

The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: A Global Allergy and Asthma European Network (GA²LEN) article

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Background: Randomized trials provide evidence to inform treatment decisions. The Consolidated Standards of Reporting Trials (CONSORT) Statement is a set of recommendations for the reporting of trials.

Objective: We sought to assess the quality of reporting allergen-specific immunotherapy trials according to CONSORT criteria. **Methods:** The reporting of the procedure, randomization, dropouts, strict conduct of intention-to-treat (ITT) analysis, and sample size calculation according to CONSORT were assessed in the 46 subcutaneous and 48 sublingual immunotherapy (SLIT) blind, placebo-controlled randomized trials published between 1996 and 2009 in English.

Results: One subcutaneous immunotherapy (2.2%) and 3 SLIT (6.6%) trials met CONSORT Statement criteria. These were used for the registration of sublingual tablets to the European Medicines Agency. In subcutaneous immunotherapy, 16 (35%) studies reported a CONSORT flow chart, and 12 (26%) provided a description of dropouts. Adequate randomization

was reported in 9 (35%) studies, and incomplete randomization was reported in 15 (33%). Power analysis was reported in 15 (33%) studies. In SLIT, 20 (42%) studies reported a CONSORT flow chart, and 16 (32%) a description of dropouts. ITT analysis was carried out in 1 (2.2%) SLIT study, and a modified ITT analysis was used in 1 (2.2%) subcutaneous immunotherapy study and 2 (4.4%) SLIT studies. Adequate randomization was reported in 6 (12%) studies, and incomplete randomization was reported in 16 (32%). Power analysis was reported in 15 (27%) studies.

Conclusion: As in other areas of medicine, the quality of reporting of most immunotherapy trials is low, and only 4.2% of SLIT randomized controlled trials met all of the criteria of the CONSORT Statement. Use of the CONSORT criteria should be encouraged. (*J Allergy Clin Immunol* 2010;■■■■:■■■■-■■■■.)

Key words: Subcutaneous immunotherapy, sublingual immunotherapy, allergen, CONSORT, randomized clinical trial

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Abbreviations used

CONSORT: Consolidated Standards of Reporting Trials
 DBPC: Double-blind, placebo-controlled
 EMA: European Medicines Agency
 ITT: Intention-to-treat
 PP: Per protocol
 RCT: Randomized controlled trial
 SCIT: Subcutaneous immunotherapy
 SIT: Specific immunotherapy
 SLIT: Sublingual immunotherapy

Subcutaneous immunotherapy (SCIT) is the standard form of immunotherapy,¹ but sublingual immunotherapy (SLIT) has become extremely common, particularly in Europe.² Randomized controlled trials (RCTs) are essential for the critical evaluation of interventions,³ including specific immunotherapy (SIT).⁴ The European Medicines Agency (EMA) has made clear recommendations for phase III trials.⁵ Three types of RCTs are proposed: trials for short-term effects during the first year of treatment, for sustained effects after more than 1 year, and for long-lasting effects after SIT discontinuation. However, for physicians, it is often difficult to appraise the quality of evidence and to judge whether high-quality RCTs support treatment effectiveness.

In various fields of medicine, RCTs suffer from important methodological limitations.⁶⁻⁸ For SCIT and SLIT, the quality of RCTs and factors associated with quality have been studied using the Jadad scale,⁹ but there is a general agreement that summary scores have important limitations.¹⁰ The inclusion or exclusion of RCTs in systematic reviews and meta-analyses on the basis of the Jadad scale has led to controversies in SLIT.¹¹

The Consolidated Standards of Reporting Trials (CONSORT) Statement is an evidence-based, minimum set of recommendations for reporting RCTs. It is a standard means of preparing reports of trial findings, facilitating their complete and transparent reporting and aiding their critical appraisal and interpretation. The statement has evolved since the first publication in 1996.¹² The CONSORT Statement used to consist of a 22-item checklist and a flow diagram,¹³ but has recently been expanded to 25 items.^{14,15} The checklist items focus on reporting how the trial was designed, analyzed, and interpreted; the flow diagram displays the progress of all participants through the trial (www.consort-statement.org/consort-statement/), and its application to SIT has recently been proposed.¹⁶

We aimed to assess the quality of reporting of double-blind, placebo-controlled (DBPC) RCTs on SCIT and SLIT for the treatment of patients with allergic rhinitis/conjunctivitis, asthma, or both, using recommendations of the CONSORT Statement adapted to the year of publication of the article.^{12,13}

METHODS**Selection criteria**

As part of the systematic review of the allergic rhinitis in asthma (ARIA) guidelines,^{17,18} we included DBPC RCTs on SCIT and SLIT for the treatment of allergic rhinitis, conjunctivitis, and asthma. Studies were searched for from 1996 (the year of publication of the first CONSORT Statement) to June 2009 (date of the start of the analysis). As recommended by the Committee for Medicinal Products for Human Use of the EMA,¹⁹ only double-blind (patient, clinician, and outcome assessor), placebo-controlled RCTs with clinical evaluations as the primary outcome were considered. Studies in which clinical experimental challenges were the only end point were excluded. We also excluded other forms of SIT and other allergic diseases. No restrictions were made regarding the patients' characteristics (eg, age group) or the length of follow-up. We used the 1996 and 2001 CONSORT Statements.^{12,13}

Search strategy and identification of studies

Medline, EMBASE, and the Cochrane Database of Systematic Reviews were searched for relevant SIT RCTs published in English. The evaluation of an existing Cochrane meta-analysis did not yield additional studies.²⁰ Abstracts and unpublished studies were not considered.

The search terms included the following key words: "allergen," "immunotherapy," "subcutaneous immunotherapy," "sublingual immunotherapy," "double-blind," "placebo," "rhinitis," "asthma," and "conjunctivitis." We checked the references of the retrieved articles and searched the related article function of PubMed (last search on June 30, 2009, for articles published between 1996 and June 2009). We did not include articles before 1996 because the first CONSORT Statement was issued in 1996.¹²

Study selection

Four members of the review team (D. Larenas, G. Passalacqua, M. A. Calderon, and P. J. Bousquet) independently assessed the titles and abstracts of all the identified citations. We ordered the full texts of the articles that seemed potentially eligible by one of the reviewers. Five reviewers (G. Passalacqua, D. Larenas, J. Bousquet, M. A. Calderon, and P. J. Bousquet) then independently evaluated the full texts of the articles and decided whether the study could be included.^{8,21} If there was any disagreement about inclusion and exclusion after discussion, an independent reviewer then made the decision.

Quality assessment

The items of the CONSORT Statement that were assessed are presented in Table I. The procedure of random allocation was found to be adequate if the authors reported the use of computer-generated random numbers, a table of random numbers, tossing a coin, or throwing a die. Concealment of random allocation was adequate if patients and investigators could not foresee group assignment by using, for example, centralized or pharmacy-controlled randomization, serially numbered identical containers, or an onsite computer-based system with a randomization sequence not readable until allocation or other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients.

The double-blind method had to be described, especially for placebo that should be similar to active vaccine (eg, same composition, aspect, color, and taste). However, for SLIT, no adequate placebo could mimic the local side effects induced by the allergen observed in a substantial number of patients.²²

The analysis had to be conducted as an intention-to-treat (ITT) analysis.²³ The ITT principle implies that the primary analysis should include all randomized subjects.¹³ The term ITT is inappropriately used when certain participants for whom some data are available are excluded (eg, nonadherence to the protocol). Conversely, analysis can be restricted to only participants who fulfill the protocol in terms of eligibility, interventions, and outcome assessment (per-protocol [PP] analysis). Any study using only a PP analysis for the primary outcome was classified as of reduced quality. Attempts for reducing dropouts reduce the potential attrition bias. Although there are no known fixed rates for dropout that are associated with quality, some authors suggest that dropout rates should be less than 25%.²⁴ If the dropout rate is greater, then a sensitivity analysis is needed to evaluate the reliability of the results.²³

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TABLE I. CONSORT recommendations evaluated

- Reporting of dropouts
- Dropout rate <25%; if over, a sensitivity analysis is needed
- Mention of the ITT analysis or inappropriate use of ITT analysis
- Patients with efficacy data not excluded from the ITT analysis; this is the case for patients who withdrew because of nonadherence to the protocol or “for lack of efficacy” and for those who were excluded during the immunotherapy procedure before analysis of efficacy.
- No PP analysis for the primary outcome
- CONSORT flow chart or adequate description of the items of the chart
- Adequate blinding
- Other major flaw, such as no report of CIs.

Calculation of sample size is requested in the CONSORT Statement. Because the objective of the study was to assess the quality of reporting, we did not make any efforts to contact the authors to clarify or complete the data extraction from the articles.

Analysis of the studies

The reasons for including or excluding articles are presented in Table I. We then analyzed the included articles more closely, and RCT publication was evaluated based on the criteria of the most recent previously published CONSORT Statement.^{12,13} It was decided to use all-or-none criteria to score the immunotherapy articles. The rationale provided in one (ie, that all criteria should be adhered to) is the reason for the all-or-none approach. Statistical analysis was carried out with χ^2 and Fisher exact tests.

RESULTS

SCIT

We identified 46 blind, placebo-controlled RCTs investigating strict SCIT, including 3,315 patients (see Table E1 in this article's Online Repository at www.jacionline.org).²⁵⁻⁷⁰ Two RCTs included more than 200 patients, 8 included between 101 and 200 patients, 11 included between 51 and 100 patients, and 25 included less than 50 patients. One RCT on homeopathic mite SCIT included 244 patients, and 1 RCT on grass SCIT included 411 patients.

There was a large heterogeneity among RCTs: 13 studied grass pollen, 6 studied *Parietaria* species pollen, 12 studied house dust mites, and 15 studied other allergens. Only 1 RCT studied allergen mixtures. Twenty RCTs used alum-adsorbed extracts, and 8 used various forms of allergoids.

One (2.2%) study using SCIT met the CONSORT requirements. Sixteen (35%) studies reported a CONSORT flow chart, and 12 (26%) studies reported a description of dropouts. Forty RCTs used a PP analysis or an ITT analysis, with the number of patients analyzed lower than those randomized. Eleven trials did not report 95% CIs or SDs/SE. Adequate randomization was reported in 16 (35%) studies, and incomplete randomization was reported in 11 (24%) studies. The power analysis was reported in 15 (33%) studies. Dropout rates were not reported in 5 RCTs.

It did not appear that the reporting quality of studies was better in recent SCIT articles (published after 2005) than in older articles (published before 2005, Table II).

SLIT

We identified 48 DBPC RCTs investigating strict SLIT, including 5,978 patients (see Table E2 in this article's Online

Repository at www.jacionline.org).⁷¹⁻¹¹⁸ One trial was published for the primary end point in one article¹⁰⁶ and for the secondary end point in a second article¹¹⁹; only the first article was considered in the analysis. Seven RCTs included more than 200 patients, 12 included between 101 and 200 patients, 15 included between 51 and 100 patients, and 14 included less than 50 patients.

There was a large heterogeneity among SLIT RCTs: 22 studied grass pollen (6 studies with tablets, 2 studies with drops and tablets as a maintenance therapy, and 1 study with tablet allergoids), 13 studied house dust mites (2 with tablet allergoids), and 13 studied other allergens.

The publication of only 1 study met all CONSORT requirements.⁹⁹ This was the only study using a strict ITT analysis. Two other RCTs met, at least partly, the CONSORT requirements (see Table E2).^{107,118} These 2 trials excluded patients without any clinical data. Twenty (42%) studies reported a CONSORT flow chart, and 16 (32%) reported a description of dropouts. Ten trials did not report 95% CIs or SDs/SDs. The study of Wahn et al¹¹⁸ did not clearly report the randomization procedures, but this study used the Didier et al¹⁰⁷ criteria, and both were used for the registration of SLIT to the EMA. One study was on children.¹¹⁸ All studies were short-term trials in patients with grass pollen allergy. Adequate randomization was reported in 6 (12%) studies, and incomplete randomization in 16 (32%). The power analysis was reported in 13 (27%) studies.

It appeared that the reporting quality of studies was better in recent SLIT articles (published after 2005) than in older articles (published before 2005, Table III). However, the vast majority of study reports failed to meet CONSORT criteria for the ITT analysis. The number of patients per study was increased from the earliest to the latest studies. In particular, 64% of studies published after 2005 enrolled more than 100 patients.

DISCUSSION

Main findings

In a moderately large set of SCIT and SLIT RCTs, the reports of the majority of trials were of low methodological quality because 1 (2.2%) of the SCIT trials and only 6.6% of the SLIT trials were found to report with sufficient adequacy on randomization, ITT analysis, or other important methodological issues according to the CONSORT Statement. These results confirm the low quality of reporting in many areas of medicine. Methodological limitations are known to substantially bias treatment effects toward an overestimation of the treatment effects.^{6-8,21}

Strengths and limitations

One strength of this study is the analysis of the complete set of SCIT and SLIT DBPC RCTs published since 1996. We began selecting articles in 1996 because this was the year of publication of the first CONSORT Statement. One limitation of our study is that we could only assess the reporting of important markers of internal validity but not what the investigators actually did because the CONSORT Statement does not directly evaluate the quality of the studies. Thus, it is possible that some misclassification occurred. Moreover, we were less stringent about randomization than would have been proposed by the CONSORT Statement because it is known that insufficient reporting of randomization does not mean that the correct method has not been used¹²⁰ and appropriate reporting was

TABLE II. Summary outcomes for SCIT

Publication data	1997-2000	2001-2004	≥2005	P value
No. of studies	14	13	19	
No. of patients per study				Patient per study = .15
<50	10 (71%)	9 (69%)	7 (37%)	
51-100	1 (7%)	2 (15%)	8 (42%)	
>100	3 (21%)	2 (15%)	4 (21%)	
CONSORT flow chart				
Chart	1 (7%)	7 (54%)	8 (42%)	.03
Description or incomplete chart	2 (14%)	2 (15%)	4 (21%)	.86
No dropouts (not needed)	3 (21%)	0	2 (11%)	.2
No information	8 (57%)	4 (31%)	5 (24%)	.17
ITT analysis specified	1 (7%)	1 (8%)	5 (26%)	.23
ITT analysis				
Specified and fully applied	0	0	2 (11%)	
Dropouts before any data	0	0	1 (2.2%)	
No ITT analysis specified				
No dropouts	3 (21%)	0	2 (11%)	
Randomization				
Well reported	1 (7%)	5 (38%)	3 (16%)	.37
Partly reported	4 (29%)	4 (31%)	6 (32%)	
Not reported	8 (57%)	4 (31%)	10 (53%)	
Sample size				
Reported and adequate	2 (10%)	5 (38%)	8 (42%)	

Statistical analysis was performed by using the χ^2 or Fisher exact test.

TABLE III. Summary outcomes for SLIT

Publication data	1997-2000	2001-2004	≥2005	P value
No. of studies	12	14	22	
No. of patients per study				Patient per study = < .006
<50	6 (50%)	4 (29%)	2 (9%)	
51-100	4 (33%)	7 (50%)	6 (27%)	
>100	1 (17%)	3 (21%)	14 (64%)	
CONSORT flow chart				
Chart	4 (33%)	3 (21%)	13 (59%)	.07
Description or incomplete chart	3 (25%)	6 (43%)	7 (32%)	.62
No dropouts (not needed)	1 (17%)	3 (21%)	1 (5%)	.26
No information	4 (33%)	2 (14%)	1 (5%)	.08
ITT analysis specified	1 (17%)	1 (7%)	14 (64%)	<.001
ITT analysis				
Specified and fully applied	0	0	1 (5%)	
Dropouts before any data	0	0	2 (9%)	
No ITT analysis specified				
No dropouts	1 (17%)	3 (21%)	1 (5%)	.49
Randomization				
Well reported	0	1 (7%)	9 (41%)	<.04
Partly reported	3 (25%)	3 (21%)	6 (27%)	
Not reported	9 (75%)	10 (71%)	9 (41%)	
Sample size				
Reported	1 (17%)	2 (14%)	10 (46%)	<.03

Statistical analysis was performed by using the χ^2 or Fisher exact test.

provided in some,^{99,107} but not all,^{98,116,118} RCTs carried out identically and used for registration.

It is only recently that the use of the CONSORT Statement is a requirement for the publication of RCTs and has been endorsed by the International Committee of Medical Journal Editors in its “Uniform requirements for manuscripts submitted to biomedical

journals” (available at www.icmje.org). Although the journals have subscribed to adherence to the CONSORT Statement, the requirements for reporting are not always implemented. Whether or not the journal editors are partially responsible, the ultimate responsibility rests with the authors, who should follow submission guidelines, and who, as trialists, must be aware of the CONSORT

Statement. The ability of an author to report a study adequately is a mark of rigor and scientific involvement and denotes the quality of the work.

The CONSORT Statement is still not required for regulatory agencies.³ This is particularly the case of the RCT by Dahl et al,⁹⁸ which was used for registration at the EMA and reports different numbers of patients and results in the publication compared with EMA files published in subsequent years.¹²¹

The CONSORT Statement, as well as medical agencies, request studies to be analyzed using the ITT principle. An ITT analysis is based on the assumption that, as in real life, all patients do not receive optimal treatment, despite this being the initial intention. Empiric evidence suggests that participants who adhere to treatment tend to do better than those who do not adhere, even after adjustment for all known prognostic factors and irrespective of assignment to active treatment or placebo.¹²² ITT analysis provides information on the potential effects of treatment policy rather than on the potential effects of specific treatment. In the present study, for SCIT, 2 RCTs were carried out using the ITT principle, and 1 used the worst-case-scenario methodology. For SLIT, only 1 RCT followed the ITT principle in its analysis,⁹⁹ and 2 others were considered to be adequate because all patients evaluated were included in the analysis.^{107,118} Five of these RCTs were used for SLIT registration to the EMA.^{98,99,107,116,118}

Reporting of RCTs

Our analysis showed that the quality of SLIT trials published after 2006 was higher compared with that of earlier trials. However, only 3 articles followed the CONSORT Statement. Although most of the SLIT RCTs presented in Table II were included in meta-analyses using the Jadad scale, other criteria are needed for the assessment of the risk of bias in RCTs.¹¹ On the other hand, only 1 of the SCIT trials met the CONSORT criteria, even the most recent ones. This is particularly the case for the largest studies, which used PP analysis.^{38,54}

Sample size

It should be noted that all RCTs with small sample sizes used PP analysis or a deviation of the ITT analysis. This is due to the relatively high dropout rate of RCTs, which are carried out over longer periods of time than many pharmacologic trials. Sample size calculations of RCTs should be considered before the beginning of the study. They can be estimated from previous RCTs and observational and other data.^{99,107}

Conclusion

This study shows that the quality of reporting according to the CONSORT Statement of most RCTs on SCIT and SLIT is low but similar to that seen in other disease areas.^{8,123,124} However, recent adequately powered, well-designed, and appropriately reported RCTs have been published for SIT. It is important to note that SLIT studies published after 2005 show better quality of reporting and that their sample sizes are larger. Some of these studies would have fulfilled CONSORT Statement requirements if they had used ITT analysis.

The Global Allergy and Asthma European Network therefore strongly recommends that investigators should be encouraged to adhere to the CONSORT Statement when reporting their RCTs

or, even better, to emphasize the need to consider important aspects of internal validity during the planning stage of a trial. Editors of journals should also follow these recommendations. Thereby, RCT reports based on CONSORT Statement criteria will provide more valid estimates of treatment effects and serve as a reliable basis for the development of evidence-based guidelines.

Clinical implications: As in other areas of medicine, the quality of reporting of most allergen-specific immunotherapy trials is low. Use of the CONSORT Statement criteria should be encouraged for publication to better inform physicians and guidelines.

REFERENCES

1. Bousquet J, Lockey R, Malling H. WHO Position Paper. Allergen Immunotherapy: therapeutic vaccines for allergic diseases. *J Allergy Clin Immunol* 1998; 102:558-62.
2. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;64(suppl 91):1-59.
3. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 2009;64:669-77.
4. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;62:317-24.
5. Committee for medicinal products for human use (CPMP). Guideline on allergen products: production and quality issues. London: European Medicines Agency; 2008. EMEA/CHMP/BWP/304831/2007.
6. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13.
7. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336:601-5.
8. Bausch B, Spaar A, Kleijnen J, Puhan MA. Quality of randomised trials in COPD. *Eur Respir J* 2009;34:1060-5.
9. Jadad AR. "Are you playing evidence-based medicine games with our daughter?" [letter]. *Lancet* 1996;347:274.
10. Clark HD, Wells GA, Huet C, McAlister FA, Salmi LR, Fergusson D, et al. Assessing the quality of randomized trials: reliability of the Jadad scale. *Control Clin Trials* 1999;20:448-52.
11. Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009;124:157-61, e1-32.
12. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276:637-9.
13. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191-4.
14. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
15. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010;7:e1000251.
16. Bousquet PJ, Brozek J, Bachert C, Bieber T, Bonini S, Burney P, et al. The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. *Allergy* 2009;64:1737-45.
17. Brozek J, Bousquet J, Baena-Cagnani C, Bonini S, Canonica G, Casale T, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
18. Brozek JL, Baena-Cagnani CE, Bonini S, Canonica GW, Rasi G, van Wijk RG, et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma guideline 2008 update. *Allergy* 2008;63:38-46.
19. Committee for Medicinal Products for Human Use. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. London: European Medicines Agency; 2008. CHMP/EWP/18504/2006.

20. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4-12.
21. Schulz KF, Altman DG, Moher D. Allocation concealment in clinical trials. *JAMA* 2002;288:2406-7, author reply 8-9.
22. Casale TB, Canonica GW, Bousquet J, Cox L, Lockett R, Nelson HS, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;124:665-70.
23. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670-4.
24. Sackett D, Straus S, Richardson W, Rosenberg W, Haynes R. Evidence-based medicine: how to practice and teach evidence-based medicine. 2nd Edition. Oxford: Churchill Livingstone; 2000.
25. Astarita C, Scala G, Sproviero S, Franzese A. Effects of enzyme-potentiated desensitization in the treatment of pollinosis: a double-blind placebo-controlled trial. *J Investig Allergol Clin Immunol* 1996;6:248-55.
26. Dolz I, Martinez-Cocera C, Bartolome J, Cimarra M. Placebo-controlled study of immunotherapy with grass pollen extract Alutard SQ during a 3 year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
27. Adkinson N Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
28. Ariano R, Panzani RC, Augeri G. Double-blind placebo controlled specific immunotherapy with mixed Cupressaceae taxodiaceae pollens in respiratory allergy to *Cupressus sempervirens*. *Allergol Immunopathol (Madr)* 1997;25:23-9.
29. Di Stanislao C, Di Berardino L, Bianchi I, Bologna G. A double-blind, placebo-controlled study of preventive immunotherapy with E.P.D., in the treatment of seasonal allergic disease. *Allerg Immunol (Paris)* 1997;29:39-42.
30. Olsen O, Larsen K, Jacobsen L, Svendsen U. A one year placebo-controlled double-blind house dust mite immunotherapy study in asthmatic adults. *Allergy* 1997;8:853-9.
31. Pichler C, Marquardsen A, Sparholt S, Løwenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D farinae* results in decreased bronchial hyperactivity. *Allergy* 1997;52:274-83.
32. Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed *Parietaria*-pollen allergoid: a 2- year, double-blind, placebo-controlled study. *Allergy* 1997;52:65-74.
33. Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:23-9.
34. Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven pre-seasonal injections of molecular standardized allergens. *Allergy* 1998;53:740-8.
35. Altintas D, Akmanlar N, Guner S, Burgut R, Yilmaz M, Bugdayci R, et al. Comparison between the use of adsorbed and aqueous immunotherapy material in *Dermatophagoides pteronyssinus* sensitive asthmatic children. *Allergol Immunopathol (Madr)* 1999;27:309-17.
36. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with *Parietaria*. Clinical and immunologic effects in a randomized, controlled trial. *Allergy* 1999;54:313-9.
37. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
38. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;56:498-505.
39. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinnepain MT, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2001;31:988-96.
40. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
41. Arvidsson MB, Lowhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol* 2002;109:777-83.
42. Basomba A, Tabar AI, de Rojas DH, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of *Dermatophagoides pteronyssinus*: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002;109:943-8.
43. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy—a one-year, randomised, double-blind, placebo-controlled study. *Allergy* 2002;57:297-305.
44. Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *BMJ* 2002;324:520.
45. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ* 2003;327:251-4.
46. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003;33:1076-82.
47. Crimi N, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect on bronchial hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int* 2004;19:98-108.
48. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59:45-53.
49. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004;113:643-9.
50. Mirone C, Albert F, Tosi A, Mocchetti F, Mosca S, Giorgino M, et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2004;34:1408-14.
51. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 2004;59:1224-8.
52. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy* 2005;35:572-8.
53. Ameal A, Vega-Chicote JM, Fernandez S, Miranda A, Carmona MJ, Rondon MC, et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of *Dermatophagoides pteronyssinus* in allergic asthma. *Allergy* 2005;60:1178-83.
54. Corrigan CJ, Kettner J, Doerner C, Cromwell O, Narkus A. Efficacy and safety of pre-seasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;60:801-7.
55. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Prilozi* 2005;26:113-29.
56. Ferrer M, Burches E, Pelaez A, Munoz A, Hernandez D, Basomba A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol* 2005;15:283-92.
57. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;116:608-13.
58. Blumberg G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006;61:843-8.
59. Chakraborty P, Roy I, Chatterjee S, Chanda S, Gupta-Bharracharya S. *Phoenix sylvestris* Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. *J Investig Allergol Clin Immunol* 2006;16:377-84.
60. Colas C, Monzon S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol* 2006;117:810-6.
61. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattignavong AP, Lindblad R, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445-55.
62. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25.
63. Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006;118:1026-32.
64. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol* 2006;117:263-8.

65. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy* 2006;61:191-7.
66. Charpin D, Gouitaa M, Dron-Gonzalez M, Fardeau MF, Massabie-Bouchat YP, Hugues B, et al. Immunotherapy with an aluminum hydroxide-adsorbed *Juniperus ashei* foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007;143:83-91.
67. Guimarães Junqueira de Queiros M, Oliveira Silva DA, Alves R, Fukuhara Chiba H, Soares de Amaral VB, de Almeida KC, et al. Mite-specific immunotherapy using allergen and/or bacterial extracts in atopic patients in Brazil. *J Investig Allergol Clin Immunol* 2008;18:84-92.
68. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2008;122:951-60.
69. Purohit A, Niederberger V, Kronqvist M, Horak F, Gronneberg R, Suck R, et al. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy* 2008;38:1514-25.
70. Tabar AI, Lizaso MT, Garcia BE, Gomez B, Echechipia S, Aldunate MT, et al. Double-blind, placebo-controlled study of *Alternaria alternata* immunotherapy: clinical efficacy and safety. *Pediatr Allergy Immunol* 2008;19:67-75.
71. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997;8:21-7.
72. Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998;53:493-8.
73. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. *Allergol Immunopathol* 1998;26:234-40.
74. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela G, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351:629-32.
75. Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, Andre C, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998;53:662-72.
76. Bousquet J, Scheinmann P, Guinépain MT, Perrin-Fayolle M, Sauvaet J, Tonnel AB, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study [in process citation]. *Allergy* 1999;54:249-60.
77. Passalacqua G, Albano M, Riccio A, Fregonese L, Puccinelli P, Parmiani S, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: a double-blind, placebo-controlled trial [in process citation]. *J Allergy Clin Immunol* 1999;104:964-8.
78. Pradaliere A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999;54:819-28.
79. Purello-D'Ambrosio F, Gangemi S, Isola S, La Motta N, Puccinelli P, Parmiani S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999;54:968-73.
80. La Rosa M, Ranno C, Andri C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104:425-32.
81. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000;55:842-9.
82. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55:369-75.
83. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in cupressaceae allergy using an extract of *Cupressus arizonica*. A double blind study. *Allergol Immunopathol (Madr)* 2001;29:238-44.
84. Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol* 2001;32:49-55.
85. Voltolini S, Modena P, Minale P, Bignardi D, Troise C, Puccinelli P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. *Allergol Immunopathol (Madr)* 2001;29:103-10.
86. Lima MT, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002;32:507-14.
87. Andre C, Perrin-Fayolle M, Grosclaude M, Couturier P, Basset D, Cornillon J, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol* 2003;131:111-8.
88. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003;14:216-21.
89. Mortemousque B, Bertel F, De Casamayor J, Verin P, Colin J. House-dust mite sublingual-swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2003;33:464-9.
90. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to *Parietaria* pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003;33:1641-7.
91. Wuthrich B, Bucher C, Jorg W, Bircher A, Eng P, Schneider Y, et al. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003;13:145-8.
92. Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004;93:425-30.
93. Bufer A, Ziegler-Kirbach E, Stoekmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004;59:498-504.
94. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59:1285-93.
95. Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831-7.
96. Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59:491-7.
97. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90.
98. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
99. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
100. Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol* 2006;17:408-15.
101. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006;100:1374-83.
102. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME, et al. Clinical efficacy and safety of preseasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. *Allergol Immunopathol (Madr)* 2006;34:194-8.
103. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006;61:849-54.
104. Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy* 2006;61:1177-83.
105. de Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, Tunon de Lara JM, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2007;99:453-61.
106. Worm M. Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. *Eur Ann Allergy Clin Immunol* 2006;38:355-60.
107. Didier A, Mallin HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.

108. Moreno-Ancillo A, Moreno C, Ojeda P, Dominguez C, Barasona MJ, Garcia-Cubillana A, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without up dosing. *J Invest Allergol Clin Immunol* 2007;17:399-405.
109. Mosges R, Bruning H, Hessler HJ, Gotz G, Knaussmann HG. Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial. *Acta Dermatovenerol Alp Panonica Adriat* 2007;16:143-8.
110. Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007;18:47-57.
111. Roder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007;119:892-8.
112. Vervloet D, Birnbaum J, Laurent P, Hugues B, Fardeau MF, Massabie-Bouchat YP, et al. Safety and efficacy of *Juniperus ashei* sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007;142:239-46.
113. Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, et al. A randomized double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol Int* 2008;57:265-75.
114. Panzner P, Petras M, Sykora T, Lesna I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med* 2008;102:1296-304.
115. Stelmach I, Kaczmarek-Wozniak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy* 2009;39:401-8.
116. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73, e7.
117. Ott H, Sieber J, Brehler R, Folster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:1394-401.
118. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6, e3.
119. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2008;100:256-63.
120. Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, Schunemann HJ, et al. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. *J Clin Epidemiol* 2004;57:1232-6.
121. Calderon MA, Casale TB, Togias MD, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol* 2011;127:x-xxx.
122. Montori VM, Guyatt GH. Intention-to-treat principle. *CMAJ* 2001;165:1339-41.
123. Toerien M, Brookes ST, Metcalfe C, de Salis I, Tomlin Z, Peters TJ, et al. A review of reporting of participant recruitment and retention in RCTs in six major journals. *Trials* 2009;10:52.
124. Ethgen M, Boutron L, Steg PG, Roy C, Ravaud P. Quality of reporting internal and external validity data from randomized controlled trials evaluating stents for percutaneous coronary intervention. *BMC Med Res Methodol* 2009;9:24.

REFERENCES

- E1. Astarita C, Scala G, Sproviero S, Franzese A. Effects of enzyme-potentiated desensitization in the treatment of pollinosis: a double-blind placebo-controlled trial. *J Investig Allergol Clin Immunol* 1996;6:248-55.
- E2. Dolz I, Martinez-Cocera C, Bartolome J, Cimarra M. Placebo-controlled study of immunotherapy with grass pollen extract Alutard SQ during a 3 year period with initial rush immunotherapy. *Allergy* 1996;51:489-500.
- E3. Adkinson N Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
- E4. Ariano R, Panzani RC, Augeri G. Double-blind placebo controlled specific immunotherapy with mixed Cupressaceae taxodiaceae pollens in respiratory allergy to *Cupressus sempervirens*. *Allergol Immunopathol (Madr)* 1997;25:23-9.
- E5. Di Stanislao C, Di Bernardino L, Bianchi I, Bologna G. A double-blind, placebo-controlled study of preventive immunotherapy with E.P.D., in the treatment of seasonal allergic disease. *Allerg Immunol (Paris)* 1997;29:39-42.
- E6. Olsen O, Larsen K, Jacobsen L, Svendsen U. A one year placebo-controlled double-blind house dust mite immunotherapy study in asthmatic adults. *Allergy* 1997;8:853-9.
- E7. Pichler C, Marquardsen A, Sparholt S, Löwenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D farinae* results in decreased bronchial hyperreactivity. *Allergy* 1997;52:274-83.
- E8. Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed *Parietaria*-pollen allergoid: a 2- year, double-blind, placebo-controlled study. *Allergy* 1997;52:65-74.
- E9. Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:23-9.
- E10. Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven pre-seasonal injections of molecular standardized allergens. *Allergy* 1998;53:740-8.
- E11. Altintas D, Akmanlar N, Guneser S, Burgut R, Yilmaz M, Bugdayci R, et al. Comparison between the use of adsorbed and aqueous immunotherapy material in *Dermatophagoides pteronyssinus* sensitive asthmatic children. *Allergol Immunopathol (Madr)* 1999;27:309-17.
- E12. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with *Parietaria*. Clinical and immunologic effects in a randomized, controlled trial. *Allergy* 1999;54:313-9.
- E13. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
- E14. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;56:498-505.
- E15. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinépain MT, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2001;31:988-96.
- E16. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
- E17. Arvidsson MB, Lowhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol* 2002;109:777-83.
- E18. Basomba A, Tabar AI, de Rojas DH, Garcia BE, Alamar R, Olaguibel JM, et al. Allergen vaccination with a liposome-encapsulated extract of *Dermatophagoides pteronyssinus*: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002;109:943-8.
- E19. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy—a one-year, randomised, double-blind, placebo-controlled study. *Allergy* 2002;57:297-305.
- E20. Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *BMJ* 2002;324:520.
- E21. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. *BMJ* 2003;327:251-4.
- E22. Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003;33:1076-82.
- E23. Crimi N, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. A randomized, controlled study of specific immunotherapy in monosensitized subjects with seasonal rhinitis: effect on bronchial hyperresponsiveness, sputum inflammatory markers and development of asthma symptoms. *Ann Ital Med Int* 2004;19:98-108.
- E24. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59:45-53.
- E25. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004;113:643-9.
- E26. Mirone C, Albert F, Tosi A, Mocchetti F, Mosca S, Giorgino M, et al. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2004;34:1408-14.
- E27. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 2004;59:1224-8.
- E28. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy* 2005;35:572-8.
- E29. Ameal A, Vega-Chicote JM, Fernandez S, Miranda A, Carmona MJ, Rondon MC, et al. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of *Dermatophagoides pteronyssinus* in allergic asthma. *Allergy* 2005;60:1178-83.
- E30. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;60:801-7.
- E31. Dokic D, Schnitker J, Narkus A, Cromwell O, Frank E. Clinical effects of specific immunotherapy: a two-year double-blind, placebo-controlled study with a one year follow-up. *Prilozi* 2005;26:113-29.
- E32. Ferrer M, Burches E, Pelaez A, Munoz A, Hernandez D, Basomba A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol* 2005;15:283-92.
- E33. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;116:608-13.
- E34. Blumberg G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006;61:843-8.
- E35. Chakraborty P, Roy I, Chatterjee S, Chanda S, Gupta-Bharracharya S. *Phoenix sylvestris* Roxb pollen allergy: a 2-year randomized controlled trial and follow-up study of immunotherapy in patients with seasonal allergy in an agricultural area of West Bengal, India. *J Investig Allergol Clin Immunol* 2006;16:377-84.
- E36. Colas C, Monzon S, Venturini M, Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Salsola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol* 2006;117:810-6.
- E37. Creticos PS, Schroeder JT, Hamilton RG, Balcer-Whaley SL, Khattnavong AP, Lindblad R, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445-55.
- E38. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25.
- E39. Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006;118:1026-32.
- E40. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol* 2006;117:263-8.
- E41. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy* 2006;61:191-7.
- E42. Charpin D, Gouitaa M, Dron-Gonzalez V, Fardeau MF, Massabie-Bouchat YP, Hugues B, et al. Immunotherapy with an aluminum hydroxide-adsorbed *Juniperus ashei* foreign pollen extract in seasonal indigenous cypress pollen rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007;143:83-91.
- E43. Guimaraes Junqueira de Queiros M, Oliveira Silva DA, Alves R, Fukuhara Chiba H, Soares de Amaral VB, de Almeida KC, et al. Mite-specific immunotherapy

- using allergen and/or bacterial extracts in atopic patients in Brazil. *J Investig Allergol Clin Immunol* 2008;18:84-92.
- E44. Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2008;122:951-60.
- E45. Purohit A, Niederberger V, Kronqvist M, Horak F, Gronneberg R, Suck R, et al. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy* 2008;38:1514-25.
- E46. Tabar AI, Lizaso MT, Garcia BE, Gomez B, Echechipia S, Aldunate MT, et al. Double-blind, placebo-controlled study of *Alternaria alternata* immunotherapy: clinical efficacy and safety. *Pediatr Allergy Immunol* 2008;19:67-75.
- E47. Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997;8:21-7.
- E48. Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998;53:493-8.
- E49. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. *Allergol Immunopathol* 1998;26:234-40.
- E50. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela G, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351:629-32.
- E51. Vourdas D, Syrigou E, Potamianou P, Carat F, Batard T, Andre C, et al. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998;53:662-72.
- E52. Bousquet J, Scheinmann P, Guinpepain 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 [in process citation]. *Allergy* 1999;54:249-60.
- E53. Passalacqua G, Albano M, Riccio A, Fregonese L, Puccinelli P, Parmiani S, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: a double-blind, placebo-controlled trial [in process citation]. *J Allergy Clin Immunol* 1999;104:964-8.
- E54. Pradaliere A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999;54:819-28.
- E55. Purello-D'Ambrosio F, Gangemi S, Isola S, La Motta N, Puccinelli P, Parmiani S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999;54:968-73.
- E56. La Rosa M, Ranno C, Andri C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104:425-32.
- E57. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000;55:842-9.
- E58. Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55:369-75.
- E59. Ariano R, Spadolini I, Panzani RC. Efficacy of sublingual specific immunotherapy in cupressaceae allergy using an extract of *Cupressus arizonica*. A double blind study. *Allergol Immunopathol (Madr)* 2001;29:238-44.
- E60. Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol* 2001;32:49-55.
- E61. Voltolini S, Modena P, Minale P, Bignardi D, Troise C, Puccinelli P, et al. Sublingual immunotherapy in tree pollen allergy. Double-blind, placebo-controlled study with a biologically standardised extract of three pollens (alder, birch and hazel) administered by a rush schedule. *Allergol Immunopathol (Madr)* 2001;29:103-10.
- E62. Lima MT, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002;32:507-14.
- E63. Andre C, Perrin-Fayolle M, Grosclaude M, Couturier P, Basset D, Cornillon J, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol* 2003;131:111-8.
- E64. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003;14:216-21.
- E65. Mortemousque B, Bertel F, De Casamayor J, Verin P, Colin J. House-dust mite sublingual-swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2003;33:464-9.
- E66. Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to *Parietaria* pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003;33:1641-7.
- E67. Wuthrich B, Bucher C, Jorg W, Bircher A, Eng P, Schneider Y, et al. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003;13:145-8.
- E68. Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004;93:425-30.
- E69. Bufer A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004;59:498-504.
- E70. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59:1285-93.
- E71. Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831-7.
- E72. Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N, et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59:491-7.
- E73. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90.
- E74. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
- E75. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
- E76. Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol* 2006;17:408-15.
- E77. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006;100:1374-83.
- E78. Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML, Bruno ME, et al. Clinical efficacy and safety of pre-seasonal sublingual immunotherapy with grass pollen carbamylated allergoid in rhinitic patients. A double-blind, placebo-controlled study. *Allergol Immunopathol (Madr)* 2006;34:194-8.
- E79. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006;61:849-54.
- E80. Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy* 2006;61:1177-83.
- E81. de Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, Tunon de Lara JM, et al. Sublingual-swallow immunotherapy with standardized 3-grass pollen extract: a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2007;99:453-61.
- E82. Worm M. Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. *Eur Ann Allergy Clin Immunol* 2006;38:355-60.
- E83. Didier A, Mallin HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
- E84. Moreno-Ancillo A, Moreno C, Ojeda P, Dominguez C, Barasona MJ, Garcia-Cubillana A, et al. Efficacy and quality of life with once-daily sublingual immunotherapy with grasses plus olive pollen extract without up dosing. *J Investig Allergol Clin Immunol* 2007;17:399-405.
- E85. Mosges R, Bruning H, Hessler HJ, Gotz G, Knaussmann HG. Sublingual immunotherapy in pollen-induced seasonal rhinitis and conjunctivitis: a randomized controlled trial. *Acta Dermatovenereol Alp Panonica Adriat* 2007;16:143-8.
- E86. Pham-Thi N, Scheinmann P, Fadel R, Combebiass A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced

- allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007;18:47-57.
- E87. Roder E, Berger MY, Hop WC, Bernsen RM, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007;119:892-8.
- E88. Vervloet D, Birnbaum J, Laurent P, Hugues B, Fardeau MF, Massabie-Bouchat YP, et al. Safety and efficacy of *Juniperus ashei* sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. A double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2007;142:239-46.
- E89. Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, et al. A randomized double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol Int* 2008;57:265-75.
- E90. Panzner P, Petras M, Sykora T, Lesna I. Double-blind, placebo-controlled evaluation of grass pollen specific immunotherapy with oral drops administered sublingually or supralingually. *Respir Med* 2008;102:1296-304.
- E91. Stelmach I, Kaczmarek-Wozniak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy* 2009;39:401-8.
- E92. Bufer A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73, e7.
- E93. Ott H, Sieber J, Brehler R, Folster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:1394-401.
- E94. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6, e3.
- E95. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2008;100:256-63.

TABLE E1. DBPC randomized controlled trials in SCIT published after 1996

Author	Age	Pts A/P	Drop outs A/P	Allergen	CONSORT Flow chart	ITT OR Per Protocol*		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified	Protocol used			
Astarita 1996 ^{E1}	M=25	10/10	Not reported	Enzyme potentiated <i>Parietaria</i>	Not needed, no dropouts	No	No dropouts	No	CI not reported	No
Dolz 1996 ^{E2}	15-35	30	2/0 (group not specified)	Grass alum	No	No	PP	No	No CI reported	No
Adkinson 1997 ^{E3}	M=9.2	61/60	8/3	Mixture	No, but adequate description of dropouts	No	PP	Incomplete		Yes
Ariano 1997 ^{E4}	13-62	10/10	Not reported	Cypress	Not needed, no dropouts	No	No dropouts	No		No
Di- Stanislao 1997 ^{E5}	M=27	20/20	Not reported	Enzyme potentiated grass	Not needed, no dropouts	No	No dropouts	No	No CI reported	No
Olsen 1997 ^{E6}	18-64	21/10	4/4	Der p- Der f alum	No, adequate description of dropouts	No	PP	Incomplete	No CI reported	No
Pichler 1997 ^{E7}	20-46	16/14	3 but group unclear	Der p alum	No	No	PP	No	Study mostly reporting BHR and challenge	No
Tari 1997 ^{E8}	13-50	20/20	0/1	<i>Parietaria</i> alum	No	No	PP	No		No
Zenner 1997 ^{E9}	16-53	45/42	4/1	Grass alum	No, adequate description of dropouts	No	PP	Incomplete		Yes
Balda 1998 ^{E10}	18-58	51/60	4/2	Birch, alder, elm allergoid alum	No, adequate description of dropouts	Yes	but PP probably used	Yes	No CI reported	Yes
Altintas 1999 ^{E11}	5-18	P: 5 A1: 10 A2: 10 A3: 9	1 dropout	Different Der p extracts	No, adequate description of dropouts	No	PP probably used	No	No clear primary outcome	No
Ariano 1999 ^{E12}	13-62	13/12	1/1	<i>Parietaria</i> allergoid	No, adequate description of dropouts	No	PP	No		No
Durham 1999 ^{E13}	M=38, 42	16/16	2/3	Grass alum	Yes	No	37 patients enrolled in study at baseline, 32 analyzed: PP	Not applicable to the study: double-blind trial of discontinuation study		NO, all patients willing to continue

(Continued)

TABLE E1. (Continued)

Author	Age	Pts A/P	Drop outs A/P	Allergen	CONSORT Flow chart	ITT OR Per Protocol*		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified	Protocol used			
Drachenberg 2000 ^{E14}	18-60	81/60	7/10	MPL-grass	No, adequate description of dropouts	No	PP	Incomplete		No
Leynadier 2001 ^{E15}	18-44	16/13	1/1	Grass calcium phosphate	No	No	PP	Incomplete		No
Walker 2001 ^{E16}	22-64	22/22	2/5	Grass alum	Yes	Yes	probably PP (see fig BHR)	Incomplete		Yes
Arvidsson 2002 ^{E17}	19-45	24/25	2/1	Birch alum	No, insufficient description of dropouts	No		Yes		Yes
Basomba 2002 ^{E18}	14-50	29/26	4/1	Der p liposomes	Yes	No	PP	No		Yes, but unclear
Bodtger 2002 ^{E19}	19-46	17/18	0/1	Birch-alum	Yes	No	PP	Incomplete		Yes
Lewith 2002 ^{E20}	M=38	122/120	21/19	Der p homeopathy	Yes	No	Probably PP	Yes	Co- primary end point: FEV ₁ and “mood” on a bipolar scale	Yes
Radcliffe 2003 ^{E21}	M : 37-38	90/93	11/6	Enzyme potentiated grass	Yes	No	PP	Yes	Primary end point not validated	Yes, post hoc
Varney 2003 ^{E22}	19-50	13/15	4/4	Der p alum	No, adequate reporting of dropouts	No**	PP	Yes		No
Crimi 2004 ^{E23}	20-54	15/15	1/0	<i>Parietaria</i> alum	Yes	No	PP	Yes		No
Kinchi 2004 ^{E24}	adults	24/24	5/9 (end)	Birch calcium phosphate	Yes	No	PP	Yes	Second year without pollen	No
Maestrelli 2004 ^{E25}	8-43	49/46	8/15	Derp-Derf- alum	No, adequate reporting of dropouts	No	PP	No	CI not reported for clinical outcomes, primary outcome: lung function	Yes
Mirone 2004 ^{E26}	23-60	14/16	6/3	Ragweed alum	Yes	No	PP	No	Large dropout rate	No

(Continued)

TABLE E1. (Continued)

Author	Age	Pts A/P	Drop outs A/P	Allergen	CONSORT Flow chart	ITT OR Per Protocol*		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified	Protocol used			
Polosa 2004 ^{E27}	20-54	15/15	1/0	<i>Parietaria</i> alum	1 patient lost in active treatment, no reason	No	1 patient lost	No		No
Alvarez Cuesta 2005 ^{E28}	17-58	25/28	0/0	Grass+olive Depigoid alum	Yes	ITT	No dropouts	Incomplete		No
Ameal 2005 ^{E29}	14-48	32/31	3/5	Der p depigoid alum	Yes	No	PP	No	Primary outcome : BPT	Yes
Corrigan 2005 ^{E30}	18-60	77/77	11/15	Grass allergoid alum	No, insufficient description of dropouts	No	PP	No	Range but no CI reported	No
Dokic 2005 ^{E31}	18-62	20/20 (1 center)	0/0	Der p allergoid alum	Not needed no dropouts	No	No dropouts	Yes	- Multicenter study, but results of 1 center reported because insufficient recruitment in the other center. - No mean value and CI for primary end point	Yes but only 71% of the planned patients recruited
Ferrer 2005 ^{E32}	15-55	28/29	6/9	<i>Parietaria</i> alum	Yes	No	PP	No		No
Jutel 2005 ^{E33}	21-30	64	Nb analyzed 29/28	Recombinant grass	No, adequate description of dropouts	No	PP	Incomplete		Yes
Blumberga 2006 ^{E34}	18-60	26/28	6/3	Der p alum	Yes	ITT		No	No CI reported	Yes
Chakraborty 2006 ^{E35}	20-59	18/17	0/0	Phoenix	Not needed No dropouts	No	No dropouts over 2 yrs	No	Statistical analysis not described, CI not reported	No
Colas 2006 ^{E36}	18-50	43/20	2/1	<i>Salsola</i> depigoid alum	No, insufficient description of dropouts	No	PP	Incomplete		Yes

(Continued)

TABLE E1. (Continued)

Author	Age	Pts A/P	Drop outs A/P	Allergen	CONSORT Flow chart	ITT OR Per Protocol*		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified	Protocol used			
Creticos 2006 ^{E37}	23-60	14/11	4/2	CPG-Amb al	No, adequate description of dropouts	ITT	PP	Yes	Primary outcome : NPT	No
Frew 2006 ^{E38}	18-60	P : 103 AL : 104 AH : 203	P : 14 A : 15 A : 16	Grass alum (A : low (L) or high(H) dose)	Yes	ITT analysis excluding dropouts with no efficacy data	PP	Incomplete		Yes
Garcia- Robaina 2006 ^{E39}	M :24	32/32	5/5	Der p Der f depigoid alum	No, insufficient description of dropouts	ITT, worst- case scenario		No	Primary outcome : BPT	Yes
Roberts 2006 ^{E40}	3-16	18/17	4	Grass alum	Yes	No	PP	Incomplete		Yes
Wang 2006 ^{E41}	6-45	64/65	2/1	Der p alum	No, adequate description of dropouts	No	Probably PP	No		No
Charpin 2007 ^{E42}	24-66	20/20	6/4	<i>Juniperus</i> alum	Yes	No	PP	Incomplete		No
Guimaraes 2008 ^{E43}	6-50	P: 15 A: 15 A+B: 20 B: 23	P: 1 A+AB: 6	A: Der p B: bacteria	No, insufficient description of dropouts	No	PP	No		No
Pauli 2008 ^{E44}	18-50	P : 36 R1 : 32 R2 : 33 A : 33	P : 6 R1 : 3 R2 : 5 A : 7	Recombinant Birch : R Birch : A	Yes	No	PP	No		No
Purohit 2008 ^{E45}	22-56	P : 49 R1 : 38 R2 : 37	P : 12 R1 : 19 R2 : 10	Recombinant Birch : R	No	No	PP	Yes	High rate of dropouts, no sensitivity analysis	No
Tabar 2008 ^{E46}	M: 13-15	14/14	1/4	<i>Alternaria</i>	No, adequate description of dropouts	No	“patients analyzed until dropout”	No		No

*: ITT strictly followed: intent-to-treat analysis specified in methods and all randomized patients included in analysis of efficacy.

**: Insufficient data to perform an ITT analysis

PP: Per protocol analysis or ITT analysis but all randomized patients were not included in analysis of efficacy

A: Standardized allergen extract

R1, R2, R3: Recombinant allergens

Adequate reporting ☐Insufficient reporting ☐Inadequate reporting ☐

TABLE E2. DBPC randomized controlled trials in SLIT published after 1996

Author Year	Age	Patients A/P	Dropout rate A/P*	Allergen	CONSORT Flow chart	ITT OR Per Protocol**		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified				
Hirsch 1997 ^{E47}	6-16	15/15	1/0	HDM Drops	No		Insufficient description	Incomplete	1 dropout but analysis on 21/30 enrolled patients	Yes
Clavel 1998 ^{E48}	8-55	136 enrolled	16 dropouts 62/58 in analysis	Mixed Grasses Drops	No		Insufficient description	No	Primary end point: medications needed to control patients	No
Hordijk 1998 ^{E49}	18-45	69 randomized 27/30	3/1	Mixed Grasses Drops	No	ITT	57 of 69 enrolled patients used for final analysis	No		No
Passalacqua 1998 ^{E50}	15-46	10/10	0/1	HDM allergoid Tablet	Yes		Patients excluded for noncompliance	Incomplete		No
Vourdas 1998 ^{E51}	7-17	34/32	1/1	Olive Drops	No		Insufficient description	No		No
Bousquet 1999 ^{E52}	7-42	42/43	17/18	HDM Drops	Yes		Insufficient description	No	Large dropout rate	No
Passalacqua 1999 ^{E53}	15-42	15/15	1/2	<i>Parietaria</i> Drops	No but description of dropouts		Patients excluded for noncompliance	No		No
Pradaliere 1999 ^{E54}	7-58	63/63	3/4	Mixed Grasses Build up: Drops Maintenance: Tablets	Yes		Patients excluded for noncompliance	No		No
Purello 1999 ^{E55}	14-50	14/16	0/0	<i>Parietaria</i> Drops	No but no dropouts		No dropouts	No	CI for symptom score not reported	No
La Rosa 1999 ^{E56}	6-14	20/21	4/4	<i>Parietaria</i> Drops	No but description of dropouts		1 patient excluded for noncompliance	No		No
Pajno 2000 ^{E57}	8-15	12/12	0/3	HDM Drops	No but description of dropouts		Probably PP	incomplete	CI for symptom score not reported	No
Guez 2000 ^{E58}	6-51	36/36	11/12	HDM Drops	Yes		Patients excluded with evaluable clinical data	No	Large dropout rate	No
Ariano 2001 ^{E59}	19-50	10/10	0/0	Cypress Drops	No but no dropouts		No dropouts	No	CI for nasal provocation	No
Baheccilier 2001 ^{E60}	7-15	8/7	0/0	HDM Drops	No but no dropouts		No dropouts	No	Statistics not corrected for multiplicity CI for clinical data not reported	No
Voltolini 2001 ^{E61}	15-52	15/15	1/2	Alder-Birch- Hazel Drops	No		Insufficient information	No	CI not reported	No
Lima 2002 ^{E62}	16-48	28/28	2/5	Grass Drops	No but description of dropouts		Insufficient information	Yes	Efficacy analyzed PP	Yes
Andre 2003 ^{E63}	7-55	53/53	10/4	Ragweed Drops	No but description of dropouts		Patients excluded with evaluable clinical data	No		No
Ippoliti 2003 ^{E64}	5-12	47/39	0/0	HDM Drops	No but no dropouts		No dropouts	No	CI for clinical data not reported	No

(Continued)

TABLE E2. (Continued)

Author Year	Age	Patients A/P	Dropout rate A/P*	Allergen	CONSORT Flow chart	ITT OR Per Protocol**		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified				
Mortemousque 2003 ^{E65}	6-60	30/30	4/11	HDM Drops	No but description of dropouts		Patients excluded with evaluable clinical data	No		No
Pajno 2003 ^{E66}	8-14	A: 15 P: 15+8	A: 1 P: 2+1	<i>Parietaria</i> Drops	No but description of dropouts		Not clearly described but probably PP	Incomplete		No
Wutrich 2003 ^{E67}	4-11	14/14	4/2	Grass Drops	No		Patients excluded with evaluable clinical data	No	No CI reported	No
Bowen 2004 ^{E68}	6-58	43/40	15/11	Ragweed Drops	Yes	ITT	Patients excluded with evaluable clinical data	No	Large dropout rate	No
Bufe 2004 ^{E69}	6-13	83/78	8/7 (yr 1) + 7/7 excluded for compliance	Grass Drops	No but description of dropouts		Patients excluded for noncompliance	Incomplete	Study used to validate a symptom- medication score further used as a primary outcome. Results given at yr 4 (1 yr placebo- controlled)	No
Rolinck- Werninghaus 2004 ^{E70}	3-14	49/48	2/3 (yr 1) 11/11 (yr 3)	Mixed Grasses Drops	Yes		Patients excluded with evaluable clinical data	Incomplete		Yes
Smith 2004 ^{E71}	18-60	P: 45 A1: 44 A2: 47	Impossible to determine precisely	Mixed Grasses Drops	No Description of dropouts unclear		Patients excluded with evaluable clinical data	No		No
Tonnel 2004 ^{E72}	7-45	15/17	5/9	HDM Drops	Yes		Patients excluded with evaluable clinical data	No	Large dropout rate	No
Dahl 2006 ^{E73}	18-64	74/40	13/8	Grass Tablet	Yes	PP		No	Primary outcome: safety	No
Dahl 2006 ^{E74}	23-35	316/318	42/46	Grass Tablet	Yes	ITT	Patients excluded with evaluable clinical data	Incomplete***		Yes
Durham 2006 ^{E75}	18-66	569/286	39/26	Grass Tablet	Yes	ITT	All randomized patients	Yes		Yes
Lue 2006 ^{E76}	6-12	10/10	0/0	HDM Drops	No but no dropouts		No dropouts	No		No
Niu 2006 ^{E77}	6-12	56/54	7/6	HDM Drops	No but description of dropouts	ITT	Patients excluded with evaluable clinical data	No		No
Palma- Carlos 2006 ^{E78}	19-43	17/16	4/9	Grass Allergoid Tablet	Yes but incomplete		Insufficient information	No	CI not reported for primary outcome Large dropout rate	No
Passalacqua 2006 ^{E79}	18-50	34/34	6/6	HDM Allergoid Tablet	Yes but incomplete		Insufficient information	Incomplete information		No
Valovirta 2006 ^{E80}	5-14	65/33	8/6	Hazelnut, birch, elm Drops	Yes	ITT	Patients excluded with evaluable clinical data	No		Yes

(Continued)

TABLE E2. (Continued)

Author Year	Age	Patients A/P	Dropout rate A/P*	Allergen	CONSORT Flow chart	ITT OR Per Protocol**		Method of randomization reported	Flaw in method	Power analysis
						ITT or PP specified				
De Blay 2007 ^{E81}	12-41	61/57	9/8	Mixed Grasses Drops	Yes	ITT	Patients excluded with evaluable clinical data	No		No
Worm ^S 2006 ^{E82}	18-59	94/91	17/8 (yr 1)	Mixed Grass Drops	Yes	ITT	Only PP results reported	Yes	No CI reported (even for PP analysis)	No
Didier 2007 ^{E83}	25-47	472/156 (3 active groups)	59/10	Mixed Grasses Tablets	Yes	ITT	ITT analysis excluding drop outs with no efficacy data	Incomplete		Yes
Moreno 2007 ^{E84}	14-55	53/52	11/9	Olive+ Mixed Grasses Drops	Yes but incomplete		Patients probably excluded before season	Incomplete	Study carried out over 2 seasons due to low recruitment CI not reported for primary outcome	No
Mosges 2007 ^{E85}	18-50	48/53	6/5	Mixed Grasses Updosing: Drops Maintenance: Tablets	No but description of dropouts	ITT	1 patient excluded from analysis	No	CI not reported for primary outcome	No
Pham-Ti 2007 ^{E86}	5-16	55/56	11/8	HDM Drops	Yes	ITT	2 patients excluded with evaluable clinical data	Incomplete		Yes
Roder 2007 ^{E87}	6-18	108/96	26/24	Mixed Grasses Drops	Yes	ITT with LOCF	Patients excluded with evaluable clinical data	Yes		Yes
Vervloet 2007 ^{E88}	19-60	38/38	2/4	Juniper Drops	No but description of dropouts		Patients possibly excluded with evaluable clinical data	Incomplete	Tolerance study more than efficacy study. Study carried out over 2 pollen seasons	No
Okubo 2008 ^{E89}	25-55	38/23	1/1	Cedar Drops	No but description of dropouts		Patients excluded with evaluable clinical data	No	CI not reported	No
Panzner 2008 ^{E90}	7-50	20/15	3	Mixed Grasses Drops	No			Incomplete		No
Stelmach 2009 ^{E91}	6-17	25/25	5/10	Mixed Grasses Drops	Yes	ITT	Patients excluded with evaluable clinical data	Yes	Large drop out rate	Yes
Bufe 2009 ^{E92}	5-16	126/127	12/7	Grass Tablet	Yes	ITT	Patients excluded with evaluable clinical data	No ***		Yes

(Continued)

TABLE E2. (Continued)

Ott 2009 ^{E93}	8-65	142/67	43/18: ITT 58/34: PP	Mixed Grasses Drops	Yes	ITT	Patients excluded with evaluable clinical data	No	Large dropout rate	Yes
Wahn 2009 ^{E94}	5-17	139/139	4/8	Mixed Grasses Tablet	Yes	ITT	Exclusion of dropouts without efficacy data	No****		Yes

*: A: Active, P: Placebo. In many papers without a CONSORT flow chart, the dropouts were insufficiently described

**: ITT strictly followed: intent-to-treat analysis specified in methods and all randomized patients included in analysis of efficacy. PP: Per protocol analysis or ITT analysis but all randomized patients were not included in analysis of efficacy. LOCF: Last observation carried forward.

***: Randomization not fully reported in the paper, but the study used was for registration to EMA and was based on the same protocol as the study of Durham et al^{E75} which reported adequate randomization

****: Randomization not fully reported in the paper, but the study used was for registration to EMA and was based on the same protocol as the study of Didier et al^{E83} which reported almost adequate randomization

S: The paper of Pfaar et al^{E95} reports the secondary analysis of the results of the paper of Worm.^{E82} Only the paper of Worm was considered.

HDM: house dust mites

Adequate reporting ☐

Insufficient reporting ☐

Inadequate reporting ☐