

Original article

The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper

The methodology of randomized clinical trials is essential for the critical assessment and registration of therapeutic interventions. The CONSORT (Consolidated Standards of Reporting Trials) statement was developed to alleviate the problems arising from the inadequate reporting of randomized controlled trials. The present article reflects on the items that we believe should be included in the CONSORT checklist in the context of conducting and reporting trials in allergen-specific immunotherapy. Only randomized, blinded (in particular blinding of patients, health care providers, and outcome assessors), placebo-controlled Phase III studies in this article. Our analysis focuses on the definition of patients' inclusion and exclusion criteria, allergen standardization, primary, secondary and exploratory outcomes, reporting of adverse events and analysis.

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The methodology of randomized controlled trials (RCTs) is essential for the proper evaluation of interventions and reduces concerns about validity during critical appraisal (1) in allergen-specific immunotherapy (SIT). A study under the auspices of the World Allergy Organization (WAO) on the methodology of SIT RCTs (2) presented key points. They were more detailed in the recent WAO Position Paper on SLIT. Moreover, recommendations for Phase III trials were made clear by the European Medicines Agency (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 and other related European regulatory issues (3, 4). However, for physicians, it is often difficult to appraise the quality of evidence and to judge whether there are high-quality RCTs supporting the effectiveness of treatments.

In various fields of medicine, many RCTs suffer from important methodological limitations (5, 6). CONSORT (Consolidated Standards of Reporting Trials) was developed to alleviate the problems arising from the inadequate reporting of RCTs. The CONSORT Statement is an evidence-based, minimum set of recommendations for reporting RCTs. The statement has evolved since the first report (7). The CONSORT Statement comprises a 22-item checklist and a flow diagram (8). It has been extended to cover certain specific issues such as nonpharmacological interventions (9). Although SIT is a nonpharmacological intervention, blinded, placebo-controlled RCTs can be performed and reported using the unmodified CONSORT statement.

However, the reporting of SIT RCTs is largely insufficient and most studies are not written according to the CONSORT statement (PJ Bousquet, in preparation). These reporting deficiencies may be a result of poor trial conduct or poor reporting practice in a well conducted trial.

The present paper summarizes how the methodology of Phase III RCTs in SIT is related to the CONSORT statement. It is a result of work by GA²LEN (10, 11) to evaluate how CONSORT criteria apply to clinical research in Allergy and to improve the quality of RCTs reporting on Allergy. A consensus meeting of experts was held in Rome, Italy, 13 July 2009, to develop modules pertinent to Allergy for the CONSORT Statement checklist. The participants proposed to include allergy statements in six of the items of the CONSORT Statement.

Randomized controlled trials in specific immunotherapy

Participants

The type of participants enrolled in RCTs will influence how applicable results are to clinical practice and the real world. Many subjects with positive skin tests and/or

serum-specific IgE do not present with symptoms (12). Therefore, most of these patients would, because of the lack of important disease burden, not be considered for treatment. In addition, it is possible that the biology of the disease in patients who have positive skin tests and/or serum-specific IgE but no symptoms differs from those who do present with symptoms. Given these considerations, researchers should consider including only patients with an accurate diagnosis of an allergic disease, and in whom the allergen sensitization is correlated with symptoms in RCTs. For example, patients enrolled in SIT studies should have a minimal level of symptoms during exposure (possibly historical for pollen trials or at baseline).

Allergic diseases should be classified in terms of duration and severity (or control) according to accepted classifications, such as ARIA for allergic rhinitis (13) and GINA for asthma (14).

As most allergic patients are polysensitized (15), it is important to characterize the different inhalant allergens to which the patients are sensitized, to differentiate mono- and polysensitized subjects, and to consider cross-reactivities between allergens. For example, the exposure to relevant allergens overlapping with the allergen used in an SIT trial can lead to misleading results because treatment efficacy can be influenced by co-exposure with other allergens.

Many patients do not suffer from isolated diseases. However, relative treatment effects in RCTs are only influenced by the presence of co-morbidities if there is an interaction between the treatment and the co-morbidity, i.e. the treatment effects differ whether or not a co-morbidity is present. As the absence of interaction is difficult to prove without including patients with co-morbidities and the inclusion of patients with co-morbidities will further enhance applicability of the trial results to real world patients, there is little reason to not include patients with co-morbidities. These co-morbidities should be recorded and reported and, if necessary, adjusted for in the analyses.

Patients should not have had any form of immunotherapy within the previous years as requested by CHMP (16).

Co-medication and allergen avoidance

The indication of SIT with inhalant allergens is not to replace pharmacological treatment, but to improve the control of patients who are insufficiently controlled using other medication (17). Concomitant medications are therefore needed in most patients. Randomization will likely balance these co-interventions (just like any other possible imbalance) in large trials, but unfortunately, most trials are too small to achieve balance for all factors that can influence the efficacy of treatment. Adjustments, restriction and stratification are therefore of great importance for randomized trials (18).

Allergen avoidance is a matter of discussion. For some allergen such as tree or grass pollen, avoidance is not feasible. For others efficacy is controversial as single measures to avoid mites are not effective in asthma or rhinitis (19). It has, however, been proposed that patients should have a control of mites in SLIT trials (16). The bottom line is that RCTs should generally compare interventions against possible best standard therapy that is equally applied to all patients in a trial.

Quality and standardization of allergen vaccines

The quality of the allergen vaccine is critical. Whenever possible, standardized vaccines of known potency and shelf-life should be used (17, 20). (3). In any RCT using allergen extracts, the characteristics and potency of the vaccine need to be included, in particular the content of representative major allergens in mass units ($\mu\text{g/ml}$) (17, 20).

Placebo

Many groups can and should be blinded in RCTs. These groups include patients, clinicians, investigators, outcome assessors and statisticians. Blinding is particularly important if the outcome is influenced by knowledge about which treatment a patient receives. For example, blinded, placebo-controlled, SIT studies have found that up to 65% of subjects on active treatment with allergen versus under 30% on placebo have had local allergy symptoms, and that some patients treated with SCIT experience systemic reactions. Given the higher anticipated occurrence of local side-effects blinding of patients through the use of placebo is critical to avoid bias in the outcome assessment or other aspects of trial conduct based on whether side-effects occur. In SCIT, some studies have used a histamine placebo to mimic side-effects of allergens, but there is no gold standard (14). However, in SLIT, there is no substance which can mimic the local side-effects of allergens.

Randomized controlled trial

A randomized, parallel group, placebo-controlled and blinded design remains the gold standard for determining the efficacy and safety of allergen products (3) (2, 21). Superiority studies need to be carried out (16) and noninferiority or equivalence studies must be carefully planned and justified. As recommended by many institutions and agencies, RCTs should be registered (<http://www.who.int/ictpr/en/> or clinicaltrials.gov).

Three types of RCTs have to be considered for SIT depending on the objective (3). Trials assessing:

- Short-term effects during the first year of treatment,
- Sustained effects after more than one year.
- And long lasting effects after discontinuation of SIT.

New studies will need to incorporate cost-effectiveness parameters in their design (22–25) and comparison with other forms of SIT (26).

Baseline assessment

In pollen allergy, the inclusion of a baseline period of observation, e.g. one pollen season before randomization, would be optimal. However, as a result of the unpredictability and variability of allergenic exposure to pollen allergens during this baseline period, it is difficult to interpret comparisons between treatment years (27, 28). Adjustment on the pollen season is therefore recommended.

In house dust mite allergy, a baseline may be used (29), and the fluctuations in the levels of indoor allergens may be observed throughout the studies (30). In the case of corticosteroid-withdrawal studies, a baseline observation period is needed to stabilize asthma and to assess the baseline level of inhaled corticosteroids.

Dropouts

Dropouts are difficult to avoid as a result of the length of the trials (months or even years). Attempts for reducing dropouts are essential to reduce a potential attrition bias. Explanation of dropout and withdrawal reasons has to be reported in detail. Properly applied intention to treat analysis needs to be part of any analysis protocol. The acceptability or interpretation of drop out in an RCT is a function of the event rate of outcomes and the drop out rate. Larger drop out rates will probably influence RCT interpretation with high event rates less than those with low event rates.

Assessment of allergen exposure

In pollen RCTs, pollen counts should be measured and pollen traps located to match the pollen season of all patients of the study. Pollen season and pollen peak exposure have also to be defined. However, there is only a poor association between pollen counts and individual patients' symptoms.

In mite studies, the major allergen content of house dust in patients' homes may be measured serially during the trial. These measurements will help understanding results of RCTs better.

Primary outcome parameters

The primary end point should, ideally, be a single end point globally assessing the patient and the comorbidities. Outcomes should be validated in proper studies. In most SIT RCTs, rescue medications are proposed and have an impact on symptom severity. The use of rescue medication will differ importantly

Table 1. The CONSORT Statement checklist for allergen-specific immunotherapy randomized controlled trials

CONSORT requirements		GA ² LEN proposals for specific immunotherapy (if nothing mentioned, the CONSORT requirements should be applied without specific additional considerations)		References
TITLE & ABSTRACT	1	How participants were allocated to interventions (e.g., 'random allocation', 'randomized', or 'randomly assigned').		
INTRODUCTION Background	2	Scientific background and explanation of rationale.		
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	Description of disease Assess all sensitizations (mono- or polysensitization) Prove concordance of sensitization and symptoms as not all sensitizations are clinically relevant Assess severity of symptoms Report co-morbidities Exclude patients who received SIT in previous years Allergen vaccine	Rhinitis, conjunctivitis, asthma, other Panel of allergens Skin prick tests and/or allergen-specific IgE Optional: Allergen challenge (4, 16) (4, 16) For EU: (47)
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	Composition: Single allergen or mixtures If mixtures: Homologous allergens Defined standardization (if available). Differ depending on vaccine Allergen content (µg) Maximum daily dose (if possible µg allergen) Protocol to reach maintenance Number of doses per week (mean dose: µg allergen) Duration of the study Cumulative dose (mean dose: µg allergen) Co-seasonal administration (if any)	(3) (48) (17, 19)
Objectives	5	Specific objectives and hypotheses.	Treatment of allergic symptoms: short-term trial Sustained clinical effect: 2–3 year trial Disease modifying effect: 3-year trial and efficacy after discontinuation (Prevention)	(4, 16)
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	Total symptom score Combined symptom-medication score Quality-of-life (QOL) Rescue medications Standardized list Weighted medication score	(4, 16)

Table 1. (Continued)

CONSORT requirements		GA ² LEN proposals for specific immunotherapy (if nothing mentioned, the CONSORT requirements should be applied without specific additional considerations)		References
		Secondary	Rescue medications Individual symptoms Preference instruments (e.g. visual analogue scale (VAS)) For asthma: if possible co-primary: FEV1 or PEF Asthma control Symptom-free days Physician and patient rated clinical global improvement Evolution of nasal/conjunctival/bronchial allergen challenges. Evolution of skin tests to allergens. Specific immunoglobulins Other immunological parameters Nonspecific bronchial hyperreactivity (asthma) Inflammatory biomarkers: induced sputum, FeNO (asthma), nasal secretions, etc.	(4, 16)
		Exploratory	Pollen counts Mite allergen content in individual homes	(4, 16)
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	Assessment of exposure to allergen	
Randomization – Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)		
Randomization – Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.		
Randomization – Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.		
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	Placebo-controlled	(4, 16) The best placebo is still a matter of discussion for SCIT There is no placebo which mimics the local side-effects of SLIT

Table 1. (Continued)

CONSORT requirements		GA ² LEN proposals for specific immunotherapy (if nothing mentioned, the CONSORT requirements should be applied without specific additional considerations)		References
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	Superiority trial Intent-to-treat analysis (<i>stricto sensu</i>) for primary outcome For primary outcome: analysis during allergen exposure (or if prespecified during peak of allergen exposure)	(4, 16)
RESULTS				
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.		
Recruitment	14	Dates defining the periods of recruitment and follow-up.		
Baseline data	15	Baseline demographic and clinical characteristics of each group.		
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by 'intention-to-treat'. State the results in absolute numbers when feasible (<i>e.g.</i> , 10/20, not 50%).		
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (<i>e.g.</i> , 95% confidence interval).		
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.		
Adverse events	19	All important adverse events (AEs) or side-effects in each intervention group.	MedDRA Report using CONSORT statement Report of severity of AEs and anaphylactic reactions using published scales	(43) (44) (45)
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.		
Generalizability	21	Generalizability (external validity) of the trial findings.		
Overall evidence	22	General interpretation of the results in the context of current evidence.		

between groups if the treatment under investigation is highly efficacious. To account for such differences, rescue medication should be administered in a standard way to assess differential use of rescue medication as an indicator of efficacy (31). A primary end point reflecting both symptom severity and intake of rescue medication is of interest but no standardized method has yet been accepted (32). Validated symptom scales are preferred. Finally, the minimal important difference for outcome measures should be considered instead of single statistical difference (33, 34). Quality-of-life measurements may soon become primary outcomes and prove to be of great value in SIT.

In allergic rhinitis (conjunctivitis) induced by pollens, it is advisable to use the total symptom score including all nasal symptoms (nasal obstruction, rhinorrhea, sneezing and pruritus) with one or more ocular symptom (35–37).

For a claim of efficacy in asthma, specific trials should be performed.

As secondary outcomes, the control of the disease and quality-of-life (if not used as a primary outcome) are the most important parameters. Exploratory outcomes such as nonspecific bronchial hyperresponsiveness may complement the study. Moreover, patients should have sufficient symptoms to demonstrate a significant difference between placebo and SIT (38). Most guidelines propose to avoid SIT in moderate to severe asthmatics because of the increased rate of severe asthmatic reactions. However, a recent SCIT study suggested that patients with moderate asthma may be safely treated by SCIT (39). If new studies are carried out, it will be of great importance to scrutinize the safety carefully.

In asthma, many studies have attempted to find a sparing effect of treatments on asthma control or symptoms. However, many of these studies were inconclusive with medications because the effect of the *verum* was not significantly larger than the observed placebo effect (40, 41).

Studies in children

The European Medicinal Agency (EMA Directive 2001/20/EC) and FDA state clearly that 'children are not small adults' and that specific trials should be conducted in this age group. In particular, allergy is difficult to demonstrate in preschool children. Special ethics should be considered as children cannot usually give their informed consent. Both, parents' and children's understanding and likely adherence to the treatment have to be clearly established before enrolling a child in an RCT.

Secondary and exploratory outcome parameters

Several secondary outcome parameters can be used (Table 1).

Safety

Safety is a key concern for any SLIT trial and may differ depending on the sensitization of the patient (42). Adverse drug reactions (ADR) should be coded using MedDRA (Medical Dictionary for Regulatory Activities) (43).

A CONSORT statement has been published for the report of ADRs in RCTs (44).

In addition, anaphylactic ADRs should be defined according to the Second Symposium on the Definitions of Anaphylaxis (45), and the ADR severity needs to be reported using the proposals of the European Academy of Allergology and Clinical Immunology (46).

Sample size

The RCT sample size of the trials must be considered before the study is started. The hypothesis, the power, the type of test and the degree of the first type error have to be reported. The sample size should include the expected dropout/withdrawal. It should also integrate the impact of interim analysis when such analysis is performed. However, interim analyses for stopping RCTs early due to benefit should be avoided (47).

The CONSORT statement checklist for immunotherapy trials

The CONSORT Statement is an evidence-based, minimum set of recommendations for reporting RCTs. The statement has evolved as the first document (7). The CONSORT Statement comprises a 22-item checklist and a flow diagram (8).

Table 1 presents the CONSORT statement checklist adapted for RCTs in SIT.

Conclusions

The quality of most RCTs in SCIT or SLIT is low (Bousquet, in preparation). However, recent well-designed and appropriately reported RCTs have been published. Investigators should be encouraged to continue to adhere to the CONSORT statement when reporting their RCTs or, even better, to emphasize the need to consider important aspects of internal validity as early as during the planning stage of a trial. In this study, we describe how the items in the CONSORT checklist relate to allergic disease. The adherence to conduct and reporting of RCTs according to CONSORT will provide more valid estimates of treatment effects and serve as a reliable basis for the development of evidence-based guidelines.

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