Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

POSITION PAPER

Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper

O. Pfaar[1], P. Demoly[2,3], R. Gerth van Wijk[4], S. Bonini[5], J. Bousquet[2,6], G. W. Canonica[7], S. R. Durham[8], L. Jacobsen[9], H. J. Malling[10], R. Mösges[11], N. G. Papadopoulos[12,13], S. Rak[14], P. Rodriguez del Rio[15], E. Valovirta[16,17], U. Wahn[18] & M. A. Calderon[8]

[1]Center for Rhinology and Allergology Wiesbaden, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Mannheim, Mannheim, Germany; [2]Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier; [3]Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, Paris, France; [4]Section of Allergology, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands; [5]Second University of Naples and Institute of Translational Pharmacology, Italian National Research Council (IFT-CNR), Rome, Italy; [6]1018, Respiratory and Environmental Epidemiology Team, INSERM, CESP Centre for research in Epidemiology and Population Health, Villejuif, France; [7]Respiratory Diseases & Allergy Clinic, University of Genova, IRCCS AOU San Martino, Genova, Italy; [8]Section of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College, London, UK; [9]ALC, Allergy Learning and Consulting, Copenhagen; [10]Allergy Clinic, University Hospital Gentofte, Copenhagen, Denmark; [11]Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne, Cologne, Germany; [12]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece; [13]Centre for Paediatrics and Child Health, Institute of Human Development, University of Manchester, Manchester, UK; [14]Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Goteborg, Sweden; [15]Department of Allergy, Niño Jesús University Hospital, Madrid, Spain; [16]Department of Clinical Allergology and Pulmonary Diseases, University of Turku; [17]Suomen Terveystalo Allergy Clinic, Turku, Finland; [18]Department for Pediatric Pneumology and Immunology, Charité Medical University, Berlin, Germany

To cite this article: Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, Durham SR, Jacobsen L, Malling HJ, Mösges R, Papadopoulos NG, Rak S, Rodriguez del Rio P, Valovirta E, Wahn U, Calderon MA. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014; **69**: 854–867.

Keywords
allergen immunotherapy; clinical endpoints; clinical outcomes; combined symptom and medication score; randomized controlled trials.

Correspondence
Prof. Dr. med. Oliver Pfaar, Department of Otorhinolaryngology, Head and Neck Surgery, Center for Rhinology and Allergology Wiesbaden, University Hospital Mannheim, Wiesbaden, Germany.
Tel.: +49-611-308608250
Fax +49-611-308608255
E-mail: oliver.pfaar@allergiezentrum.org

Accepted for publication 2 February 2014

DOI:10.1111/all.12383

Edited by: Thomas Bieber

Abstract

Background: Allergen immunotherapy (AIT) has been thoroughly documented in randomized controlled trials (RCTs). It is the only immune-modifying and causal treatment available for patients suffering from IgE-mediated diseases such as allergic rhinoconjunctivitis, allergic asthma and insect sting allergy. However, there is a high degree of clinical and methodological heterogeneity among the endpoints in clinical studies on AIT, for both subcutaneous and sublingual immunotherapy (SCIT and SLIT). At present, there are no commonly accepted standards for defining the optimal outcome parameters to be used for both primary and secondary endpoints.
Methods: As elaborated by a Task Force (TF) of the European Academy of Allergy and Clinical Immunology (EAACI) Immunotherapy Interest Group, this Position Paper evaluates the currently used outcome parameters in different RCTs and also aims to provide recommendations for the optimal endpoints in future AIT trials for allergic rhinoconjunctivitis.
Results: Based on a thorough literature review, the TF members have outlined recommendations for nine domains of clinical outcome measures. As the primary outcome, the TF recommends a homogeneous combined symptom and medication score (CSMS) as a simple and standardized method that balances both symptoms and the need for antiallergic medication in an equally weighted manner. All outcomes, grouped into nine domains, are reviewed.
Conclusion: A standardized and globally harmonized method for analysing the clinical efficacy of AIT products in RCTs is required. The EAACI TF highlights the CSMS as the primary endpoint for future RCTs in AIT for allergic rhinoconjunctivitis.

Allergen immunotherapy (AIT) represents the only immune-modifying and causal treatment available for patients suffering from respiratory allergies (1, 2). The efficacy and safety of any therapeutic allergen product must be demonstrated by randomized controlled trials (RCTs) that follow the guidance in 'Good Clinical Practice: Consolidated Guidance' (ICH E6) adopted by the ICH in 1996 (3).

In accordance with the ICH E9 guidance on 'Statistical Principles for Clinical Trials', clinical studies should define primary parameters as follows: 'capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial' (4). In 2000, the US Department of Health and Human Services Food and Drug Administration (FDA) published a draft guidance document on outcome parameters in clinical development programs for drug products in allergic rhinitis (5). This was followed, in 2008, by the 'Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases' by the European Medicines Agency (EMA; 6). In this guideline, the EMA Committee for Medicinal Products for Human Use (CHMP) emphasizes that in AIT trials, the primary endpoint has 'to reflect both, symptom severity as well as the intake of rescue medication' and recommends the following outcomes as possible secondary endpoints: total symptom score, total medication score, individual symptom scores, Health-Related Quality of Life (HRQL; validated questionnaires), symptom load on a visual analogue scale (VAS), symptom-free days, physician- and patient-rated clinical global improvement and provocation tests (CHMP/EWP/18504/2006; 2008; 6).

There is a large and inevitable clinical and methodological heterogeneity on the outcome parameters used among clinical studies on AIT, including both subcutaneous and sublingual immunotherapy (SCIT and SLIT, respectively; 7). The EMA guideline states that, at present, no symptom scores (SS) or medication scores (MS) have been validated for clinical trials in AIT and that any proposed method must be scientifically justified (6).

Due to the lack of a validated method for combining SS and MS, and without strict consensus/direction from academia or regulatory authorities, a large number of different methodologies for calculating combined scores presently exist leading to difficulties when comparing results between studies (Appendix S1; based on 7 and 8).

The European Academy of Allergy and Clinical Immunology (EAACI) Immunotherapy Interest Group (IT IG) has conducted a Task Force (TF) on 'Recommendations for the standardization of clinical outcomes used in AIT trials for allergic rhinoconjunctivitis'. The aim was (i) to collect and evaluate current clinical measures of efficacy (clinical outcomes) used in clinical trials of AIT and (ii) to recommend a consensus position from a panel of experts regarding the optimal clinical outcomes supporting the future registration of products in AIT for allergic rhinoconjunctivitis (ARC).

Methodology

A first workshop on 'outcomes in AIT' was held in Madrid on 10 and 11 March 2012. The primary objectives were (i) to review the current methodologies for (both primary and secondary) outcome measures in AIT clinical research aimed to provide comparisons of clinical data published, (ii) to investigate the different methodologies published in terms of validation, (iii) to consent promising outcome measures for clinical research on AIT and (iv) to comment on the status of different outcome measures and develop further unmet needs. Based on this work, the second and third TF meetings were held in London (UK) on 2 June 2012 and in Geneva (CH) on 18 June 2012. These meetings involved methodologists and expert advisors from the Paul Ehrlich Institute (PEI), Langen, Germany, and from the EMA, London, UK. Subgroups of the TF drafted sections on the background, advantages, disadvantages and current critical issues as well as on the unmet needs and recommendations for possible outcomes. During a final 2-day workshop on the 9 and 10 of March 2013, the sections were thoroughly discussed and

Abbreviations

ACQ5, Asthma Control Questionnaire; ACS™, Allergy-Control-SCORE™; AdSS, Adjusted Symptom Score; AIT, allergen immunotherapy; AQLQ, Asthma Quality of Life Questionnaire; ARC, allergic rhinoconjunctivitis; ARCT, Allergic Rhinitis Control Test; ARIA, Allergic Rhinitis and its Impact on Asthma; CARAT, Control of Allergic Rhinitis and Asthma Test; CDSS, clinical decision support systems; CHMP, Committee for Medicinal Products for Human Use; CPT, conjunctival provocation test; CSMS, combined symptom and medication score; dMS, daily medication score; dSS, daily symptom score; EAACI, European Academy of Allergy and Clinical Immunology; ECC, environmental challenge chamber; EFA, European Federation of Allergy and Airways Diseases Patients' Associations; EMA, European Medicines Agency; ESPIA, Satisfaction Scale for Patients Receiving Allergen Immunotherapy; FDA, Food and Drug Administration; GA^{2}LEN, The Global Allergy and Asthma European Network; HDM, house dust mites; HRQL, Health-Related Quality of Life; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICP, integrated care pathways; ICT, Information and Communication Technology; IgE, immunoglobulin E; IT IG, Immunotherapy Interest Group; LOCF, last observation carried forward; MCID, minimal clinically important difference; MS, medication scores; NPT, nasal provocation test; PADQLQ, Pediatric Allergic Disease Quality of Life Questionnaire; PAR, persistent allergic rhinitis; PBI, Patient Benefit Index; PEI, Paul Ehrlich Institute; PNIF, peak nasal inspiratory flow; PP, Position Paper; QoL, quality of life; RAPP, RhinAsthma Patient Perspective; RC-ACS™, Rhino-Conjunctivitis Allergy-Control-SCORE™; RCAT, Rhinitis Control Assessment Test; RCSS, rhinoconjunctivitis symptom score; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SCIT, subcutaneous immunotherapy; SCUAD, severe chronic upper airway diseases; SF, (Medical Outcomes Study) Short-Form Health Survey; SLIT, sublingual immunotherapy; SS, symptom scores; ST, skin test; TF, Task Force; TSS, total symptom scores; VAS, visual analogue scale; WAO, World Allergy Organization.

revised. After this consensus meeting, the TF committee was responsible for drafting the Position Paper (PP) in a final form, which was circulated once again to all TF members for critical review.

The PP consists of recommendations elaborated by the workshop participants for nine domains of clinical outcome measures in AIT for ARC: (i) total symptom scores (TSS), (ii) MS, (iii) combined symptom medication score (CSMS), (iv) HRQL, (v) VAS, (vi) well and severe days, (vii) global assessments and patient satisfaction, (viii) rhinitis control and (ix) allergen provocation tests. Health economic outcomes were not considered within the scope of this paper.

European Academy of Allergy and Clinical Immunology is solely responsible for this PP, which does not represent an official document of any governmental agency such as the PEI or the EMA.

Results

Total symptom scores

Individual ARC patients are affected by nasal and ocular symptoms (2). Ideally, the interpretation of symptom scores requires a qualitative and quantitative recording of the relevant allergen exposure. The onset and duration of allergen exposure may vary significantly, from week to week, season to season (e.g. pollens) and over the annual period [e.g. house dust mites (HDM), animal danders].

The most frequently used primary efficacy criterion for symptom severity is the mean total rhinoconjunctivitis symptom score (RCSS) over a specified period related to the exposure of allergens (e.g. the entire pollen season to be precisely defined for grass pollen AIT and a selected period of HDM exposure or direct exposure to animals). The mean total RCSS is based on the daily evaluation of six to eight individual rhinitis and conjunctivitis symptoms, usually on a four-point scale.

Advantages

- There exists a well-defined terminology for two symptoms in the eye (ocular itching/grittiness/redness and ocular tearing) and for four symptoms in the nose (nasal itching, sneezing, rhinorrhoea and nasal obstruction; 5, 6).
- The 0–3 symptom score accepted by the FDA and the EMA is simple and easy to use (5, 6). The score is: 0 = no symptoms (or signs); 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated); 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable); 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

Disadvantages and current critical issues

- The mean total RCSS may include from six to eight symptoms and this may lead to discrepancies between studies and variable effect sizes.
- At present, no psychometric validation for the mean RCSS has been published.
- From the patient's perspective, the current terminology for rhinoconjunctival symptoms may not be useful universally and could be interpreted differentially (e.g. by country-specific differences).
- Because there is no consensus on the grading of symptom severity, different numerical scales have been used, making intersurvey comparisons difficult.
- A mean of daily RCSS calculated for long periods (for instance, the total season) may result in low scores, thereby underestimating the contribution of days with a high RCSS.

Unmet needs and recommendations

- We recommend the use of a homogeneous terminology for nasal and, when appropriate, conjunctival symptoms using the four to six organ-related categories as the 'daily symptom score' (dSS; Table 1a).
- We recommend that the dSS 'alone' may be used as a secondary parameter, as it does not take into account the impact of any concomitant (antiallergic) drug use. However, it should be combined with the need of rescue medication as a primary endpoint. Separated nasal and conjunctival scores may be useful as secondary endpoints when predefined and justified for the respective question of AIT trials.

Medication scores

For ethical reasons due to the long duration of RCTs, rescue medication should be prescribed to every patient in all AIT natural exposure prospective RCTs (6, 9). Allergen immunotherapy reduces symptoms as well as the use of medication in the allergic individual (2). Because the use of rescue medication has an impact on symptom severity/scores, it must be recorded on a daily basis as the MS (6, 9).

Advantages

- The MS is an indicator of AIT efficacy.
- The MS could be used as part of the assessment of the pharmacoeconomic impact of the disease.

Disadvantages and current critical issues

- Published RCTs often lack a homogeneous MS, particularly in terms of:
  - the precise medications used,
  - the indication used (stepwise or on a patient demand approach),
  - the scoring for each medication (Appendix S1).
- Patients may respond to rescue medication differently due to individual variation in drug metabolism and/or pharmacotherapy response.

Unmet needs and recommendations

- Rescue medication use is mandatory, but should be simplified and standardized. Although thorough comparative data on pharmacotherapy potency are lacking, a *stepwise approach* for rescue medication use is recommended as follows [Table 1b, modified from Canonica et al. (9)]:

Table 1 The Task Force recommendation providing (a) a homogeneous terminology for nasal and conjunctival symptoms using the six organ-related categories in the daily symptom score (dSS), (b) a stepwise use of rescue medication summed in the daily medication score (dMS) and (c) a scoring system for a combined symptom and medication score (CSMS), which is based on an equal weight of the dSS and of the dMS (based on and modified from 5, 6, 9, 13)

a) Symptom score		
Nasal symptoms	(Score 0–3)	0 = no symptoms 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated) 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable) 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)
	Itchy nose	0–3
	Sneezing	0–3
	Runny nose	0–3
	Blocked nose	0–3
Conjunctival symptoms	Itchy/red eyes	0–3
	Watery eyes	0–3
(Total) daily symptom score (dSS)*		0–3 (*max score is 3, i.e. 18 points/divided by 6 symptoms*)
b) Medication score		
	Oral and/or topical (eyes or nose) nonsedative H1 antihistamines (H1A)	1
	Intranasal corticosteroids (INS) with/without H1A	2
	Oral corticosteroids with/without INS, with/without H1A	3
(Total) daily medication score (dMS)		0–3 (*max score is 3*)
c) Combined symptom and medication score		
CSMS	**dSS (0–3) + dMS (0–3)**	**0–6**

*Max score 18/6 (i.e. 4 nasal symptoms, max score 12 and 2 conjunctival symptoms, max score 6) is optimal for studies of seasonal pollinosis. This could possibly be modified for studies of perennial allergies (e.g. in mite-allergic patients), for example max score 12/4 (i.e. 4 nasal symptoms with omission of eye symptoms). By assigning 0–3 for all individual symptoms and dividing by total number of symptoms, the symptom range 0–3 and maximum symptom score 3 would remain the same.

  - step 1: oral and/or topical (eyes or nose) nonsedative H1 antihistamines (H1A)
  - step 2: if step 1 fails, add intranasal corticosteroids (INS)
  - step 3: if step 2 fails, add oral corticosteroids
- This stepwise approach has not yet been validated, but is based on the clinical effects of pharmacotherapy on symptom reduction (9–12):
  - step 1: nonsedative H1A have a mild effect on the TSS
  - step 2: INS have a moderate effect on the TSS
  - step 3: oral corticosteroids ameliorate all symptoms
- It has been demonstrated that such an approach is associated with a large effect size in immunotherapy trials, thereby providing high power to show treatment efficacy (13).
- For standardization purposes, we recommend the use and supply of precise drugs alongside with advised daily dosages in each study and for each step (2).
- We recommend analysing the 'daily medication score' (dMS) based on this stepwise use of rescue medication (Table 1b). However, this endpoint needs further validation.

Combined symptom medication score

The EMA emphasizes that no validated system for a 'weighted' symptom and medication score in a single combined score exists (6). Therefore, initiatives for establishing a balanced and validated scoring system would be helpful for future assessments and should be encouraged and supported by the interested parties.

Advantages

- A standardized CSMS is recommended as an easy-to-understand analysis of the daily burden of the disease (as the primary outcome measure; 4) by both the FDA and EMA (a primary outcome parameter in AIT trials should 'reflect both, symptom severity as well as the intake of rescue medication'; 6).
- The use of a standardized CSMS as the primary outcome parameter will allow direct comparisons between different clinical trials.
- The principle of equally combining symptom scores and medication scores has been found to be associated with a large effect size, thereby leading to a high power to show treatment efficacy (13).

Disadvantages and current critical issues

- At present, this CSMS has not been validated.

Unmet needs and recommendations

- We recommend a scoring system for the CSMS (Table 1c, modified from ref. 5, 6, 9, 13) based on an equal weight of the dSS (0–3) and of the dMS (0–3) in the daily total CSMS (0–6). The proposed dSS (Table 1a) uses a well-defined and easy-to-understand terminology for symptoms of the nose (itchy nose, sneezing, runny nose, blocked nose) and of the eye (itchy/red eyes, watery eyes). The dMS (Table 1b) is based on the World Allergy Organization (WAO) recommendations on a stepwise approach in giving rescue medication (9).
  The recommendations follow the EMA guideline (6) with the exception that we have used input from patient organizations to simplify the symptom terminology (middle panel) for participants in clinical trials.
- Psychometric validation of the CSMS in multicentre, multinational trials is needed.
- The use of this CSMS is recommended in future clinical trials of AIT for allergic rhinoconjunctivitis.
- If assessments aim to analyse 'real-life' data (optimal control combining medications and AIT), then novel methodologies using decision aids [information and communication technology (ICT), clinical decision support systems (CDSS)] may be useful (see section 'Outlook – Future developments in analysing endpoints'; 14, 15).

Health-Related Quality Of Life

The importance of HRQL in allergic diseases has been well recognized. Generic questionnaires [such as the SF-36 (16) and the SF-12 (17)] measure physical, psychological and social domains in all health conditions, irrespective of the underlying disease. Disease-specific instruments (such as the Rhinoconjunctivitis Quality of Life Questionnaire, RQLQ) have been designed by asking patients what kind of problems they experience from their disease and how AIT can prevent the impairment in QoL during relevant allergen exposure.

As disease-specific instruments are more responsive to change, these questionnaires are appropriate for use in RCTs. The most frequently used rhinoconjunctivitis specific instruments – the RQLQ (18) and its variations for adults [standardized RQLQ (19), mini-RQLQ (20)] and other age groups [Paediatric (21) and Adolescent RQLQ (22)] – are used in AIT trials. The RHINASTHMA (23) – an instrument capturing both rhinitis and asthma – has been used in observational studies only (24, 25).

Advantages

- The RQLQ has been validated. It has been tested in terms of internal consistency and reproducibility, distinguishing severe, controlled and uncontrolled patients and/or healthy subjects. It has been compared with other outcomes such as daily nasal symptoms (26), VAS (27, 28) and nonspecific nasal hyperreactivity (26).
- The RQLQ appears to be responsive to change. It has been shown that the mini-RQLQ is more responsive to change than the classical version (20).
- It addresses the patient's perspective.
- The EMA acknowledges its importance. From a regulators' point of view, efficacy and safety endpoints are essential for the approval of a new medicinal product. Health-Related Quality of Life assessment can be included as an endpoint when improvement in quality of life is a claim upon registration. Furthermore, the EMA has put forward HRQL assessment as a possible secondary endpoint (6).
- The minimal clinically important difference (MCID) for the RQLQ has been derived from the method used for the Asthma Quality of Life Questionnaire (AQLQ; 29) and from a study including a limited number of seasonal allergic rhinoconjunctivitis adult patients (30). For the RQLQ (19) and mini-RQLQ (20), the MCID is 0.5 and 0.7, respectively. This is only useful for the measurement of change in HRQL within the group (and not between groups). For this, a baseline measurement is needed for a proper analysis.
- The RQLQ has been translated and validated in different languages. This comprises a formal process of translation, back-translation and analysis of the psychometric characteristics of the translated questionnaire.

Disadvantages and current critical issues

- The RQLQ and its variants are lengthy. This might be cumbersome for patients if a trial design were to require repeated measurements. The mini-RQLQ (20) can be seen as an attempt to reduce this.
- The RQLQ comprises a 1-week evaluation. Relevant days of significant exposure (with symptoms) can be missed.
- The RQLQ and its variants might be re-evaluated. Items from the 'other', 'non-hay fever' and 'emotional' domains of the RQLQ (using the paediatric respectively the adolescent RQLQ) do not substantially change during the pollen season (31). Although well accepted, the MCID of 0.5 for the RQLQ has been extrapolated from small studies on allergic diseases (29, 30) and from two studies on patients with heart and lung diseases (32, 33).
- In some RCTs, the RQLQ score improves by up to 1 in the placebo group and the MCID of 0.5 appears not to be confirmed (34). This may require further evaluation.

Unmet needs and recommendations

- Health-Related Quality of Life assessments should be included in all AIT trials. From a clinical perspective, inclusion of the HRQL instrument is a valuable addition.
- Re-evaluation of existing instruments and validation of new tests might be recommendable.

Visual analogue scale

The VAS is a psychometric response scale that assesses global rhinoconjunctivitis discomfort. It can also assess every single symptom and its impact. Patients grade their symptoms by putting a vertical line on a 10-cm line representing severity from 0: 'no symptoms' to 10: 'highest level of symptoms' (9). The continuous (or 'analogue') aspect of the VAS differentiates it from discrete scales such as the numerical rating scale. The VAS has been widely used for the assessment of subjective symptoms, such as pain (35).

Advantages

- The VAS has been fully validated in adult patients (27) and correlates well with the severity of allergic rhinitis (according to ARIA; 28). It provides a quantitative evaluation of disease severity (27).
- The VAS is a simple measure of severity and possibly control.
- It is easy to use and well accepted by the patient.
- It can be easily translated.
- It has been proved to be sensitive to pharmacotherapy treatment response in adults (27) and correlates well with both symptom scores and the RQLQ (36).
- It has been used in AIT RCTs, both in adults (37, 38) and in children (39, 40).
- The VAS is also useful when comparing individual patients during the study period.

Disadvantages and current critical issues

- Assessment is clearly subjective.
- It does not represent the duration of symptoms.
- It has not yet been fully validated in paediatric populations.

Unmet needs and recommendations

- We recommend using the VAS in AIT RCTs as a secondary outcome.
- Visual analogue scale measurement could be implemented through the use of new technologies and portable devices in postmarketing studies.

Well and severe days

Both 'well days' and 'bad/severe days' have been proposed as secondary and exploratory outcomes (41–48). The EMA has recommended implementing a report of efficacy in the guideline with the evaluation of 'days with symptom control' as defined as 'days without intake of rescue medication and a symptom score below a predefined and clinically justified threshold' (6). The EMA has also recommended the inclusion of symptom-free days as secondary endpoints (6).

'Well days' have been analysed in an increasing number of AIT RCTs (41–46, 49, 50). However, the definition of the 'clinically justified threshold' symptom score is heterogeneous between different trials (8).

Among the many definitions proposed for the 'severe days' concept, it was recently defined as 'a symptom score of 3 in any of the six rhinoconjunctivitis symptoms' (48, 51).

Advantages

- It is easy to assess once the SS and MS have been collected.
- Including well and severe days, assessment as secondary outcomes in the same study could give an approximation of the extreme values and the range of severity scores of the patients. There is a significant and reliable correlation between days with severe symptoms and the RQLQ (51).

Disadvantages and current critical issues

- The definition of 'clinically justified threshold' is too imprecise, leading to divergent approaches.
- The inevitable high numbers of 'well days' in both active- and placebo-treated participants during the season make the test poorly discriminating, whereas this may not be the case for 'bad/severe' days.

Unmet needs and recommendations

- We recommend combining the definition for both well and severe days.
- We recommend running and validating both variables in AIT RCTs prospectively.

Global assessments and patient satisfaction

In an attempt to measure patient satisfaction and the global efficacy of allergic rhinitis treatments, several tools have been proposed such as the 'Satisfaction Scale for Patients Receiving Allergen Immunotherapy' (the ESPIA questionnaire; 52). This tool consists of a 16-item questionnaire divided into four categories. The 'Patient Benefit Index' (PBI; 53) is based upon 25 questions that are run to the patient twice and that, after some calculation, elicit a satisfaction index for the treatment of allergic rhinitis. Other approaches have been carried out previously by simply asking the patient the following question: 'Compared to your symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season?' (45).

Advantages

- It retrospectively assesses the individual patient's response to therapy.
- It is quick and easy to answer.
- The questionnaires have been validated (psychometric analyses; 52, 53).
- Floor/ceiling effects are low (52): minimizing outliers.
- The results of the questionnaires correlate well with a reduction in eye and nose symptoms and with HRQL (53).

Disadvantages and current critical issues

- So far, there is no multilanguage version.
- There is a risk of retrospective bias (overestimation of interventional effects).
- The use in AIT RCTs is limited as of yet.

Unmet needs and recommendations

- It could be improved using new electronic technologies proposed for VAS or for other control questionnaires.
- We recommend exploring these tools in AIT RCTs prospectively.

Rhinitis control

Disease control is now being considered as an alternative to disease severity in the management of patients with respiratory disease. Several allergic rhinitis control questionnaires have been built and validated in noninterventional studies (Control of Allergic Rhinitis and Asthma Test (CARAT10; 54, 55), Rhinitis Control Assessment Test (RCAT; 56), Allergic Rhinitis Control Test (ARCT; 57) and RhinAsthma Patient Perspective (RAPP; 25)). Some of these new tools such as the CARAT are being digitalized.

Advantages

- The questionnaires are quick and easy to answer.
- They have been validated (psychometric analyses).
- They address other aspects of the disease (correlation of the CARAT with the Asthma Control Questionnaire (ACQ5) and symptoms VAS; 55).
- Most questions are multilingual.

Disadvantages and current critical issues

- They have not yet been used in AIT RCTs.
- They have not yet been validated in paediatric populations.

Unmet needs and recommendations

- We recommend exploring these tools in AIT RCTs prospectively.

Allergen provocation tests

Allergen provocation testing involves the administration of a single concentration or incremental concentrations of allergen locally to the skin or target organ (conjunctiva, nose or bronchi) in order to provoke a subjective and objective allergic response. The result may be expressed either as the quantitative response to a single concentration or as the provocation concentration to induce a predetermined allergic response. Provocation tests comprise allergen skin test (ST) titration, conjunctival (CPT) and nasal provocations (NPT) as well as environmental challenge chamber (ECC).

Advantages

- Allergen provocation tests directly measure the changes in allergen sensitivity in target organs.
- Allergen provocation testing provides the opportunity for more standardized procedures, the ability to control the environment (e.g. temperature, humidity), an avoidance of seasonal variation and the performance of single-centre studies requiring fewer participants. It also enables mechanistic studies.
- ST was validated for research use by Dreborg (58, 59) and was used as a surrogate marker in several AIT trials (60–63).
- CPT was validated by Moller et al. (64) (methodical details in 65, 66). This test has also been used to document conjunctival response to AIT (67), with results highly comparable to those observed in NPT (68) and bronchial inhalation challenge testing (69). In one long-term trial on grass pollen AIT, there was a 10- to 30-fold decrease in immediate conjunctival allergen sensitivity that paralleled clinical improvement and persisted for 3 years after discontinuation of AIT (70). Moreover, a decrease in conjunctival inflammatory parameters in the course of AIT has been demonstrated (71).
- For NPT, several objective methods for evaluating (nasal) airflow such as rhinomanometry and peak nasal inspiratory flow (PNIF) can be used to combine (subjective) symptom scores with (objective) results to assess the changes in nasal allergen sensitivity (72). This organ-specific challenge test has been used in multiple proof-of-concept studies (62, 73) and for evaluating mechanisms and the dose–response relationship for AIT, in order to select an appropriate dose for phase II/III trials (6). Explorative studies revealed a decrease in nasal allergen sensitivity after AIT (74–76). Nasal fluid may be sampled by lavage (77, 78). Bronchial challenge has also been used for proof-of-concept studies (69, 79) but is time-consuming and not without risks.
- ECC is presented as an attractive alternative surrogate for natural allergen exposure (80). Several studies have shown the onset of AIT effects (81, 82) and a good correlation between symptom responses during pollen exposure in the ECC compared to natural seasonal exposure in the same individuals (83–85).

Disadvantages and current critical issues

- In general, allergen provocation testing can never represent 'real-life' studies (i.e. surrogacy unproven), and standardization and validation vary for the different challenges.
- Recent data on ST support that suppression of the late skin response may be necessary, but not sufficient for the therapeutic effect of AIT (60).
- CPT comprises mostly subjective parameters (scoring system of symptoms), but does not include easily objective parameters. Moreover, at present, a heterogeneity of the scoring system for CPT exists (64, 67, 86).
- NPT is more complex than CPT and ST. Moreover, objective methods (rhinomanometry, PNIF and others)

are not thoroughly standardized and have not been validated.
- Not all available allergen products are authorized for both diagnostic and therapeutic use.
- To date, only a few ECC exist internationally. The reproducibility of ECC within and between sites has not yet been determined (83–85).

Unmet needs and recommendations
- At present, there is no substitute for the clinical response to natural allergen exposure as the primary outcome in phase III RCTs. Hence, the relationship of allergen challenge methods to clinical efficacy merits further investigation.
- Allergen provocation tests are recommended for understanding underlying mechanisms, biomarker discovery, proof-of-concept for onset of action, novel AIT approaches and allergen dose ranging (6).
- Further studies are also warranted for standardization and full validation. Pending results, ECC is likely to be a good option as an adjunct to natural exposure studies for phase III RCTs.

Outlook – future developments in analysing endpoints: telemonitoring, integrated care pathways and clinical decision support systems to select patients and assess efficacy of AIT

Patient stratification is needed to identify the most appropriate patients for whom AIT is sufficient. It is critical for the delivery of a cost-effective health system. Although studies are not all consistent, in many diseases, tools including integrated care pathways (ICPs), telemonitoring and CDSS have improved the management of patients with chronic diseases (14, 87).

These innovative tools are currently being developed for the management of allergic rhinitis [AIRWAYS-ICPs led by the European Innovative Partnership on Active and Healthy Ageing, and the Sentinel Network (GA^2LEN and the European Parliament; 88)] and can be combined to assess some of the unmet needs of AIT:
- Assessment of the prevalence and severity of allergic diseases.
- Phenotypic characterization of allergic patients, stratification of patients, characterization of uncontrolled severe chronic upper airway diseases (SCUAD) patients (89) and characterization of patients to be treated by AIT.
- Randomized controlled trials (placebo-controlled or real-life cluster randomized trials).
- Follow-up of patients in clinical settings during AIT and after AIT has been stopped.

Discussion

Several clinical parameters are commonly used to assess the clinical efficacy of AIT as primary and secondary endpoints (6, 8, 9). However, in the current literature on both SCIT and SLIT clinical trials, a wide variety of endpoints for clinical efficacy has been described (7), and there is a major need for harmonization. This EAACI Task Force PP clearly overviews different outcome measures as described in recent AIT trials, emphasizes the pros and cons of different measures and, finally, gives clear recommendations on the feasibility and implementation of these measures.

In the 2008 guidelines, the EMA clearly states that both SS and MS should be assessed as primary endpoints in AIT trials but leaves the question open as to whether they should be generally analysed together in a combined score (6). Moreover, no clear guidance is given on how both scores should be ideally 'weighted'. Besides such a combined analysis, the regulators accept more than one primary endpoint (co-primary endpoints) if ranked and predefined for pan-European authorization but, in this scenario, they all need to be positive (43). As a consequence, current trials from different manufacturers are using primary endpoints which are related to the EMA and WAO recommendations in some way. However, these analyses are based on different SS and different calculations of the MS (Appendix S1). At present, no combined scores have been validated aiming to reproduce a 'weighted' balance between the SS and MS as proposed by the WAO (6, 8, 9).

The FDA and EMA recommendation of scoring individual rhinoconjunctival symptoms on a scale between 0 and 3 (5, 6) is a standardized method with easy feasibility from the patients' point of view. As such, six individual rhinoconjunctival allergic symptoms are preferably to be assessed in pollen-allergic patients. Patients with persistent allergic rhinitis (PAR) due to sensitization, for example to mites, are mostly affected by nasal symptoms and may therefore be analysed without taking conjunctival symptoms into account. The proposed terminology for the individual symptoms in this document was elaborated with the European Federation of Allergy and Airways Diseases Patients' Associations (EFA). The mean dSS will range between 0 and 3 points (0–18 points/six symptoms in pollen-allergic patients respectively 0–12 points/four symptoms in PAR patients). We recommend not to include symptoms of the lower airways for analysis of the primary endpoint in AIT trials for ARC. They may, however, be included in the secondary outcomes for patients who suffer from both rhinoconjunctivitis and asthma.

In clinical trials on AIT, allergic patients are provided with medication for ethical reasons (9). This will alleviate the daily 'symptom load' of the underlying disease in both active and placebo-treated patients. Because of these interdependencies between symptoms and drug use, the TF recommends the assessment of both SS and MS as a 'combined score' for a primary endpoint. In line with the WAO recommendations (9), we recommend a stepwise approach of supplying rescue medication. The daily dosage of the medication should comply with the summary of the product characteristics. In accordance with this stepwise approach, the mean dMS will range from 0 to 3 points. The daily combined symptom medication score (CSMS) is calculated by equally adding the dSS and the dMS to a scale of between 0 and 6 points (based on and modified from 5, 6, 9, 13). Although not yet validated, this proposal attempts to standardize the practice of rescue medication in clinical

trials. Among other combined symptom and medication scores developed (Appendix S1), a novel 'Rhino-Conjunctivitis Allergy-Control-SCORE' (RC-ACS™; 90) for daily nasal and conjunctival symptoms as well as the 'Allergy-Control-SCORE' (ACS™; 91) recording daily nasal, conjunctival and lung symptoms have been developed and validated. Another methodology has been published as the average 'Adjusted Symptom Score' (AdSS) as a primary endpoint (92). This carries forward the TSS from the day before rescue medication is taken until the medication is paused again ['last observation carried forward' (LOCF)]. The aim is to reflect the interactions of rescue medication on the daily 'symptom load' of patients. This approach does not take into account the stepwise approach as recommended by the WAO (9) and the pharmacologically weighted impact of the different class of antiallergic medication on the TSS.

Taken together, the TF recommends this homogeneous CSMS described above as an easy and standardized method to balance both symptoms and the need of antiallergic medication in an equally weighted manner. The CSMS should be used in future clinical (phase III) AIT trials for allergic rhinoconjunctivitis in the aim to achieve a better comparability of results from different studies. In a next step, this CSMS should be validated in a multinational, well-powered phase III study. By this validation process, a definition of the minimal clinically important difference may be feasible.

Multiple methods are recommended by the EMA guidelines as secondary outcome measures in AIT trials such as total symptom score, total medication score, individual symptom scores, HRQL, symptom load on a VAS, symptom-free days, physician- and patient-rated clinical global improvement and provocation tests (6, reviewed in 8). Some of these measures have already been validated. Moreover, certain tools for patient-reported outcomes and their practical use in clinical trials have been reported in the GA^{2}LEN recommendations (93). Under these recommendations, the Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ; 94) as well as the RQLQ, as disease-specific questionnaires, assess the disease from the patients' perspectives. The RQLQ has been validated for adults (18, 19), adolescents (22) and children (21) with (allergic) rhinoconjunctivitis symptoms. These questionnaires have also been translated and validated in different languages and have been widely used in clinical trials on both sublingual AIT (43, 95, 96) and subcutaneous AIT (38, 97). The importance of this measure is related to an adequately powered dose-range phase IIb study on SCIT with 410 grass pollen-allergic patients (UKIS; 38), which indicates this secondary parameter as an useful instrument in the interpretation of dose-related clinical effects of subcutaneous AIT.

However, in a recently published clinical trial comparing the RQLQ of pollen-allergic children and adolescents, the three domains 'other', 'non-hay fever' and 'emotional' were not able to discriminate pollen season values from out-of-season values (31). Although the RQLQ can be considered as one of the best validated outcome measures in this field (18, 19), these recently published data suggest that the RQLQ could be further optimized. It might be recommendable to re-evaluate and validate RQLQ domains and the MCID for paediatric, adolescent and adult patients.

As another method of assessing the disease from the patients' perspectives, the VAS is a useful, easy and (partially) validated measure to be included in clinical trials on AIT aimed to provide a quantitative evaluation of disease severity (27). Despite some of the disadvantages outlined above, we recommend the use of this validated measure in future clinical AIT trials. Its advantages may also be expanded by using new technologies combining a smartphone application and a decision clinical support system using integrated care pathways as elaborated under the umbrella of GA^{2}LEN and the European Parliament (88). We also recommend these technologies for global assessments such as the validated 'Satisfaction Scale for Patients Receiving Allergen Immunotherapy' (52) and others which can retrospectively quickly assess the patient's response and satisfaction to AIT. At present, the use of these assessments in AIT RCTs is limited but may be improved by exploring these new electronic technologies for these measures.

As described above, all of these endpoints have their advantages and disadvantages. Among children, especially young children, the evaluation of the efficacy of AIT is performed mainly by the parents. Even though the PADQLQ (94) and (paediatric-specific) RQLQ (21) may have found cross-sectional and longitudinal validity, thus providing a potentially useful outcome measure in the evaluation of systemic treatments, there are still some risks of under- or overestimation of the outcome measures by the parents. This is also true for all of the above-mentioned other outcome measures. The unmet need is how to optimize, for example, the diaries in order to meet this challenge and to get the individual opinion of the child, without (too much) influence from the parents. We have not yet been able to solve this problem sufficiently.

Besides assessing the 'symptom load' as a primary endpoint or as several secondary endpoints as outlined above, the EMA guidelines recommend to also evaluate days 'without intake of rescue medication and a symptom score below a predefined and clinically justified threshold' (6, reviewed in 8). As a consequence of this imprecise definition, divergent definitions of the 'clinically justified thresholds' for TSS have been elaborated, mostly in recent studies on sublingual AIT (41–47). Although this measure may allow an approximation of the extreme values or 'range of severity' and a good correlation with the TSS and the RQLQ, it is also influenced by disadvantages hampering symptom/MS as outlined above. Taken together, we recommend the development of a standardized definition for both well and severe days (48), which should be the basis for further prospective evaluation in clinical AIT trials.

Another validated psychometric analysis is the 'rhinitis control' assessed in questionnaires and used in noninterventional studies on allergic rhinitis patients (54, 56, 57, 98). Below these, the 'ARCT' has been evaluated in 902 allergic patients and has revealed a correlation with the disease burden of rhinitis as well as improvement under treatment (57, 98). Further exploration is justified for future planned trials.

A major hurdle for the studies of AIT has been the variability of natural seasonal pollen exposure, low pollen counts having a substantial impact on the ability to detect differences between active and placebo treatments (51). In this context, it is reasonable to revisit/explore alternative solutions. The EMA guideline underlines that 'provocation tests (e.g. conjunctival, nasal or bronchial provocation or allergen exposure in allergen challenge chambers) and/or clinical endpoints may be used as primary endpoints' in early-stage, proof-of-concept and dose-ranging (phase II) trials (6).

At present, it would appear that if problems of standardization and reproducibility can be demonstrated for challenge methods such as ST, NPT and CPT, then clinical trials are justified for proof-of-concept and dose-ranging studies. The ECC might be a reasonable adjunct to natural pollen exposure for phase II/III trials, whereas provocation testing (particularly NPT and CPT) retains a place for proof-of-concept studies, concepts for understanding the immunological mechanisms and for AIT dose-ranging studies (6).

Conclusion

At present, a validated and generally accepted method for combining symptom and medication scores (as primary endpoints) as well as for defining and standardizing secondary endpoints is still lacking. Furthermore, there is no strict consensus/direction from academia or regulatory authorities for clinical AIT trials. As a consequence, a large number of different methodologies for analysing clinical results of AIT trials have been described.

Therefore, this PP on clinical outcomes in AIT trials, as proposed by the EAACI Immunotherapy Interest Group, has reviewed all of the relevant current clinical measures of efficacy (clinical outcomes) used in clinical AIT trials of ARC patients with/without asthma. These measures have been reviewed in the light of their potential advantages as well as their respective drawbacks. Furthermore, unmet needs and specific recommendations on all nine domains have been addressed. This EAACI PP recommends the CSMS as the primary endpoint for future clinical trials in AIT for allergic rhinoconjunctivitis.

Acknowledgments

The TF was financed by EAACI. The authors would like to thank EAACI for their financial support in the development of this TF report and also Ms Anna Bedbrook for her assistance with the English language which was financed by a grant provided by EAACI. We warmly thank Prof Dr Stefan Vieths and Dr Susanne Kaul (Paul Ehrlich Institute, Langen, Germany) for their helpful comments. We also thank Breda Flood and Susanna Palkonen from the European Federation of Allergy and Airways Diseases Patients' Association (EFA) for their advice on the proposed terminology for the individual symptoms as well as for their review and fruitful comments on this document. Additionally, we thank Simon Lawton (ALK Abello, Hørsholm, Denmark) for his critical review and comments.

Conflicts of interest

Oliver Pfaar (OP) has received research grants from ALK-Abello (Denmark), Allergopharma (Germany), Stallergenes (France), HAL-Allergy (The Netherlands), Artu Biologicals (The Netherlands), Allergy Therapeutics/Bencard (UK/Germany), Hartington (Spain), Lofarma (Italy), Novartis/Leti (Germany/Spain), GlaxoSmithKline (UK/Germany), Essex-Pharma (Germany), Cytos (Switzerland), Curalogic (Denmark), Roxall (Germany), Biomay (Austria), ThermoFisher (Germany) and MEDA-Pharma GmbH (Germany) and/or he has served as advisor and on the speakers' bureaus for some of the aforementioned companies. OP has received travel grants from HAL-Allergy (Netherlands/Germany) and Allergopharma (Germany) and is a consultant for Bencard (Germany), HAL-Allergy (The Netherlands), Novartis (Germany), MEDA (Germany) and Stallergenes (France). OP is the current chairman of the EAACI Immunotherapy Interest Group and secretary of section ENT of DGAKI.

Pascal Demoly (PD) is a consultant and a speaker for Stallergenes, ALK, Circassia, Allergopharma, Pierre Fabre Médicaments and Chiesi and a speaker for Merck, Astra Zeneca, Menarini and GlaxoSmithKline. PD is VP Education & Specialty for EAACI.

R. Gerth van Wijk (RGW) received fees for consultancy for MSD, HAL, Novartis and Crucell. He received research grants from NWO, STW, Novartis, Biomay, DBV and ALK. He received payment from lectures from Allergopharma and payment for manuscript preparation from Chiesi. Royalties from De tijdstroom and Bohn, Stafleu, van Loghum.

Sergio Bonini (SB) reports personal fees from Stallergenes, outside the submitted work; and Expert-on-Secondment at the European Medicine Agency (EMA).

Jean Bousquet (JB) has received honoraria for:

Scientific and advisory boards – Actelion, Almirall, MEDA, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach.

Lectures during meetings – Almirall, AstraZeneca, Chiesi, GSK, MEDA, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering Plough, Takeda, Teva, Uriach.

Board of Directors – Stallergenes.

Giorgio Walter Canonica (GWC) has been in the last five years consultant as a single scientist or in national/international boards, researcher in scientific trials in university or in collaboration with other research institutions, speaker in scientific meetings, seminars and educational activities devoted to specialists, general practitioners and other healthcare professionals, totally or partially supported by the following commercial companies: ALK-Abello, Allergopharma, Allergy Therapeutics, Anallergo, HAL, Lofarma, Merck, Stallergenes.

Stephen R. Durham (SRD) has received grants via Imperial College from ALK Denmark, and Honoraria for lectures and/or consultancy fees via Imperial College for ALK, Merck, Stallergenes, Circassia and Boehringer Ingelheim.

Lars Jacobsen (LJ) is a consultant for EAMG (European Allergen Manufacturers Group) and individual members hereof.

Hans-Jørgen Malling (HJM) declares that he has served as a consultant for and received payment for providing expert testimony on behalf of ALK-Abello (Denmark) and Stallergenes (France); has received grant support to his institution from ALK-Abello (Denmark), Stallergenes (France), Biomar (Austria), Anergis (Switzerland), Danish National Institute of Health, Tryg Foundation and EU commission.

Ralph Mösges (RM) reports personal fees and nonfinancial support from ALK-Abello, personal fees and nonfinancial support from Allergy Therapeutics/Bencard, personal fees from Allergopharma, grants and personal fees from Biotech Tools, nonfinancial support from Dr. Beckmann/Roxall, grants, personal fees and nonfinancial support from Lofarma, personal fees from MSD, personal fees from Leti, personal fees from Novartis, personal fees from Paladin, grants and personal fees from Stallergenes, outside the submitted work.

N. G. Papadopoulos (NGP) has received payment for consultancy from AbbVie, Novartis, Menarini, MEDA for lectures from Novartis, URIACH, GSK, ALLERGOPHARMA, Stallergenes for the development of educational presentations from URIACH, MEDA and grants from Nestle, MSD and GSK.

Sabina Rak (SR) has received research grants, been speaker and served on advisory board for Stallergenes and also participated in clinical studies. She has been speaker and received grants for Allergopharma and speaker for ALK. SR served on advisory board for Circassia and received research grants from Allergis.

Pablo Rodriguez-del-Rio (PRR) declares that he has no conflict of interest.

Erkka Valovirta (EV) declares that he has no conflict of interest.

U. Wahn (UW) has received research grants from Danone, Hipp, Symbiopharma, Stallergenes and Allergopharma. He received Honoraria for Consultation and Speakers Fees from Thermo-Fisher, Allergopharma, Merck, MEDA, Stallergenes, Novartis and Danone.

Moises A Calderon (MAC) has received lecture honorarium from ALK, Stallergenes, Allergopharma and Merck and consultancy honorarium from ALK, Stallergenes and HAL-Allergy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Examples of different formulae for calculating the combined symptom and medication score in recently published clinical trials on AIT.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108** (Suppl 5):S147–S334.
2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86):8–160.
3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). ICH E 6: Guidance for Industry. Good Clinical Practice: Consolidated Guidance. 1996.
4. The European Agency for the Evaluation of Medicinal Products (EMA). ICH E 9: Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96) 1998.
5. U.S. Department of Health and Human Serviced, FDA Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Allergic Rhinitis: Clinical Development Programs for Drug Products. Draft Guidance. 2000.
6. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases. 2008.
7. Calderon MA, Eichel A, Makatsori M, Pfaar O. Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials. *Curr Opin Allergy Clin Immunol* 2012;**12**:249–256.
8. Pfaar O, Kleine-Tebbe J, Hormann K, Klimek L. Allergen-specific immunotherapy: which outcome measures are useful in monitoring clinical trials? *Immunol Allergy Clin North Am* 2011;**31**:289–309.
9. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;**62**:317–324.
10. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;**116**:338–344.
11. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466–476.
12. Canonica GW, Compalati E. Minimal persistent inflammation in allergic rhinitis: implications for current treatment strategies. *Clin Exp Immunol* 2009;**158**:260–271.
13. Clark J, Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. *Allergy* 2007;**62**:1023–1028.
14. Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2011;**10**:CD001431.
15. Drug and Therapeutics Bulletin. An introduction to patient decision aids. *BMJ* 2013;**347**:f4147.
16. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;**94**:182–188.
17. Laforest L, Bousquet J, Pietri G, Sazonov Kocevar V, Yin D, Pacheco Y et al. Quality of life during pollen season in patients with seasonal allergic rhinitis with or without asthma. *Int Arch Allergy Immunol* 2005;**136**:281–286.
18. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77–83.
19. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol* 1999;**104**:364–369.

20. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire. *Clin Exp Allergy* 2000;**30**:132–140.
21. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol* 1998;**101**:163–170.
22. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994;**93**:413–423.
23. Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy* 2003;**58**:289–294.
24. Sieber J, Gross A, Shah-Hosseini K, Mosges R. The RHINASTHMA GAV scores without SLIT, at the beginning and at the end of seasonal SLIT. *Asian Pac J Allergy Immunol* 2010;**28**:232–236.
25. Braido F, Baiardini I, Stagi E, Scichilone N, Rossi O, Lombardi C et al. RhinAsthma patient perspective: a short daily asthma and rhinitis QoL assessment. *Allergy* 2012;**67**:1443–1450.
26. de Graaf-in 't Veld T, Koenders S, Garrelds IM, Gerth van Wijk R. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. *J Allergy Clin Immunol* 1996;**98**:508–513.
27. Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. *J Allergy Clin Immunol* 2009;**123**:1349–1354.
28. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Mechin H, Daures JP et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007;**62**:367–372.
29. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;**47**:81–87.
30. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;**98**:843–845.
31. Roder E, Berger MY, Hop WC, de Groot H, van Wijk RG. The relevance of patient-reported outcomes in a grass pollen immunotherapy trial in children and adolescents with rhinoconjunctivitis. *Pediatr Allergy Immunol* 2013;**24**:39–48.
32. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;**10**:407–415.
33. Guyatt GH, Nogradi S, Halcrow S, Singer J, Sullivan MJ, Fallen EL. Development and testing of a new measure of health status for clinical trials in heart failure. *J Gen Intern Med* 1989;**4**:101–107.
34. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol* 2012;**129**:1282–1289.
35. Langley GB, Sheppeard H. The visual analogue scale: its use in pain measurement. *Rheumatol Int* 1985;**5**:145–148.
36. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy* 2013;**43**:881–888.
37. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;**60**:801–807.
38. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**117**:319–325.
39. Kuna P, Kaczmarek J, Kupczyk M. Efficacy and safety of immunotherapy for allergies to Alternaria alternata in children. *J Allergy Clin Immunol* 2011;**127**:502–508.
40. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;**109**:251–256.
41. Worm M. 'Well days' after sublingual immunotherapy with a high-dose 6-grass pollen preparation. *Allergy* 2009;**64**:1104–1105.
42. Wahn U, Klimek L, Ploszczuk A, Adelt T, Sandner B, Trebas-Pietras E et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2012;**130**:886–893.
43. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**117**:802–809.
44. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;**61**:185–190.
45. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**118**:434–440.
46. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;**123**:167–173.
47. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;**120**:1338–1345.
48. Durham SR, Birk AO, Andersen JS. Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy* 2011;**66**:120–123.
49. DuBuske LM, Frew AJ, Horak F, Keith PK, Corrigan CJ, Aberer W et al. Ultra-short-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc* 2011;**32**:239–247.
50. Pfaar O, Urry Z, Robinson DS, Sager A, Richards D, Hawrylowicz CM et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy*. *Allergy* 2012;**67**:272–279.
51. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;**129**:717–725.
52. Justicia JL, Cardona V, Guardia P, Ojeda P, Olaguibel JM, Vega JM et al. Validation of the first treatment-specific questionnaire for the assessment of patient satisfaction with allergen-specific immunotherapy in allergic patients: the ESPIA questionnaire. *J Allergy Clin Immunol* 2013;**131**:1539–1546.
53. Franzke N, Schafer I, Jost K, Blome C, Rustenbach SJ, Reich K et al. A new instrument for the assessment of patient-defined benefit in the treatment of allergic rhinitis. *Allergy* 2011;**66**:665–670.
54. Nogueira-Silva L, Martins SV, Cruz-Correia R, Azevedo LF, Morais-Almeida M, Bugalho-Almeida A et al. Control of allergic rhinitis and asthma test–a formal approach to the development of a measuring tool. *Respir Res* 2009;**10**:52.
55. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Sa-Sousa A, Azevedo LF,

Ferreira J et al. Control of Allergic Rhinitis and Asthma Test (CARAT) can be used to assess individual patients over time. *Clin Transl Allergy* 2012;**2**:16.
56. Nathan RA, Dalal AA, Stanford RH, Meltzer EO, Schatz M, Derebery J et al. Qualitative Development of the Rhinitis Control Assessment Test (RCAT), an Instrument for Evaluating Rhinitis Symptom Control. *Patient* 2010;**3**:91–99.
57. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. *Clin Exp Allergy* 2011;**41**:860–868.
58. Dreborg S, Frew A. Allergen standardization and skin tests. EAACI Position paper. *Allergy* 1993;**48**(Suppl 44):49–82.
59. Malling H-J, Weeke B. Immunotherapy. Position Paper of the European Academy of Allergology and Clinical Immunology (EAACI). *Allergy* 1993;**48**(Suppl 14):9–35.
60. Francis JN, James LK, Paraskevopoulos G, Wong C, Calderon MA, Durham SR et al. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. *J Allergy Clin Immunol* 2008;**121**:1120–1125.
61. Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;**51**:430–433.
62. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;**82**:439–446.
63. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. *J Allergy Clin Immunol* 1990;**85**:460–472.
64. Moller C, Bjorksten B, Nilsson G, Dreborg S. The precision of the conjunctival provocation test. *Allergy* 1984;**39**:37–41.
65. Moller C, Elsayed S. Seasonal variation of the conjunctival provocation test, total and specific IgE in children with birch pollen allergy. *Int Arch Allergy Appl Immunol* 1990;**92**:306–308.
66. Sacchetti M, Micera A, Lambiase A, Speranza S, Mantelli F, Petrachi G et al. Tear levels of neuropeptides increase after specific allergen challenge in allergic conjunctivitis. *Mol Vis* 2011;**17**:47–52.
67. Riechelmann H, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy* 2010;**24**:e104–e109.
68. Riechelmann H, Epple B, Gropper G. Comparison of conjunctival and nasal provocation test in allergic rhinitis to house dust mite. *Int Arch Allergy Immunol* 2003;**130**:51–59.
69. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. *J Allergy Clin Immunol* 1993;**91**:709–722.
70. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; **341**:468–475.
71. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;**351**:629–632.
72. Hellings PW, Scadding G, Alobid I, Bachert C, Fokkens WJ, Gerth van Wijk R et al. Executive summary of European Task Force document on diagnostic tools in rhinology. *Rhinology* 2012;**50**:339–352.
73. Bousquet J, Hejjaoui A, Clauzel AM, Guerin B, Dhivert H, Skassa-Brociek W et al. Specific immunotherapy with a standardized Dermatophagoides pteronyssinus extract. II. Prediction of efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;**82**:971–977.
74. Klimek L, Mewes T, Wolf H, Hansen I, Schnitker J, Mann WJ. The effects of short-term immunotherapy using molecular standardized grass and rye allergens compared with symptomatic drug treatment on rhinoconjunctivitis symptoms, skin sensitivity, and specific nasal reactivity. *Otolaryngol Head Neck Surg* 2005;**133**:538–543.
75. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol* 2009;**124**:150–156.
76. Pfaar O, Barth C, Jaschke C, Hormann K, Klimek L. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study. *Int Arch Allergy Immunol* 2011;**154**:336–344.
77. Naclerio RM, Proud D, Moylan B, Balcer S, Freidhoff L, Kagey-Sobotka A et al. A double-blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol* 1997;**100**:293–300.
78. Scadding GW, Calderon MA, Bellido V, Koed GK, Nielsen NC, Lund K et al. Optimisation of grass pollen nasal allergen challenge for assessment of clinical and immunological outcomes. *J Immunol Methods* 2012;**384**:25–32.
79. Bousquet J, Calvayrac P, Guerin B, Hejjaoui A, Dhivert H, Hewitt B et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. I. In vivo and in vitro parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;**76**:734–744.
80. Krug N. Usefulness of pollen chamber in the evaluation of clinical trials with allergen products. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M* 2006;**95**:167–170.
81. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol* 2013;**131**:103–109.
82. Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol* 2009;**124**:471–477.
83. Krug N, Hohlfeld JM, Larbig M, Buckendahl A, Badorrek P, Geldmacher H et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2003;**33**:1667–1674.
84. Hohlfeld JM, Holland-Letz T, Larbig M, Lavae-Mokhtari M, Wierenga E, Kapsenberg M et al. Diagnostic value of outcome measures following allergen exposure in an environmental challenge chamber compared with natural conditions. *Clin Exp Allergy* 2010;**40**:998–1006.
85. Jacobs RL, Harper N, He W, Andrews CP, Rather CG, Ramirez DA et al. Responses to ragweed pollen in a pollen challenge chamber versus seasonal exposure identify allergic rhinoconjunctivitis endotypes. *J Allergy Clin Immunol* 2012;**130**:122–127.
86. Radcliffe MJ, Lewith GT, Prescott P, Church MK, Holgate ST. Do skin prick and conjunctival provocation tests predict symptom severity in seasonal allergic rhinoconjunctivitis? *Clin Exp Allergy* 2006;**36**:1488–1493.
87. Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;**10**: E26.
88. Bousquet J, Tanasescu CC, Camuzat T, Anto JM, Blasi F, Neou A et al. Impact of early diagnosis and control of chronic respiratory diseases on active and healthy ageing. *Allergy* 2013;**68**:555–561.
89. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ et al. Unmet needs in severe chronic upper airway

disease (SCUAD). *J Allergy Clin Immunol* 2009;**124**:428–433.
90. Hafner D, Reich K, Zschocke I, Lotzin A, Meyer H, Kettner J et al. Prospective validation of the "rhino conjunctivitis allergy-control-SCORE(c)" (RC-ACS(c)). *Clin Transl Allergy* 2012;**2**:17.
91. Hafner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORE(TM) ': a novel symptom-medication score for clinical trials. *Allergy* 2011;**66**:629–636.
92. Grouin JM, Vicaut E, Jean-Alphonse S, Demoly P, Wahn U, Didier A et al. The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. *Clin Exp Allergy* 2011;**41**:1282–1288.
93. Braido F, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A et al. Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: a GALEN taskforce position paper. *Allergy* 2010;**65**:959–968.
94. Roberts G, Hurley C, Lack G. Development of a quality-of-life assessment for the allergic child or teenager with multisystem allergic disease. *J Allergy Clin Immunol* 2003;**111**:491–497.
95. Didier A, Melac M, Montagut A, Lheritier-Barrand M, Tabar A, Worm M. Agreement of efficacy assessments for five-grass pollen sublingual tablet immunotherapy. *Allergy* 2009;**64**:166–171.
96. Frolund L, Durham SR, Calderon M, Emminger W, Andersen JS, Rask P et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy* 2010;**65**:753–757.
97. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;**116**:608–613.
98. Demoly P, Calderon MA, Casale T, Scadding G, Annesi-Maesano I, Braun JJ et al. Assessment of disease control in allergic rhinitis. *Clin Transl Allergy* 2013;**3**:7.