Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

New approaches to the design of sublingual immunotherapy clinical trials

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The aim of this article is to assess and discuss the recently raised key issues concerning the new approaches in conducting clinical trials for sublingual immunotherapy (SLIT), with a special remark on the need for real-life studies exploring those factors able to affect the clinical relevance of the treatment. Although SLIT clinical efficacy in respiratory allergy has been investigated by numerous double-blind, randomized trials and meta-analyses, shortcomings in the execution and reporting of some studies may explain the difficulties in identifying a potential role of SLIT for allergic diseases therapy. This issue prompted the international scientific communities to discuss and reach a consensus on the mainstays to follow during clinical trial designing, carrying out and reporting. It was found that particular attention should be paid to the methodological aspects. Indications about patients' selection, baseline assessment, statistical analysis, choice of primary and secondary end points and types of allergen vaccines have been suggested to ensure the robustness of findings. The Consolidated Standards of Reporting Trials checklist should be considered in the phase of reporting the studies to improve transparency, paying attention to the measures aimed at reducing the probability of selection and publication bias. Being safe is a crucial aspect, uniform classifications of adverse events are also desirable to support reliable assessments worldwide. Beyond methodological issues, SLIT should be explored in the context of real-life studies. Clinical trials, rigorous in their methodology and characteristics, extended to all the most relevant allergens, are needed to provide clear evidence of short-term and disease-modifying effects of SLIT in respiratory allergy.

Keywords: clinical trials • methodology • quality of evidence • study design • sublingual immunotherapy

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Sublingual immunotherapy: from meta-analyses to clinical trials

Allergen-specific immunotherapy is the practice of administering increasing amounts of allergen(s) (the allergenic extract or vaccine) to allergic subjects, in order to achieve hypo-sensitization towards the allergen itself [1], that is, a reduction of symptoms under the natural exposure. In recent decades, sublingual immunotherapy (SLIT) gained progressive interest among researchers and clinicians as a valid alternative to traditional subcutaneous immunotherapy for respiratory allergy treatment [2]. Owing to its safety profile, this route of administration has been widely accepted in most European, Asian and South American countries, while registration trials for the market are still ongoing in the USA.

Sublingual immunotherapy efficacy was largely discussed in the past, before a number of scientific evidences exploring its effect became available [3]. Randomized-controlled trials (RCTs) are experimental studies aimed at evaluating the efficacy

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of a treatment in a particular population; in general, they constitute high quality evidence when free from important limitations [4].

In the last decade, owing to the large number of available RCTs on SLIT, systematic reviews including different populations and target diseases were carried out, in order to explore a larger population size [5]. The available meta-analyses reported an overall significant effect of SLIT versus placebo. Nevertheless, some discrepancies among their results, together with possible publication bias, led to some concerns about their reliability [6]. On the other hand, differences between reviews published in various years, exploring many clinical scenarios and including different studies and methods in data extraction and analysis, are not surprising; despite this, consistent outcomes were retrieved, suggesting that generalized judgments are not appropriate [7]. Interestingly, all the meta-analyses demonstrated an important inter-study heterogeneity, which found explanation in the clinical and methodological variability of the included studies [5]. However, there is no substantial or formal demonstration that the potential sources of clinical heterogeneity (e.g., different allergens, extracts, administration regimens, doses, durations and populations) may really affect the treatment course in a relatively short follow-up period. Conversely, the methodological limitation of some RCTs, mainly those carried out in pediatric populations and the most dated ones, may be considered reasonable drawbacks able to affect a definitive conclusion about SLIT efficacy and safety [8]. These observations are confirmed by a recent systematic review on grass pollen SLIT, where the dropout rate of individual studies, which may be viewed as a surrogate of methodological quality, resulted to significantly affect the overall estimation of the effect [9].

For these reasons, conclusions from meta-analyses on SLIT should be interpreted with caution to accurately judge the value of this treatment. Recent data from large Phase III studies of SLIT tablets in grass pollen allergic rhinitis has allowed the assessment of efficacy and safety with a higher degree of confidence [10]. However, studies administering grass pollen and mite extracts cover approximately 70% of the existing RCTs and further investigation should be extended to other allergens.

Although more than 60 double-blind, randomized, placebo-controlled trials are currently available, and more than 80% of them report positive findings, the difficulties in identifying a potential role of SLIT and its appropriate placement in guidelines for the therapy of allergic diseases are likely due to the methodological shortcomings of some studies. The recent revision of the 'Allergic Rhinitis and Its Impact on Asthma' (ARIA) guidelines confirmed the presence of relevant limitations and the need for improvement in the conduction of future clinical trials [11].

Following a careful evaluation, it was discovered that even those studies that failed in meeting their end points showed relevant limitations [12]. These reasons explain the efforts of the scientific communities to identify the relevant critical issue with regard to the conduction and reporting of existing trials. The qualitative assessment allowed to underline specific recommendations in performing and reporting future SLIT studies with correct methodology and following the Consolidated Standards of Reporting Trials (CONSORT) checklist [3,13]. Moreover, since the methodology of randomized clinical trials is essential for the critical assessment and registration of therapeutic interventions, some recommendations for Phase III trials were made clear by the EMA Committee For Medicinal Products For Human Use (CHMP) Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases [101].

The methodology of clinical trials for SLIT

Evaluation and management of allergic disorders is intrinsically affected by the variability in individual clinical response and in allergen exposure, in addition to the subjectivity of symptoms assessment [14]. For these reasons, double-blind, placebo-controlled superiority trials, following the principles of Good Clinical Practice and the guidelines adopted by the governmental regulatory institutions (e.g., the EMA and US FDA) should be adopted to investigate the SLIT efficacy [15,102]. Owing to their variable, but in general small sample size, these studies are not adequate to provide reliable information about the safety issue, thus confirmatory trials should be based on long-term controlled studies and postmarketing observations.

A number of specific considerations can be addressed concerning the planning, the conduction and finally the reporting of clinical studies on SLIT **(Table 1)**. We wish to sequentially summarize and argue the main issues raised by recent experts' roundtables and international discussion boards [3,12].

Methodological aspects

A rigorous methodology in the RCTs conduction should be guaranteed by measures aimed at minimizing the risk of bias in allocation concealment and by an unpredictable centralized randomization using permutation blocks, generated by computer, with a specific list within each site in case of multicenter trials [3]. A transparent description of the stratification (i.e., by age, gender and severity of the disease), the adjustments and their method, such as the blinding method with respect to

participants, care providers and outcome assessors for the whole duration of the study, should be reported (Figure 1).

Inclusion and exclusion criteria should be rigorously respected and explicitly described. Trials should be carried out following the intention-to-treat analysis principles, and all deviations from allocation or withdrawals should be reported in accordance to the CONSORT flowchart [16,17]. Per-protocol analyses are sometimes reasonable due to the fact that the duration of immunotherapy studies may be long and with a relevant, yet unavoidable, number of dropouts.

Efforts to avoid an attrition bias are essential to maintain the benefits of randomization; as a matter of fact, dropouts are difficult to avoid in studies that last many months or even years. Attempts to reduce dropouts are recommended, but if the rate overcomes the 20% of randomized patients, a sensitivity analysis is necessary to assess the reliability of the study findings [18].

Post hoc and subgroups analyses should be interpreted with great caution and only if planned *a priori* with respect to the conduction of the study, in order to avoid a selective reporting of outcomes [14]. Moreover, these represent exploratory investigations; their findings are not suitable to draw generalized conclusions and should be confirmed in specifically designed studies.

Table 1. Issues to be carefully considered during trials conduction.

Issue	Suggestions to be addressed
Methodological aspects	Randomization/allocation concealment/blinding Power calculation Intention-to-treat analysis Sensitivity and dropout analysis Unbiased outcome selection Average measures of effect with measure of variance Placebo effect Clinical relevance of results
Baseline assessment	Pollen counts, indoor levels assessment Overlapping seasons
Patients' characteristics	Appropriate diagnosis Baseline level of symptoms Symptoms severity Comorbidities Mono-poly-sensitization No previous immunotherapy within 5 years
End points	Symptoms and medication scores as primary outcome Secondary outcomes Exploratory and surrogate outcomes
Allergen vaccines	Standardized Known potency and major allergen content in mass units Description of administration regimens
Safety	Uniform codification of adverse events (MedDRA)
Follow-up	Duration adequate to the main outcome Open fashion for long-term studies
Reporting	Following the CONSORT checklist

CONSORT: Consolidated Standards of Reporting Trials; MedDRA: Medical Dictionary for Regulatory Activities.

Baselines assessment

A prospective baseline period of observation (at least one season for pollens) should be used to include patients who experience an appropriate minimum number of symptoms before being randomized, and also to exclude patients without a clear increase in symptoms during the season, or patients with symptoms out of season [14].

Pollen count is crucial and SLIT clinical effects should be recorded during the entire pollen season. However, the unpredictability and variability of allergen exposure, especially to pollen allergens, may limit the value of information obtained from a baseline period [3]. Moreover, symptoms assessment before the onset of treatment in these patients is not feasible due to the fact that a SLIT course typically begins at least 8 weeks before the beginning of the season [19]. In order to have consistent well-defined pollen seasons, RCTs should involve similar sites with a large number of subjects. In the case of large multicenter studies performed in different geographical areas and with highly variability in pollen counts and seasons, data should be normalized for the two weeks of peak (weeks including 50% of the total pollen load) [12].

In house dust mites allergy, the baseline data should be assessed together with the serially measured fluctuations in the levels of indoor allergens throughout the study. Measures to avoid mites in SLIT trials are suggested, although the role of allergen avoidance is a matter of debate and does not seem particularly effective [20]. A progressive reduction of mites levels should also be expected during the studies [21].

Patients' characteristics

For immunotherapy courses, the documentation of the causal role of the allergen is crucial. Therefore, eligible patients for RCTs should have an accurate allergic disease diagnosis (by skin or serological demonstration of IgE sensitization). Symptom onset and duration should precisely correlate with the allergen sensitization for at

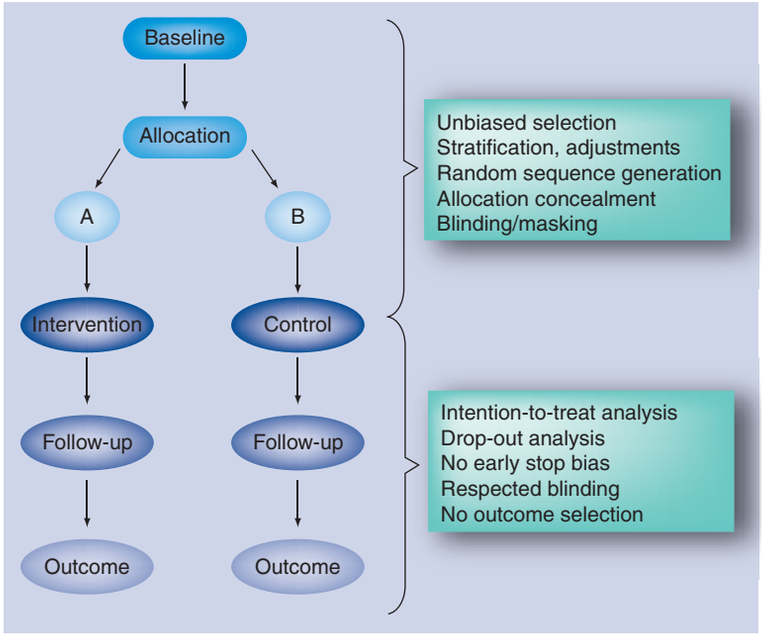

Figure 1. Features to be considered in a study to ensure appropriate methodology.

least 2 consecutive years [3,103]. This clinical relevance should be possibly assessed by nasal and/or conjunctival allergen challenge in particularly unclear cases. The disease should be classified in terms of severity and duration according to the most recent guidelines, such as the ARIA for allergic rhinitis and Global Initiative for Asthma for asthma [1,104]. Patients enrolled in studies should have a minimal level of symptoms (historical for pollen trials or at baseline). Studies involving only mono-sensitized patients are more likely to demonstrate SLIT effects . However, since in real-life most allergic patients are poly-sensitized, a precise differentiation of mono- and poly-sensitized subjects, also considering crossreactivities between allergens, is fundamental [22]. Mono-sensitized patients or patients poly-sensitized to noncrossreacting allergens with nonoverlapping pollen seasons are perfect for a single allergen study. Particular attention should be paid to the possibility of overlapping exposition between allergen used in the trial and other allergens relevant to the patient in order to avoid confounding factors. Avoiding conclusions based on the comparison between unmatched groups with respect to disease severity, as occurred in some past studies [23], is desirable. Moreover, comorbidities should be clearly investigated to prevent misleading results and to more precisely identify 'difficult' patients (patients with severe chronic upper airway diseases) [24]. No immunotherapy courses should have been assumed during the previous 5 years [21]. Since, as stated by the FDA, children are not 'young adults', medical recommendations for adults should not be extended to pediatric population. On the contrary, specific trials should be conducted in this age group to support dedicated evidences [25].

End points

The definition of surrogate markers of clinical efficacy is still a matter of discussion with regard to allergic diseases; for this reason, trials assessing SLIT clinical efficacy usually adopt the reduction in patients' total nasal, ocular, bronchial symptoms (to assess separately the effect of the treatment on each target organ), in individual symptoms scores and in rescue medication need.

As a matter of fact, rescue medications on demand are allowed for ethical reasons during studies, since it is unexpected that immunotherapy completely abolishes symptoms at least during the peak season. Recommended drugs include: oral second-generation H1-antihistamine, inhaled short-acting β-2-bronchodilator, ocular H1-antihistamine, intranasal antihistamine and oral corticosteroid (short courses). Possible controller therapies, such as intranasal or inhaled corticosteroids, should be maintained at stable dose and not modified during the study.

Common nasal (obstruction, itching, rhinorrhea and sneezing), ocular (gritty feeling/itching and tearing) and pulmonary (wheezing, chest tightness/shortness of breath and cough) symptoms are measured in a 4-point scale (from 0-absent to 3-severe), in a reflective or instantaneous way and averaged daily, weekly, monthly or for the whole season. However, there is no universally accepted system to measure symptoms. Symptoms should be recorded by patients on a diary card, although electronic devices are recommended [3].

An alternative approach of symptom scoring is the use of a visual analog scale, since this device is sufficiently sensitive over a long-period observation. Patients are asked to grade retrospectively their symptoms severity within a 0–10 cm line (from absence to highest level) [14].

Most past studies included symptoms as a primary outcome without taking into account the use of concomitant rescue medications, thus inducing misinterpretation since permitted drugs alleviate symptoms, producing a bias in favor of a positive effect of the treatment. Since these two end points are strictly linked, their combination into an adjusted single symptom/medication score can be advantageous, but no validated method currently exists [3]. A consensus on a standardized list of drugs and of the different values to assign to the different classes of medication is remarkable; in general, for the clinical effects of drugs of different magnitude and duration, the lowest score is given to antihistamines

and anti-allergic topical medications, an intermediate score to topical steroids and the highest score to oral corticosteroids [14].

Individual symptoms scores, patient's or physician's global assessments of treatment response, days free of symptoms or medications, objective assessments such as nasal peak inspiratory flow, rhinometry, lung function, change in specific bronchial reactivity (BHR) and blood parameters, should be used as secondary outcomes [3].

Following recent recommendations, particular attention should be given to the patients' reported outcomes assessment in RCTs [26]. So far, limited investigation has been carried out in SLIT studies to demonstrate effect on quality-of-life (QoL). This assessment, through validated specific and not specific questionnaires, reflects a disease impact that is not detected by organ-specific symptom and medication use (i.e., tiredness or lack of concentration). A way to adjust this kind of evaluation for the rescue medication use might enable the use of QoL as a primary outcome in the near future [14].

Some meta-analyses support the clinical benefit of SLIT in asthma, although their primary focus was on patients with concomitant allergic rhinitis; few studies were specifically designed to explore the effect on asthma outcomes [3,5]. For a claim of efficacy in asthma, specific trials should be performed. Bronchial symptoms (e.g., wheezing, shortness of breath and cough) should be used as primary outcomes, in association with forced expiratory volume in 1 s or peak expiratory flow as co-primary end points. Asthma control, number of exacerbations, inhaled steroid consumption, QoL and BHR seem appropriate secondary outcomes. Moreover, since uncontrolled and severe asthma is considered a contraindication to immunotherapy, strict safety monitoring is required.

In some studies, exploratory end points may include the progressive changes of allergen provocation tests, skin tests, specific immunoglobulins, immunological parameters, nonspecific BHR of induced sputum and exhaled nitric oxide.

Power calculation & study duration

Many of the existing SLIT studies last less than 12 months and involve small numbers of subjects. Small studies are known to be potentially misleading for their risk of overestimating the size effect of intervention or missing modest effects (risk of a statistical type II error).

Recent Phase III trials showed that a number of 150–200 patients per group seems to be reasonable [27–29]. An appropriate prior calculation performed according to the primary outcome is necessary, in order to estimate the population variability (standard deviation) and the expected magnitude of effect, and to guarantee the likelihood of showing a difference in respect to control [30,31]. Absence of power calculation should be considered unethical outside pilot studies, because of the risk of treating a number of patients that is actually needed to achieve the study outcome with placebo. An estimation of the dropout rate will finally give the number of patients to be enrolled. A biostatistical review of study protocols is generally recommended before starting any clinical trial [3].

When interpretating findings, the use of p-value alone to assess statistical significance is not sufficient in drawing conclusions about the relevance of the therapeutic effects [14]. Average measures with confidence intervals are requested. Magnitudes of efficacy inferior to that obtained by pharmacological treatment with antihistamines are not considered clinically relevant, thus a percentage at least 20% higher than placebo has been arbitrary selected as reliable cut-off [14]. Moreover, when baseline data are available, the calculation of the relative improvement produced by both SLIT and placebo versus baseline is suggested. A robust method to assess the clinical effect is the measurement of the AUC of the symptom scores over the entire time period.

With regard to the duration of a study, this should be tailored in accordance with the main outcome. For studies exploring symptoms, short-term follow-up is sufficient, but to assess long-term and disease-modifying effects, at least 2–3 years should be contemplated. The outcomes should be measured in all patients during the same period of the year (in pollen allergy during the season) [3].

Placebo effect

Owing to the relevant and long-lasting (<2 weeks) local side effects of SLIT compared with placebo preparations, an appropriate blinding of studies may be corrupted [12]. On the other hand, neither histamine nor other substances can elicit the same effects of the allergen in the oral mucosa, thus they are not useful to simulate an active preparation. This issue is currently unsolved and should be taken into account during efficacy evaluations since it may produce a bias.

A recommendation for trials is to use placebo preparations more similar to the active preparations and to describe with great attention the local side effects, separately reported from systemic signs and associated to the eventually different doses administered [12].

Allergen vaccines

The use of standardized vaccines of well-known potency and shelf-life, reporting their content of representative major allergens in mass units (mg/ml), is desirable in RCTs [32,33]. Some difficulties in comparing the labeling of manufacturers, using different methodologies in major allergen content measurement,

concretely exist together with the different types of vaccines (e.g., native allergen extract, purified extracts, recombinant allergens and allergoids). Frequently, vaccines are labeled in units of biological potency based on skin testing in own in-house standard, but the precise measurement of major allergens is desirable [23].

The advances provided by the recent molecular recombinant techniques are likely to change the allergen analysis outlook in the near future, with an impact on the quality and characterization of allergen vaccines.

Daily, weekly and cumulative dose expressed in micrograms of major allergen should be carefully reported. Some dose-ranging studies with grass pollen vaccines showed a realistic dose-dependency of SLIT efficacy and a maintenance dose from 15 to 25 µg of major native allergen per day seems to be required [12]; with regard to allergoids, even lower doses may be adequate for their advantaged biodistribution [34]. However, similar dose-finding trials are urgently needed for all the other relevant allergens in order to define the optimal dose 3 to gain maximal efficacy without side effects.

Single allergen vaccines should be preferred, but, in case of mixtures, only homologous allergens of proven stability should be used [3].

Each trial should report the protocol used to reach the maintenance dose, specifying the number of doses per week and the adopted administration regimen (e.g., co-seasonal, precoseasonal and perennial) with detailed time-points. In general, the administration regimen ranges from once daily to weekly [35]. Currently there are no trials comparing the efficacy of the different schedules. Recently, starting with the maintenance dose without the traditional up-dosing, showed that the safety profile is not compromised [36,37].

Safety: speaking the same language

Sublingual immunotherapy raised progressive interest in clinicians for its expected favorable safety profile. In clinical trials, local side effects are reported in 60–80% of patients; they commonly have rapid onset, mild severity (e.g., itching and swelling of mouth mucosa and abdominal pain) and duration of no more than 2 weeks [3]. We already mentioned that this phenomenon can bias the interpretation of controlled trials (placebo effect). Systemic reactions such as urticaria/angioedema and asthma are infrequent, but may be dose-related and allergen-related. According to a comprehensive review, systemic reactions occurred in 169 of 314,959 patients (i.e., 54 per 100,000 doses administered), but this estimate was based on those studies specifying the severity of the reaction [38]. On the other hand, it is plausible that the under-reporting of adverse events may represent a bias.

Six cases of anaphylaxis, all occurring in atypical clinical settings and following native allergens administration, have been reported, thus suggesting that cautious behaviors should be maintained, especially at first administrations and in patients at risk [39–43].

The evidence of tolerability should come from premarketing observations but continuously confirmed in real life by postmarketing surveillance. The assessment of existing literature suggests the need for standardizing the way of classifying and reporting adverse events. As a matter of fact, under-reporting represents a concrete problem in some countries due to strictly local reasons [44].

Adverse reactions should be codified using the Medical Dictionary for Regulatory Activities (MedDRa), and, during the first month of treatment, safety should be recorded every day [3]; MedDRa is currently the only internationally recognized approach for classifying adverse events from Phase I to surveillance studies [45].

Avoiding the discrepancy of data reported in peer-reviewed journals and data reported in regulatory agencies is desirable. Recently, the relevance of a uniform classification and definition of adverse reactions to immunotherapy has prompted European and US task forces, endorsed by the World Allergy Organization, to develop a consensus document [46]. However, a crucial role is covered by the phase of local implementation.

Long-term & preventive studies

Sublingual immunotherapy has been investigated for additional effects not shared by pharmacological therapy [47]. These include long-lasting efficacy following its cessation, the prevention of new sensitizations and the reduction of the asthma-onset risk in children with allergic rhinitis. Nevertheless, for instance, the evidence concerning the last mentioned effect comes from a single randomized trial lacking a clear description of the procedures for randomization and concealment of allocation, a description of the type of analysis, it is not a blinded study and has 21% of children lost to follow-up (i.e., drop outs) [48]. For this reason, the exploration of disease-modifying effects of SLIT should be a priority for future studies and specifically designed confirmatory trials are required.

Assessing the long-lasting efficacy and the preventive effects requires long-term evaluations and this could result in high rates of dropouts, particularly in placebo groups. Therefore, planning extended follow-up phases (3–6 years) is desirable in randomized clinical trials. Since prolonging the blinding phase for so many years is unethical, open-fashion procedure seems to be the best opportunity. The effects of the intervention should be assessed using the same primary outcome discussed above and measured in the same periods during the

subsequent years as those during the clinical trial. To investigate the appearance of new sensitization, particular attention should be paid in performing diagnostic tests using the same techniques and with the same extracts.

Clinical trial reporting

In SLIT meta-analyses the possibility of publication bias cannot be excluded. This phenomenon arises from the tendency to handle the reporting of experimental positive results in respect to negative or inconclusive ones [49]. This could explain why most of the studies in systematic reviews are positive. Prospectively, it is strongly recommended that researchers report the findings of all conducted studies independently of their results, following the International Congress of Harmonization guideline [105].

Editorial policies of scientific journals should also avoid a selection bias, discouraging the acceptation of studies not registered in specific databases or regulatory boards (e.g., the FDA and EMA) at their beginning.

Trial funding should be clearly stated. Furthermore, it was argued that the results should be reported both numerically and with graphs to improve transparency and *post hoc* analyses, due to the difficulties raised during data extraction when conducting meta-analyses in poorly reported trials.

The CONSORT statement represents the minimum set of recommendations for reporting RCTs [16]. It offers a standard scheme for authors to follow when preparing the trial reports, facilitating their complete and transparent description and supporting their critical appraisal and interpretation.

Conclusive remarks: real-life perspective

It was argued that placebo-controlled randomized superiority trials provide an estimate of the absolute effect of the therapy, but they are not appropriate to explore the clinical relevance of that effect. To be clinically meaningful, results must be relevant to specific populations in specific settings. Multiple factors determine the external validity (generalizability) of RCTs: patients' characteristics, condition investigated, treatment regimens, costs, compliance, co-morbidities and concomitant treatments. For practical reasons, trials do not always take all these factors into consideration. Moreover, considering a specific population of interest and some aspects of the study design (e.g., eligibility criteria, study duration, intervention mode, outcomes, adverse events assessment or type of statistical analysis), greatly influences the degree of generalizability [106]. For these reasons, the term 'efficacy' has been distinguished from the term 'effectiveness'. Efficacy trials (explanatory trials) determine whether an intervention produces the expected result under ideal circumstances. To demonstrate effects in the 'real world', observational studies are frequently used, although it is widely documented that these experimental models tend to overestimate findings. However, a certain confidence may be attributable to methodologically strong observational studies yielding large and consistent estimates of treatment magnitude [4]. Measuring the degree of beneficial effect under real-life clinical settings, effectiveness trials (pragmatic trials) represent a useful device. In these circumstances the hypotheses and designs are formulated on conditions of routine clinical practice and on outcomes essential for clinical decisions; however, random allocation, allocation concealment and blinding are conserved, ensuring the internal validity of the trial.

With regard to SLIT, following a conclusive demonstration of clinical efficacy, the exploration of effectiveness represents a mainstay. SLIT effectiveness is in fact deeply affected by many different factors. In particular, it has been argued that compliance to treatment may represent a relevant drawback for SLIT. Since the treatment can be mostly self-administered by patients themselves, a concrete risk for patient's discontinuation seems realistic [50]. Compliance to treatment, a major problem of allergy and asthma management, is far better in RCTs than in real-life. Currently the real compliance with SLIT is unknown and real-life studies should be carried out to the purpose. Further pragmatic trials are therefore needed, possibly with the inclusion of pharmacoeconomic analyses. As a matter of fact, it was recently shown that the economic burden of SLIT courses may affect the adherence to treatment [51]; on the other hand, treatment costs have been indicated as a relevant aspect to be considered in the balance between desirable and undesirable effect of medical interventions [52].

Future perspective

The final answer with regard to SLIT efficacy will be given by future clinical trials, rigorous in their methodology and characteristics, able to provide clear evidence of the possible short-term and disease-modifying effects of SLIT in respiratory allergy. These observations should be extended to at least all the most relevant allergens. New indications to SLIT like food, venom and skin allergy, will be investigated by explanatory trials.

Clinical trials will get some benefit also from the progressive diffusion and advance in molecular techniques that will enable more accurate diagnoses and characterization of sensitization profiles, crucial in the phase of patients' selection.

Moreover, rigorous effectiveness trials and safety assessments, together with evidences on patients' reported outcomes, will support appropriate and informed recommendations in the context of clinical guidelines. Pragmatic

trials will explore those factors playing a role in real-life settings. The development of strategies aimed at improving the adherence of patients to SLIT courses are currently under investigations and their results will probably ensure an optimal management of this treatment.

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Executive summary

- The methodology of many sublingual immunotherapy (SLIT) trials was found to be insufficient, until recent large pivotal studies.
- The clinical efficacy of SLIT should be further explored for all the most important allergens in allergic rhinitis and asthma. A number of studies in children is required as well.
- A rigorous methodology in designing clinical trials represents a priority. Efforts should be directed to avoid bias and distortions in the conduction, interpretation and reporting of the studies.
- The Consolidated Standards of Reporting Trials checklist provides important support; the use of the flow diagram displaying the progress of all participants through the trial is fundamental.
- A primary end-point reflecting both symptom severity and intake of rescue medications is strongly encouraged.
- Functional measures and surrogate markers cannot replace the primary clinical outcomes, but can provide supporting evidence. Patients' reported outcomes, such as quality of life, are becoming more relevant.
- Vaccine standardization and characterization in terms of exact content of major allergen is crucial.
- Safety should be carefully monitored from Phase I to postmarketing studies using uniform and standardized classification and nomenclature of adverse events.
- Adherence to a SLIT course may represent a critical issue that is worthy of further investigation; strategies to improve compliance should be implemented.
- Assessing cost effectiveness in clinical and pharmacoeconomic studies is relevant to appropriately locate the potential role of SLIT in the contest of guidelines.

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■ **Since no validated definition of 'effective studies' exists, this report proposes criteria to distinguish pragmatic from explanatory studies.**