis	SLIT / Standard care	9 years	RCT one year follow up	493	EQ5D / QALYs	3%%	Unclear	? / DKK	3%%	ICER: 134105 DKK per QALY	N/A	Based on patients in Denmark, Sweden, England, Germany, Holland with Danish QALY weights and unit costs applied to EQ5D and resource use data. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
Reinhold, 2016, Germany (26)	CEA	Health system	29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma	SLIT (OA) vs SCIT (Allergovit) vs symptomatic treatment	9 years	RCT	?	Utility mapped to QALY	3%	Administrative data	2013/ euro	3%	SCIT dominates SLIT and has an ICER of 11000 euros per QALY against symptomatic treatment	Probabilistic and deterministic sensitivity analysis conducted	This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Ronaldson, 2014, UK (27)	CUA	Health system	5-16 year olds with grass pollen induced rhinoconjunctivitis with or without asthma	SLIT / Standard care	9 years	RCT 1 year follow up	253	Symptom scores mapped to QALYs	3.5%%	RCT Patient diaries mapped to unit costs	2008 / GBP	4%	ICER £12168 per QALY	PSA showed 90% probability of SLIT being cost effective at £30000 per QALY threshold and 60% probability cost effective at £20000 per QALY threshold	Mapping from symptom scores to QALYs not validated. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
Ruggeri, 2013, Italy (28)	CUA	Health system	Patients with grass pollen induced allergic rhinitis	SLIT / Standard care	4 years	Post-hoc analysis of 2 RCTs	?	AAdSS mapped to QALYs	3%	SIMAP study updated to 2011	2011 / Euro	3%%	At low AAdSS SLIT is dominated by standard care At medium AAdSS ICER 1024 euros per QALY At high AAdSS ICER 1035 euros per QALY	PSA showed 99% probability ICER less that 30000 euros per QALY for medium and high AAdSS	Not clear how AAdSS is converted to QALYs. Cost and effectiveness estimates taken from different studies

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Schadlich, 2000, Germany (29)	CEA	Health system	Patients with seasonal (pollen) and perennial (mite) allergy with or without asthma	SIT / Standard Care	10 years	Unclear	UC	Patients who do not develop asthma	0%	Resource use surveys	1990 / DM	0%	SLIT performed better than SCIT and was cheaper from a health system perspective	N/A	It was very unclear what data sources were used to populate the model in this study
Verheggen, 2015, Germany (30)	CEA	Payers perspective	29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma	SLIT vs blended mix of current SCIT treatments	9 years	RCT	?	QALYs mapped from Rhinitis Symptom Utility Index (RSUI)	3%	Administrative data	2013/ euros	3%	ICER of SLIT vs SCIT is 12,593 euro per QALY with a probability of being cost effective at 20,000 euro per QALY of 76%	Probabilistic and deterministic sensitivity analysis as well as scenario analysis performed	This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis Comparator is a mix of SCIT treatments rather than one specific treatment Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years
Westerhout, 2012, Germany (31)	CUA	Health system	Patients with grass pollen induced rhinoconjunctivitis without asthma	SLIT (OA) / SLIT (GRZ) / SCIT (ALD) / Standard care	9 years	Meta-analysis	N/A	QALYs	3%	Survey data	2011 / Euro	3%	SLIT (OA) dominates SLIT (GRZ) and SCIT (ALD). ICER SLIT (OA) vs Standard care 14728 euros per QALY	PSA suggests 79% probability SLIT (OA) cost effective at a threshold of £20000 per QALY	Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation• Resource use taken from external survey rather than measured in the underlying studies in meta-analysis

Table 1 Continued

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
ASTHMA ONLY STUDIES															
Reinhold, 2013, Germany (26)	CEA	Health system	Children and adolescents with mite induced allergic asthma	SCIT / Standard Care	3 years	RCT 3 year mean follow up	65	Mean morning peak flow (l/min)	0%	RCT - patient diary	2009 / Euro	0%	ICER: 11 Euros per l/min mean morning peak flow	Bootstrapping performed but not used in cost effectiveness results	No hospital costs included 5 SCIT and 1 non-SCIT patients excluded because of "outlier" levels of costs
VENOM STUDIES															
Hockenhull, 2012, England	CUA	Health system	General population as well as high risk of sting subset of population	PhVIT + HAD + AAI / HAD + AAI / avoidance advice only	10 years	Subset of RCT and survey data	337	Systemic reaction or death following sting converted to QALYs	3.50%	Administrative data and reference costs	? / GBP	3.50%	PhVIT + HAD + AAI is cost saving and more effective when compared to either HAD + AAI or avoidance advice only for patients likely to be stung more than five times a year. In the general population the ICER for PhVIT + HAD + AAI against HAD + AAI is > £18 million per QALY and against avoidance advice only is > £ 7.6 million	Extensive sensitivity analysis on wide range of model parameters	Very little data available to base the model on. Extensive use of sensitivity and scenario analysis to explore all plausible assumption and demonstrate the robustness of the findings

Table 2 CASP Economic Evaluation Checklist - Quality

Author/ year	Well defined question posed	Compre-hensive description of competing alternatives	Provides evidence of effec-tiveness	Effects identi-fied measured and valued appropriately	Resource use identified measured and valued appro-priately	Discounting to adjust for timing of costs and conse-quences	What were the results	Incre-mental analysis performed	Sensitiv-ity anal-ysis per-formed	Effec-tiveness general-isable	Costs gener-alisable	Overall quality L/M/H
ASTHMA AND RHINITIS												
Nasser 2008	Y	Y	Y	Y	Y	Y	SLIT ICER £8816 (2005) per QALY	Y	N	Y	Y	H
Ariano 2009	Y	Y	N	N	N	N	Lower cost and symptom score with SLIT	N	N	N	N	L
RHINITIS WITH OR WITHOUT ASTHMA												
Schadlich 2000	Y	Y	N	N	N	N	SIT is cost saving and reduces chances of devel-oping asthma	N	N	N	N	L
Pokladniko-va 2008	Y	Y	Y	Y	Y	Y	SLIT costs less that SCIT with similar effectiveness	N	N	N	Y	L
Peterson 2005	Y	Y	Y	N	Y	Y	SIT ICER 2784 DKK per patient year of improved well being	Y	N	N	Y	M
Poulson 2008	Y	Y	Y	Y	Y	Y	ICER SCIT 134105 KR per QALY	Y	N	Y	N	M
Canonica 2007	Y	Y	N	N	N	Y	SLIT ICER < 29000 Euros per QALY when annual cost of treatment < 1400 euro	Y	N	N	N	L
Keiding 2007	Y	Y	Y	N	Y	N	SLIT ICER 9716 to 14519 euros (2005) per QALY	Y	N	Y	Y	M
Rugerri 2013	Y	Y	Y	N	N	Y	SLIT ICER 1035 euros per QALY	Y	Y	N	N	L
Ronaldson 2014	Y	Y	Y	Y	Y	Y	SCIT £12168 (2008) per QALY	Y	Y	Y	Y	H
Bachert 2007	Y	Y	Y	Y	N	Y	SLIT ICER less than £20000 per QALY if treatment cost < 2200 euro per year	Y	N	Y	Y	M
Westerhout 2012	Y	Y	Y	Y	N	Y	SLIT (OA) ICER 14728 euro per QALY	Y	Y	Y	N	M

Table 2 Continued

Author/ year	Well defined question posed	Comprehensive description of competing alternatives	Provides evidence of effectiveness	Effects identified measured and valued appropriately	Resource use identified measured and valued appropriately	Discounting to adjust for timing of costs and consequences	What were the results	Incremental analysis performed	Sensitivity analysis performed	Effectiveness generalisable	Costs generalisable	Overall quality L/M/H
Berto 2006	Y	Y	N	N	N	N	SLIT cost saving and more effective than standard care	Y	N	N	N	L
Meadows 2013	Y	Y	Y	N	N	Y	ICER SCIT vs ST £29579 per QALY SCIT vs SLIT £24404 per QALY	Y	N	Y	Y	M
Omnes 2007	Y	Y	N	N	N	N	ICERs euros per asthma cases avoided under 3983 for SLIT and under 1327 for SCIT in all subgroups	N	N	N	N	L
Bruggenjurgen 2008	Y	Y	N	N	N	Y	ICER SCIT 8303 euro per QALY	Y	N	N	N	L
Dranitsaris 2014	Y	Y	Y	N	Y	N	SLIT (OA) cheaper than SLIT (GRX) and SCIT and similarly effective in terms of symptom control	N	N	N	Y	L
Reinhold 2016	Y	Y	Y	Y	Y	Y	SCIT (Allergovit) cheaper & more effective than SLIT (OA). ICER for SCIT against symptomatic treatment was 11000 euros per QALY	Y	Y	Y	N	H
Verheggen 2015	Y	Y	Y	Y	Y	Y	SLIT (OA) more costly & effective than SCIT. ICER of 12593 per QALY & 76% chance of being cost-effective at threshold of 20000 euro	Y	Y	N	N	H

Table 2 Continued

Author/ year	Well defined question posed	Compre-hensive description of competing alternatives	Provides evidence of effec-tiveness	Effects identi-fied measured and valued appropriately	Resource use identified measured and valued appro-priately	Discounting to adjust for timing of costs and conse-quences	What were the results	Incre-mental analysis performed	Sensitiv-ity anal-ysis per-formed	Effec-tiveness general-isable	Costs gener-alisable	Overall quality L/M/H
ASTHMA ONLY STUDIES												
Reinhold 2013	Y	Y	Y	N	N	N	ICER 11 euro per l/min morning peak flow	Y	N	N	N	L
ASTHMA AND RHINITIS STUDIES												
Nasser 2008	Y	Y	Y	Y	Y	Y	SLIT ICER £8816 (2005) per QALY	Y	N	Y	Y	H
Ariano 2009	Y	Y	N	N	N	N	Lower cost and symptom score with SLIT	N	N	N	N	L
INSECT VENOM ALLERGY												
Hockenhull, 2012 (33)	Y	Y	Y	Y	Y	Y	PhVIT + HAD + AAI dom-inates other treatments in patients likely to be stung more than 5 times a year. However not close to being cost-effective in general population.	Y	Y	Y	Y	M good study but data that it is based on is very poor

Summary of evidence

We begin by briefly summarizing the data in relation to each condition, and then synthesize findings across this body of evidence in order to highlight gaps and provide insights to inform the planning of future studies.

Allergic rhinitis

Of the 19 allergic rhinitis studies, two focussed on patients who all had both allergic rhinitis and allergic asthma (13, 14) and the remaining 17 focussed on patients who had allergic rhinitis (some of whom also had asthma, but it was difficult to know how many because of lack of clarity in the descriptions of studies). Three of these studies reported results from a societal perspective (18, 21, 23) with the remaining 16 reporting information from a health systems perspective.

Studies were based in a range of countries: Germany (N=7), Denmark (N=4), Italy (N=4), UK (N=4), Austria (N=2), Finland (N=2), France (N=2), Sweden (N=2), the Netherlands (N=2), Canada (N=1), Czech Republic (N=1), Norway (N=1) and Spain (N=1). Three studies reported including participants from more than one country (15, 18, 20).

Seven of the studies reported results against disease specific outcome measures whilst the remaining twelve reported results based on QALYs. A detailed summary of each study can be found in Table 1 and online supplement 1.

Thirteen of the studies (13-15, 18-21, 24-27, 30, 31) were based on randomized controlled trial (RCT) data or meta-analyses of RCT data including two model-based evaluations (26, 30). The remaining studies were based on a mixture of questionnaires, observational data and expert opinion. None of the studies based on non-random data attempted to control for selection bias. None of the RCT-based studies described the amount of missing data in the study or explained how if at all any missing data was imputed for in the analyses.

Study time horizons ranged between 1-15 years with the longer time horizon studies typically based on much shorter follow-up trial data (typically 1 year) and assuming constant continued treatment effects after AIT was discontinued.

Nine of the studies (13-16, 18, 25, 26, 28) compared SLIT with standard care; three studies (17, 20, 26) compared SCIT with standard care; two studies (23, 29) compared AIT (undefined) versus standard care; seven studies (19, 21, 22, 24, 26, 30, 31) compared SCIT versus SLIT, and two of these studies also compared different SLIT preparations (19, 31).

There were seven studies based on RCT data conducted from a health system perspective and using QALYs as their outcome measure. Two high quality studies were based in the UK. The first found that in patients with both rhinitis and asthma the incremental cost-effectiveness ratio (ICER) for SLIT versus standard care was £8,816 per QALY at 2005 prices inflated using NHS inflation indices (PSSRU) to £10,726 per QALY at 2014/15 prices (14). The second study found that in 5-16 year olds with rhinoconjuctivitis with or without asthma in the UK the ICER for SLIT versus standard care was £12,168 per QALY at 2008 prices. Updating to 2014/15 prices this translated to an ICER of £13,357 per QALY (27).

Three studies were conducted in Germany in patients with rhinoconjunctivitis without asthma. The first medium quality study found the ICER for SLIT (Oralair) versus standard care was €14,728 per QALY at 2011 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £11,460 per QALY (31). The remaining two studies were both of high quality. The second found the ICER for SLIT (Oralair) versus SCIT to be €12,593 per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £9,627 per QALY (30). The third German study found SCIT (Allergovit) to be cheaper and more effective than SLIT (Oralair). The ICER for SCIT (Allergovit) standard care was estimated to be €11,000 per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £8,334 per QALY (26).

A medium quality study from Denmark looked at adult patients with rhinoconjuctivitis and found the ICER for SLIT versus standard care to be 134,105 DKK per QALY (no price year was given so we assumed the study was undertaken in the publication year i.e. 2008) updating to current prices and GBP at 0.1 GBP per DKK translated this to an ICER of £15,294 per QALY at 2014/15 prices (25). Finally a further medium quality study conducted in adult patients with rhinoconjuctivitis performed in the UK in which ICERs for SCIT were calculated using healthcare data from Austria, Denmark, Finland, Germany, Sweden and the

Netherlands. The ICERs of SCIT compared to standard care in 2005 Euro per QALY were 9716, 2586, 13683, 10300, 24519 and 22675, respectively. Updating to current prices and at 0.75 GBP per Euro gave ICERs of £8,866, £2,360, £12,486, £9,399, £22,374 and £20,691 per QALY respectively at 2014/15 prices (20).

It was unclear how comparable the patient populations were between the studies. A particularly important factor that impacted on the costs and quality of life observed was the proportion of patients who also had asthma, but these proportions were not reported in many of the studies. The other interesting observation to be made is that the ICERs for AIT seemed to vary substantially between different health systems as demonstrated in Keiding *et al* 2007 (20) where ICERs ranges from £2,360 per QALY in Denmark to £22,374 per QALY in the Netherlands suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.

In general, the studies find that AIT and where defined both SLIT and SCIT were more effective than standard care, but also more expensive. The studies that compared SLIT with SCIT gave mixed results not allowing us to conclude that either treatment is necessarily more effective or more costly than the other from a health system perspective. The studies comparing SLIT (Grazax) and SLIT (Oralair) suggested SLIT (Oralair) is both more effective and cheaper than SLIT (Grazax) (19, 31).

The seven RCT studies compared, disregarding the caveats about generalizability, suggested that SLIT and SCIT treatment would be considered cost-effective in this patient population in England at the standard NICE cost-effectiveness threshold of £20,000 per QALY. However, 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.

Asthma

Three studies were deemed suitable for use in the review of AIT to treat patients with allergic asthma. Data extraction of these studies is summarized in Table 1.

Of the three health economic studies included, only one low quality study focussed on patients with allergic asthma without reported rhinitis (32). This was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease specific outcome measure (mean morning peak flow) with no attempt to convert it to a general quality of life measure such as QALYs making it impossible to assess the cost-effectiveness of the treatment. The study found that over the three years SCIT was more expensive than standard care and performed better than standard care on the disease specific outcome measure.

The remaining two studies looked at people with both allergic rhinitis and asthma. The first of these compared SLIT with standard care in a RCT (N=151) conducted in the UK, Germany, Holland, Denmark, Sweden, Spain, Austria and Italy with results evaluated from an English NHS perspective (14). This trial, which was already discussed in the rhinitis section above, used one year of treatment data and assumed a constant treatment effect over the three-year treatment period and the six years following the end of the treatment, thereby extrapolating the treatment effect over years 2-9. EQ5D was used to evaluate the treatment outcome and the ICER of SLIT as compared to standard care at 2005 prices was calculated as £8,816 per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using NHS PSSRU inflation indices translated this to an ICER of £10,726 per QALY.

The final study, also in patients with rhinitis and asthma, based on a RCT (N=70) with five years of follow-up conducted in Italy compared SLIT with standard care and found that patients on SLIT cost less and suffered less symptoms than those on standard care (13). Methods of the study were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score reported in the study to a general quality of life scale making it impossible to undertake a formal assessment of cost-effectiveness.

From the very limited set of studies found, all of which had significant methodological limitations, we can conclude that there is a suggestion that SLIT when used in patients with both allergic asthma and allergic rhinitis may be cost-effective from an English NHS perspective with an ICER of £10,726 per QALY, well below the stated NICE threshold on £20,000 per QALY.

Venom allergy

Only one study of moderate quality was found that looked at the economic evaluation of AIT for venom (33). This was a modelling study looking at the cost-effectiveness of AIT for the treatment of bee and wasp venom allergy (Table 1). The study assessed Pharmalgen venom immunotherapy (PhVIT) + high-dose anti-histamines (HDA) + adrenaline auto-injector (AAI) versus HDA + AAI and avoidance advice only. It found that AIT was not cost-effective in the general population (ICERs of £18 million and £7.6 million per QALY against HDA + AAI and avoidance advice only, respectively), but more effective than other treatment options with the potential for cost saving in patients likely to be stung more than five times a year (e.g., bee keepers).

This study, despite the fact that it was based largely on expert opinion and plausible assumptions, suggested that AIT for bee and wasp venom allergy was only likely to be cost-effective from an English NHS perspective for very high risk groups likely to be exposed to multiple exposures to venom per year. The modelling study suggested plausible ranges of exposure to such events to qualify a patient as a member of a high risk group and explored a wide range of sensitivity and scenario analyses to demonstrate the robustness of its findings.

Food allergy

We found no studies that met our inclusion criteria that looked at the cost-effectiveness of AIT for food allergy. Studies are needed in this area in order to provide information on this rapidly expanding treatment area.

Gaps in the literature

There is significant scope for future well designed studies looking at the cost-effectiveness of AIT for the treatment of patients with allergic rhinitis, allergic asthma and IgE-mediated food allergy. However, there seems little scope for further research regarding the use of AIT in patients with venom allergy. Key areas that future studies should address include: (1) effectiveness in different populations e.g. children versus adults, patients with only allergic rhinitis vs patients with allergic rhinitis and asthma; (2) well conducted RCTs with reasonable sample sizes and enough follow-up data to capture treatment effects during and after treatment; (3) directly collecting health related quality of life outcomes in the trial using instruments such as EQ5D; (4) comparison of the full range of treatment options (i.e. standard care, SCIT and SLIT) from a health system perspective; (5) using methodologically sound analyses to handle missing data and selection bias where observational data are used; and (6) fully characterizing the decision uncertainty through the use of sensitivity analyses exploring both parameter uncertainty as well as key model assumptions such as the duration of treatment effect.

DISCUSSION

Statement of principal finding

This review has found a limited amount of evidence in relation to the cost-effectiveness of AIT from a health system perspective in allergic rhinitis, allergic asthma and venom allergy and no evidence with regards to IgE-mediated food allergy. The limited studies identified looking at AIT for the treatment of allergic rhinitis suggest that SLIT and SCIT treatment would be considered cost-effective for these conditions in England at the standard NICE cost-effectiveness threshold of £20,000 per QALY. However, the quality of the studies and the general lack of attention to characterising uncertainty and handling missing data should be taken into account when interpreting these results.

Strengths and limitations

Our search strategies were robust and comprehensive filtering the vast literature pertaining to the subject. Furthermore, we actively sought expert opinions to add to the literature in case we had missed studies. There is however, always the possibility as with all such overviews, that some studies may not have been identified or have slipped through our search processes.

Studies were conducted in varied patient populations and health care settings, and used a variety of outcome measures to assess cost-effectiveness making pooling of results challenging. Where possible however, we have used QALYs from an English NHS perspective and converted costs to 2014/15 prices in GBP to compare cost-effectiveness results across the studies.

Interpretation in the light of the previous literature

This is, as far as we are aware, the first economic overview of AIT that has been conducted in relation to the conditions under study.

Implications for policy, practice and research

The findings from this overview will be considered together with the related evidence on the effectiveness and safety of AIT in drawing up guidelines and developing recommendations for practice. The findings from this analysis will be particularly helpful in relation to countries such as the UK and the Netherlands that have an explicit focus on health economic evaluations when deciding whether to promote use of interventions throughout their health systems. That said, with increasing pressure on health budgets globally the findings from this study are also likely to be of wider interest.

This work has also highlighted the need for investigators routinely to consider including formal cost-effectiveness analyses in their research plans and ensuring that these studies are undertaken to international standards. Consideration also needs to be given to undertaking health economic analyses from societal/patient perspectives as the condition can result in a significant personal societal/economic burden.

Conclusions

Overall the evidence to support the cost-effectiveness of AIT is limited and of a low methodological quality but appears to suggest that from an English NHS perspective AIT is cost-effective for allergic rhinitis, asthma and venom allergy in very high risk subgroups. No studies were identified assessing the cost-effectiveness of AIT for treating people with food allergy. There is much scope for further high quality studies addressing the methodological gaps identified in this review assessing the cost-effectiveness of AIT against various allergic conditions.

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Conflicts of interest:

M Asaria: reports grants from EAACI to carry out the review, during the conduct of the study; S Dhami: reports grants from EAACI to carry out the review, during the conduct of the study; R van Ree: reports personal fees from HAL Allergy BV, personal fees from Citeq BV, outside the submitted work; R. Gerth van Wijk reports personal fees from ALK-Abello, Circassia, and Allergopharma, during the conduct of the study; A. Muraro reports personal fees from Novartis, Meda, and Mylan, outside the submitted work; G Roberts reports that his university has received payments for work undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck; A. Sheikh reports grants from the EAACI during the conduct of the study.

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