

Review article**Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce**

Specific Immunotherapy for respiratory allergy is used since about one century and there is now solid documentation of its efficacy. Nevertheless, the methods and experimental designs used in clinical trials are quite heterogeneous and there is no unanimously accepted methodological standard. Many studies are planned with study designs that may not confirm the clinical value of SIT as an effective treatment to reduce disease severity. To ensure that patients are treated based on sound scientific evidence and to minimize the risk of misusing limited financial resources for scientific studies, the World Allergy Organization (WAO) convened a group of experts to provide guidelines for the methodology of future immunotherapy studies.

This document summarizes the recommendations for study design, patients' selection, appropriate outcomes and statistical treatment to be used in planning and performing clinical trials with specific immunotherapy.

G. W. Canonica¹, C. E. Baena-Cagnani², J. Bousquet³, P. J. Bousquet³, R. F. Lockey⁴, H.-J. Malling⁵, G. Passalacqua¹, P. Potter⁶, E. Valovirta⁷

¹Allergy and Respiratory Diseases, DIMI, University of Genoa, Genoa, Italy; ²Allergy and Respiratory Diseases, Faculty of Medicine, Catholic University, Cordoba, Argentina; ³University Hospital, Montpellier and INSERM U54, France; ⁴Allergy and Immunology, University of South Florida and James A. Haley Veterans' Hospital, Tampa, FL, USA; ⁵Allergy Unit, University Hospital, Copenhagen, Denmark; ⁶Allergy Diagnostic and Clinical Research Unit, University of Cape Town, Cape Town, South Africa; ⁷Turku Allergy Center, Turku, Finland

Key words: clinical trials; subcutaneous immunotherapy; sublingual immunotherapy.

G. W. Canonica
Allergy and Respiratory Diseases
DIMI
University of Genoa
Genoa, Italy

Endorsed by: The American Academy of Allergy Asthma and Immunology (AAAAI); The American College of Allergy Asthma and Immunology (ACAAI); The Asia Pacific Association of Allergy and Clinical Immunology (APAACI); The European Academy of Allergology and Clinical Immunology (EAACI); The Latin-American Society of Allergy Asthma and Immunology (SLAAAI).

Accepted for publication 8 December 2006

Specific allergen immunotherapy (SIT) is the practice of administering gradually increasing doses of allergens (allergen extracts or vaccines) in order to reduce allergic symptoms resulting from exposure to a specific allergen and the need for medications (1). Specific allergen immunotherapy is recognized to be a biological response modifier, capable of influencing allergen-driven immunological responses and restoring to a certain degree the

Th1/Th2 imbalance in allergic subjects. B cells, T cells, blocking antibodies, IL-10 and other cytokines are involved in the mechanisms of action of SIT (2, 3).

Subcutaneous immunotherapy (SCIT) was introduced into clinical practice at the beginning of the 20th century, but double-blind placebo controlled (DBPC) trials of efficacy commenced in the 1960s (4) and DBPC trials on sublingual immunotherapy (SLIT) started in the 1990s

(5, 6). There are now extensive reviews which confirm the efficacy, safety, and indications and contraindications of SIT (1, 7, 8).

Specific allergen immunotherapy improves the control of allergic diseases but does not completely alleviate allergic symptoms in all patients. The majority of randomized SIT clinical trials investigated the effects of SIT on symptoms and the need for rescue medications as primary outcomes. Some studies used a composite rhinoconjunctivitis score, whereas most studies used a rhinitis score only. Moreover, asthma usually was assessed as a secondary outcome, except in few studies where it was the major outcome of the trial. The need for rescue medications was sometimes assessed as a secondary outcome. In some studies, objective parameters such as pulmonary function, nasal inspiratory flow, bronchial hyperreactivity and quality of life (QoL) were used as secondary outcomes. Moreover, numerous ‘paraclinical’ parameters (or surrogate markers) of efficacy have been described and used to support the clinical effects and to define the mechanism of action. The paraclinical parameters commonly used in these trials are summarized in Table 1. Safety has always been an important outcome in clinical trials. In the future, cost-effectiveness studies will be of great importance.

Over the past 10 years, SIT has been shown to have additional effects not shared by pharmacological therapy. These include long-lasting efficacy following cessation of SIT (9), the prevention of new sensitizations (10–12) and the reduction of the risk for asthma onset in children with allergic rhinitis (13, 14). These effects have also significant pharmaco-economics implications in determining the place of SIT in healthcare systems.

Clinical efficacy of allergen-specific immunotherapy is still debated, in spite of the solid documentation based on DBPC trials and meta-analyses. Many past SIT studies have methodological flaws such as the inclusion of a small number of participants, a high frequency of withdrawals and conclusions based on studies of unmatched groups with respect to disease severity. Another potential weakness with SIT trials is that symptom and medication scores are assessed independently, whereas successful

treatment reduces both. By contrast, most clinical trials of anti-allergic drugs only assess symptoms.

Many studies are planned and initiated using study designs that may not confirm the clinical value of SIT as an effective treatment to reduce disease severity. To ensure that patients are treated based on sound scientific evidence and to minimize the risk of misusing limited financial resources for scientific studies, the World Allergy Organization (WAO) convened a group of experts to provide guidelines for the methodology of future immunotherapy studies.

Methodological aspects

The design, conducting the study, analysis of the results and reports of clinical trials should follow the principles of Good Clinical Practice and the Guidelines adopted by the government regulatory institutions (EMEA, FDA) (see <http://www.emea.europa.eu/inspections/GCPgeneral.html>; accessed 3 January 2007). There are several important methodological considerations when evaluating and designing clinical trials.

Study design

A randomized placebo-controlled and double-blind design remains the gold standard to determine the efficacy of SIT because of the variability in individual clinical responses, unpredictability and variability of allergenic exposure, and the subjective nature of symptom assessments.

The inclusion of a baseline period of observation, e.g. one pollen season before randomization, although correct in principle, is not generally recommended. The unpredictability and variability of allergenic exposure to pollen allergens and the fluctuations in the levels of indoor allergens make the use of a baseline period unadvisable, or at least not mandatory, as it is time-consuming and expensive.

A study should include a large enough number of subjects in each treatment arm to have high probability (power) to detect clinically relevant effects and statistically significant difference in the primary outcome. Inclusion of insufficient numbers of patients increases the risk of a statistical type II error.

In order to minimize imbalances between treatment groups, randomization and blinding are essential. The process of randomization should be very strict, with participants assigned to comparison groups on the basis of a random process characterized by unpredictability. The methods used to generate the random allocation sequence should minimize the risk of bias in group assignment. Restricted randomization is often used in trials, including smaller groups of patients, to achieve balance between groups in size and characteristics. Randomization could be done in blocks, allocating equal number of patients to each arm of the trial (15) and, when

Table 1. Surrogate markers and objective parameters

Allergen specific reactivity
Skin: end point skin test, late cutaneous response.
Nose, eye and bronchi: allergen specific provocation test
Nonspecific organ reactivity:
Bronchial challenge with methacholine, carbachol, histamine, AMP
Immunological parameters.
Total and allergen specific IgE and IgG subclasses
Mucosal IgA
Lymphocyte subsets and cytokines (e.g. IL-12, IFN γ , IL-5, IL-10)
Local and systemic inflammatory markers (e.g. adhesion molecules, urinary leukotrienes, sECP, tryptase)

AMP, adenosine monophosphate; sECP, serum eosinophil cationic protein.

feasible, stratifying them by age, gender and severity of the disease (16). Allocation to treatment groups using minimization (17) is still considered controversial, not encouraged by regulatory authorities (18) and if used should be justified on solid grounds. If a multicentre study is planned, the randomization should be performed for each centre using separate randomization lists. Randomization and stratification are different and are done separately. If both are used, stratification by age, gender and severity, should be the first step, followed by randomization in each group.

Patients population

The ideal efficacy study of a single allergen vaccine should be conducted in monosensitized patients or in patients concomitantly sensitized to noncross-reacting allergens, although finding patients sensitized to a single allergen is difficult, as the vast majority of subjects are polysensitized. On the other hand, SIT is allergen-specific, therefore it is necessary that the causal role of the allergen is documented and that appropriate testing excludes the relevance of other allergens to which the patient is sensitized. It is difficult to exclude the effect of concomitant sensitizations in evaluating efficacy of SIT when patients are sensitized to different allergens, unless the periods of exposure to the different allergens do not overlap. Studies involving only monosensitized patients are more likely to demonstrate the effects of SIT. Inclusion criteria should be defined in relation to age, gender, disease, disease severity, comorbid conditions and previous immunotherapy. So too, should exclusion criteria be defined, e.g. concomitant medications, other illnesses, undesirable social activities. Eligibility criteria should be clearly defined in the study protocol to evaluate the general validity of the results.

Duration

The time of exposure to allergens is highly variable and depends on the allergen. For pollen allergy, the pollen count is important and the clinical effects of SIT should be recorded during the entire pollen season. However, the primary outcome analysis can be made for clearly identified relevant periods, e.g. for weeks when the pollen load is above a predetermined level (for instance the peak pollen season, which includes 50% of the total pollen load). House dust mites and animal dander can induce both intermittent and persistent symptoms (19), thus, patients should be carefully selected with persistent rhinitis. The outcomes should be measured in all patients during the same period of the year (in pollen allergy during the season).

Outcome measures

Clinical trials of efficacy must always include a measurement of the symptoms and the use of concomitant

medications, which represent the primary outcome (see below). Both physician-rated scores and patient self-rated symptom scores have been used in clinical studies. As patients suffer the clinical manifestations, patient-rated scores are preferred as a primary outcome. While validation of scores is encouraged, it has to be noted almost all scores used have not yet been validated.

Measurement of symptoms. There is no universally accepted system to measure symptoms: ordinal scales, days free of symptoms, days free of medications, symptom scores corrected for medications and similar. The most frequently used approach in SIT clinical trials is a 4-point rating scale (from 0 = absent to 3 = severe) applied to each symptom. Mandatory symptoms to be scored for rhinoconjunctivitis are: obstruction, sneezing, rhinorrhea, nasal itching and ocular itching. Chest tightness, shortness of breath, cough and wheezing should also be considered in patients with concomitant lower airways symptoms. This kind of scoring, which is easy for subjects to understand, is commonly also used in drug trials and is therefore recommended in order to make studies comparable.

The symptoms should be recorded by patients on a diary card. The total symptom score (daily mean, mean of the week, mean of the month) can be calculated to reflect the real symptom load. Also, a powerful method to assess is the measurement of the area under the curve of the symptom scores over the entire time period (e.g. pollen season).

Studies evaluating the symptom response to perennial allergens over a long period may employ a visual analogue scale (VAS) which is sufficiently sensitive to detect changes in severity. A 10-cm line to grade the severity of symptoms from 'no symptoms' (0 cm) to 'the highest level of symptoms' (10 cm) can be utilized. Patients grade their symptoms retrospectively (e.g. in the last week or in the last month) within that range by marking on the line.

Concomitant medications. Specific allergen immunotherapy improves the control of allergic diseases but does not completely alleviate symptoms in all patients, especially when the allergen load is heavy (e.g. peak pollen season). It is therefore mandatory from an ethical point of view that all patients are provided with rescue medications. The rescue medication (20) to be used 'as needed' must be the same for all subjects, and its use recorded on the diary card. The recommended rescue medications to be used are:

- An oral second-generation H1-antihistamine (once daily).
- An inhaled short-acting beta2 bronchodilator.
- An ocular H1-antihistamine.
- An intranasal antihistamine.
- An oral corticosteroid (for short periods in the case of unresponsive/intolerable symptoms).

As the clinical effects of drugs are of different magnitude and duration, a correction factor may be applied. For instance, one point be attributed to each dose of: nasal, ocular, oral antihistamines and bronchodilator. For inhaled or nasal corticosteroids, if they are given, a score of 2 should be used. Daily use of an oral corticosteroid is scored 3. The scores for symptoms and medications are usually different in magnitude and therefore they should be normalized.

In principle, there is no reason to avoid regular treatment (7), and in some studies, it could be given to all subjects. In this case there is a risk for over-treatment resulting in no clinical symptoms to monitor. Patients should, however, be encouraged to withdraw their regular medications (e.g. intranasal steroids) during clinical trials once they are symptom free for a period on SIT. This could be a secondary end point. If controller therapies are given (intranasal or inhaled corticosteroids), they should be kept at a stable dose. For ethical reasons, some patients may need to be given the option of remaining on their concomitant medicines. In other studies, concomitant medicines may be used in a comparator group.

Primary outcome

Specific allergen immunotherapy trials often assess symptom and medication scores independently, whereas the treatment reduces both. Moreover, severity and frequency of symptoms and use of rescue medications are strictly interdependent. A pragmatic solution assumes equivalent importance of symptoms and medication scores indicating that each of these account for half of the clinical burden of the disease. Therefore it is recommended that a combined symptom + medication score be utilized as the primary outcome measure. In the considered period of observation (e.g. entire pollen season, peak pollen season), the sum of total symptom score (nasal + ocular) as described above (see *Measurement of symptoms*) plus the medication scores (see *Concomitant medications*) should be calculated. Bronchial symptoms must be included in patients with symptoms from the lower airways if a claim for asthma is requested for the trial. This global clinical score can be determined weekly, monthly, or even daily.

Secondary outcomes

Scores of the separate symptoms. Changes in the score of individual symptoms (ocular, nasal, bronchial) can be a useful secondary outcomes. This procedure allows to assess separately the effect of the treatment on each target organ. Also, in rhinitis, the effect of the treatment on each symptom (rhinorrhea, itching, sneezing and obstruction) can be assessed. Also, the effect of SIT on symptom score and drug intake score can be used separately as secondary outcomes.

Quality of life. The demonstration of the effects on the QoL is now required in studies with medications but limited investigation has been carried out in SIT studies (21–24). Quality of life reflects an objective measure of the patient’s perceived effect of the treatment. Focusing on the clinical manifestations alone (eyes, nose, lung symptoms) might not reflect the burden of allergic diseases as evidence now exists that allergy is a systemic disease resulting in nonorgan specific symptoms such as tiredness or lack of concentration. Organ-related QoL-questionnaires for rhinitis and asthma have been developed and validated and should be utilized (Table 2). If skin symptoms (e.g. atopic dermatitis) are considered, a specific questionnaire (e.g. Dermatologic Life Quality Index, DLQI) can also be used. It is important that the translated version is validated when using a questionnaire developed in a different language. Nonspecific QoL-questionnaires, like the SF-36, might also be utilized (Table 2). Quality of life cannot be used as a primary outcome for clinical efficacy (partly because there is no accepted way of correcting use of rescue medication) but is a recommended secondary outcome.

Safety. The reporting of adverse events (AE) is poor or incomplete in many SCIT trials (25), whereas recent SLIT trials report the AEs in better detail (26, 27). A good option is to report all AEs which occur in more than 5% of subjects, as included in drug trials. Severe AEs must be completely described. In the case of SIT, the untoward events specifically related to treatment must be described in detail. Side effects should be subdivided into local

Table 2. Quality of Life questionnaire suitable for specific allergen immunotherapy clinical trials

Instrument	Author	Reference
Generic		
Medical outcome study. Short Form 36 (SF-36)	Stewart	<i>Med Care</i> 1992; 30 :473–483
Medical outcome study. Short Form 20 (SF-20)	Carver	<i>Age Ageing</i> 1999; 28 :169–174
Specific		
Mini Asthma Quality of Life Questionnaire	Juniper	<i>Eur Respir J</i> 1999; 14 :32
Asthma Quality of Life Questionnaire	Juniper	<i>Thorax</i> 1992; 47 :76
Asthma Questionnaire 30 (AQ30)	Barley	<i>Respir Med</i> 1998; 92 :1207–1214
Asthma Questionnaire 20 (AQ20)	Barley	<i>Respir Med</i> 1998; 92 :1207–14
Rhinoconjunctivitis Quality of Life Questionnaire	Juniper	<i>J Allergy Clin Immunol</i> 1999; 104 :364
Mini Rhinoconjunctivitis Quality of Life Questionnaire	Juniper	<i>Clin Exp Allergy</i> 2000; 30 :132
Rhinasthma	Baiardini	<i>Allergy</i> 2003; 58 :289–294

Table 3. side effects typically related to specific allergen immunotherapy

Subcutaneous immunotherapy (SCIT) local side effects	Sublingual immunotherapy (SLIT) local side effects
Erythema/wheal-flare/induration	Oral itching
Subcutaneous nodules	Swelling of lips or tongue
	Nausea/stomachache/diarrhoea
Systemic side effects	
0	NO Symptoms or Nonspecific Symptoms
I	Mild systemic reactions: localized urticaria, rhinitis or mild asthma (PF < 20% decrease from baseline)
II	Moderate systemic reactions: slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline)
III	Severe (nonlife-threatening) systemic reactions: rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline)
IV	Anaphylactic shock: immediate itching, flushing, erythema, generalized urticaria, stridor (angioedema), asthma, hypotension

(different for SCIT and SLIT) and systemic (Table 3). The European Academy of Allergy and Clinical Immunology (EAACI) grading of severity for systemic side effects is appropriate and should be used (28). AE should be classified as probable or possible treatment-related and not treatment-related.

Objective measures. Functional measures do not replace the symptom + medication scores. Nevertheless they can provide supportive evidence for the effects of immunotherapy and therefore they are recommended as secondary outcomes, whenever possible. Examples of suitable objective functional measurements for include: Peak Nasal Inspiratory Flow (PNIF), Nasal Airway Resistance (NAR), Acoustic Rhinometry, and, for asthma, spirometry (including Forced Expiratory Volume at 1 s, FEV1 and Forced Vital Capacity, FVC) and Peak Expiratory Flow Rate.

Surrogate markers. None of the surrogate markers (or ‘paraclinical parameters’) listed in Table 1 can replace the primary clinical outcomes. The listed parameters, as well as others, can also be assessed as secondary outcomes in combination to investigate particular aspects of SIT treatments, e.g. mechanism of action.

Allergen exposure

Allergen exposure should be monitored during any SIT trial. Pollen counts using the same method and distributed evenly according to the patients’ distribution should be studied. Aerobiological data from the nearest independent monitoring station will usually be sufficient. Levels of indoor allergen should also be reported during the trial (baseline, during and end of trial) for indoor allergen SIT.

Statistical aspects

While the statistical methods used for analysing outcome data are critical, the applied statistics of many clinical trials is not appropriate. Biostatistical review of study

protocols is generally recommended before initiation of any clinical trial.

Clinical trials with SIT are often hampered by insufficient statistical planning. For example, often no proper sample size calculation is performed prior to the start of a study, resulting in insufficient patients numbers (see *Study design*). Following recent legislation, prior calculation of sample size is obligatory, and it is regarded as unethical to treat more or less patients than are actually needed to achieve the study outcome with placebo. However, this is the only one aspect where statistics in SIT trials often fails. In general the study design as well as the statistical methods used for analysis should be part of the study planning and described in the study protocol. Among others such a planning should include a statement on the primary/secondary endpoints, the hypotheses to be tested as well as the methods to be applied and a statistical justification of the planned sample size. As missing data are a major problem with SIT-studies, methods accounting for this problem should be prespecified.

Most studies assess the outcomes in terms of statistical significance (i.e. providing *P*-values). However, a sole *P*-value does not allow any conclusion on the relevance of the treatment effect to be observed. To judge the relevance of treatment effect appropriate estimates (e.g. differences of mean values, median differences between treatment groups) including their 95% confidence intervals should be given

Depending on the distribution of the data either parametric or nonparametric methods should be applied in the analysis. In case of the analysis of repeated (e.g. daily) scores (symptom and/or medication) methods for repeated measurements should be applied (29–32). Such methods are also available for non-normally distributed data (32). In case of a stratified randomization inclusion of strata into the analysis model usually increases the efficiency of the analysis. Usually the inclusion of baseline values (if available) into the analysis model also increases the efficiency of the statistical analysis.

Intention-to-treat analysis should be in principle the first choice. Nonetheless, the duration of SIT studies is

usually long and the number of dropouts/withdraws is not negligible, thus a per protocol analysis can also be assessed. Subgroup analyses can be performed. However, they should be prespecified in the protocol. Subgroup analyses, carried out after the primary outcome has been analysed, have the value of exploratory parameters to be confirmed in specifically designed studies.

Evaluation and interpretation

The interpretation of studies presenting separate data on symptom scores and medication scores may be distorted because of the relative weight of such parameters (33). Symptoms and medication usage are strictly interdependent, thus a combined score is more appropriate to evaluate global efficacy.

The magnitude of efficacy should be established as the per cent reduction of the global clinical scores in the active *vs* placebo group. Additional efficacy inferior to the one obtained by antihistamines is not considered acceptable, and consequently the minimal clinically relevant efficacy should be at least 20% higher than placebo (34). Although a baseline assessment is not recommended (see *Study design*), when it is carried out, the relative improvement of placebo and active group *vs* baseline may be also calculated.

Publication

All studies should be registered by regulatory boards (e.g. FDA or EMEA). The studies fulfilling the criteria and methodology outlined in the present document must be published, independent of their results

Special problems in clinical trials

Comparison between different routes of administration

In the recent years, the superiority or equivalence of the two main routes of administration (SCIT and SLIT) have been debated. As a comparison between the two routes must be double blinded, a double dummy design, also involving a placebo group, is mandatory in comparative studies (35, 36). This implies the use of three parallel groups (active SLIT + placebo SCIT, active SCIT + placebo SLIT, placebo SLIT + placebo SCIT). Also for comparative study, the recommendations reported above remain valid, and the symptom + medication score must be the primary outcome.

Studies in children

Studies of SIT in paediatric *vs* adult patients involve additional problems, including ethical issues, the difficulty in making an accurate diagnosis, recording symptoms and use of rescue medications, safety and acceptance

issues. This is especially true in very young children. In general, the key points for planning studies in children remain the same as indicated above (e.g. DBPC trials, symptoms + medications as primary outcome, possible secondary outcomes). In children under the age of 6 years, parents would assist the children with scoring their symptoms. Over the age of 6 years, children may score for themselves. The Juniper Paediatric Rhinitis Quality of Life Scoring System is a validated scoring system suitable for children (37, 38) completing both interviewer assisted and unassisted scoring of symptoms and QoL, but QoL cannot be used as single outcome measure (39). For SCIT, as recommended in the guidelines, the age below 5 years represents a relative contra-indication (1), whereas SLIT seems to be well tolerated in very young children, although further studies are needed. It is recommended that in studies with SIT in young children (below 5 years) a particular caution is used, especially in safety monitoring.

Recommendations for clinical trials

Based on the aforementioned considerations, it is mandatory that any future clinical trial of SIT (either SCIT or SLIT) meet some minimal methodological criteria as listed in Table 4.

Unmet needs and future directions

Specific allergen immunotherapy is a disease-modifying therapy and differs from drugs as it alters the course of the disease, and its clinical efficacy maybe maintained for years after cessation. Some data concerning these aspects have already been provided, but further confirmation is needed, preferably in large multicentre trials.

Long-term and preventive effect

Assessing the long-lasting efficacy and the preventive effects, e.g. on asthma onset or new skin sensitizations requires several years of study. This could result in high rates of dropouts, particularly of placebo groups. Therefore, it is advisable to plan an extended follow-up phase, ideally 3–6 years in randomized clinical trials so these parameters can be appropriately evaluated. Long-term effects should be assessed using the same primary outcome (symptoms + medications scores) and measured in the same periods during the subsequent years (e.g. pollen season) as those during the clinical trial. Moreover, changes in the use of medications should be recorded during the follow-up to ensure homogeneity. Skin prick tests could be carried out yearly, always with the same extract and technique. Also, confirmatory trials on the preventive effect of SIT on asthma onset is a priority for further studies.

Table 4. Summary of the recommendations

Item	Description
Study design	Randomised, double blind, placebo controlled
Randomization	Computer-generated list. Block randomization (the method must be clearly stated)
Power	Power not <90%, α 1 type error not greater than 0.05
Patients' selection	Ideally monosensitized. If polysensitized the causal role of the allergen used for IT must be clearly ascertained.
Disease	Rhinitis (rhinoconjunctivitis) and/or asthma Diseases must be defined and classified according to GINA and ARIA criteria
Exclusion criteria	Those recommended in the ARIA and WHO guidelines
Extract	Standardized vaccines must be used when available. The cumulative and maintenance dose (possibly in micrograms of allergen) must be recorded
Concomitant medications	Rescue medications (as needed) must be prescribed to all patients, and recorded on the diary card
Clinical assessment	Total score of symptoms (nasal + ocular + bronchial) must be recorded daily on the diary card. Each single symptom graded from 0 = absent to 3 = severe
Primary outcome	Total clinical score calculated as the sum of symptom score plus drugs usage also calculated as a score
Secondary outcomes	Scores of individual symptoms separately and changes in drug usage Quality of Life assessment
Surrogate markers	Safety (total number of adverse events, and SIT-related side effects)
	Functional measures (e.g. lung function, rhinometry)
	Cost-effectiveness (e.g. QALY)
	Skin tests
Dropouts/withdraws	Nasal, ocular or bronchial challenge
	Antibody measurement
	Inflammatory parameters
	Dropouts and the reasons for must be reported

GINA, Global Initiative for Asthma; ARIA, Allergic Rhinitis and its Impact on Asthma; WHO, World Health Organization; QALY, quality-adjusted life years.

Cost-effectiveness

The long-lasting and preventive effects of SIT, especially the capacity to modify the natural course of the diseases, are expected to reduce the burden of the illness in terms of direct costs (consumption of drugs, hospitalizations, extra visits) and indirect costs (loss of productivity). So far there are very few data concerning the cost-effectiveness aspects. Thus it is advisable to assess the cost effectiveness in clinical trials or to carry on formal studies using pharmaco-economic methods.

Pharmacogenomics

The search for candidate allergy genes is a promising strategy for future research. In the case of immunotherapy, the search for genes that predict the clinical response would be relevant as well. Pharmacogenomic research poses ethical problems making such studies difficult in several countries. Nevertheless, in the future, it would be advisable to include DNA sampling and storing DNA (in gene banks) for allergy genes.

References

1. Bousquet J, Malling HJ, Lockey RF. World Health Organization Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;**53**(Suppl. 54):1–15.
2. Francis JN, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. *J Allergy Clin Immunol.* 2003;**111**: 1255–1261.
3. Akdis CA, Blaser K. Mechanisms of allergen-specific immunotherapy. *Allergy.* 2000;**55**:522–530.
4. Nelson HS. Advances in upper airway disease and allergen immunotherapy. *J Allergy Clin Immunol* 2003;**111**: 793–798.

Conclusions

The present document was designed to help researchers, to design SIT clinical trials properly, and it is an official position of the scientific community on this subject. This document will be updated periodically based on the availability of new scientific evidence, clinical needs, and upon the request of regulatory and health authorities.

Acknowledgments

We warmly thank Dr Stefan Vieths (Paul Ehrlich Institut, Langen, Germany) for his helpful suggestions. A special thank is due to the following reviewers for their fruitful comments: Emilio Alvarez-Cuesta, Stephen R. Durham, Anthony J Frew (on behalf of the EAACI); Ledit RF Arduoso, Carlos Crisci (on behalf of the SLAAI); Thomas B Casale, Linda Cox, David Weldon (on behalf of the AAAAI); the ACAAI Committee on Immunotherapy and Diagnostics.

5. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003;**111**:437–448.
6. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;**60**:4–12.
7. Bousquet J, Van Cauwenberge P. Allergic Rhinitis and its Impact on Asthma. *J Allergy Clin Immunol* 2001;**108**(5 Suppl.):S146–S150.
8. Joint Task Force on Practice Parameters. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2003;**90**(Suppl. 1):1–40.
9. Passalacqua G, Canonica GW. Long-lasting clinical efficacy of allergen specific immunotherapy. *Allergy* 2002;**57**:275–276.
10. Pajno G, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;**31**:1392–1397.
11. Purello D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Paramiani S et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001;**31**:1295–1302.
12. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. 1997;**99**:450–453.
13. 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.
14. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2004;**114**:851–857.
15. Altman DG, Bland JM. How to randomise. *BMJ* 1999;**319**:703–704.
16. Enas GG, Enas NH, Spradlin CT, Wilson MG, Wiltse CG. Baseline comparability in clinical trials. *Drug Inf J* 1990;**24**:541–548.
17. MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. *BMJ* 1998;**317**:362–363.
18. European Medicine Agency. Points to consider on adjustment for baseline covariates. Publication 2003; CPMP/EWP 2863/99.
19. Durham SR, Bauchau V. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;**60**:350–353.
20. Bousquet J, van Cauwenberge P, Bachert C, Canonica GW, Demoly P, Durham SR et al. Requirements for medications commonly used in the treatment of allergic rhinitis. European Academy of Allergy and Clinical Immunology (EAACI), Allergic Rhinitis and its Impact on Asthma (ARIA). *Allergy* 2003;**58**:192–197.
21. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002;**110**:174–182.
22. Bousquet J, Scheinmann P, Guinneeppain MT, Perrin-Fayolle M, Sauvaget J, Tonnel AB et al. Sublingual swallow immunotherapy (SLIT) in patients with asthma due to house dust mites: a double blind placebo controlled study. *Allergy* 1999;**54**:249–260.
23. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;**117**:319–325.
24. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-HErranz J. Immunotherapy with a depigmented glutaraldehyde polymerized extract: changes in quality of life. *Clin Exp Allergy* 2005;**35**:572–578.
25. Malling HJ. Immunotherapy as an effective tool in allergy treatment. *Allergy* 1998;**53**:461–472.
26. Gidaro G, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005;**35**:565–571.
27. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2004;**93**:3–12.
28. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling H-J, Valovirta E. EAACI Practice Parameters for immunotherapy. *Allergy* 2006;**61**(Suppl. 82):s1–s20.
29. Bloom BS, de Pouvourville N, Libert S. Classic or Bayesian research design and analysis. Does it make a difference? *Int J Technol Assess Health Care* 2002;**18**:120–126.
30. Friedman M. The use of ranks to avoid the assumption of normality implicit in the analysis of variance. *J Am Stat Assoc* 1937;**32**:675–701.
31. Box GEP, Jenkins GM. Time series analysis. Forecasting and control. San Francisco: Holden-Day, 1976.
32. Brunner E, Domhof S, Langer S. Nonparametric analysis of longitudinal data in factorial experiments. New York, John Wiley & Sons, 2002.
33. Malling HJ. Criteria for clinical efficacy – readout and monitoring of clinical studies. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M* 2003;**94**:119–123.
34. 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.
35. Khinchi L, Poulsen LF, Carat F, Andre C, Hansen AB, Mallung HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomised, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;**59**:45–53.
36. Malling HJ. Comparison of the clinical efficacy and safety of subcutaneous and sublingual immunotherapy: methodological approaches and experimental results. *Curr Opin Allergy Clin Immunol* 2004;**4**:539–542.
37. 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.
38. Potter PC. Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial. *Ann Allergy Asthma Immunol* 2005;**95**:175–180.
39. Clarke SA, Eiser C. The measurement of health-related quality of life (QOL) in paediatric clinical trials: a systematic review. *Health Qual Life Outcomes* 2004;**22**:66.