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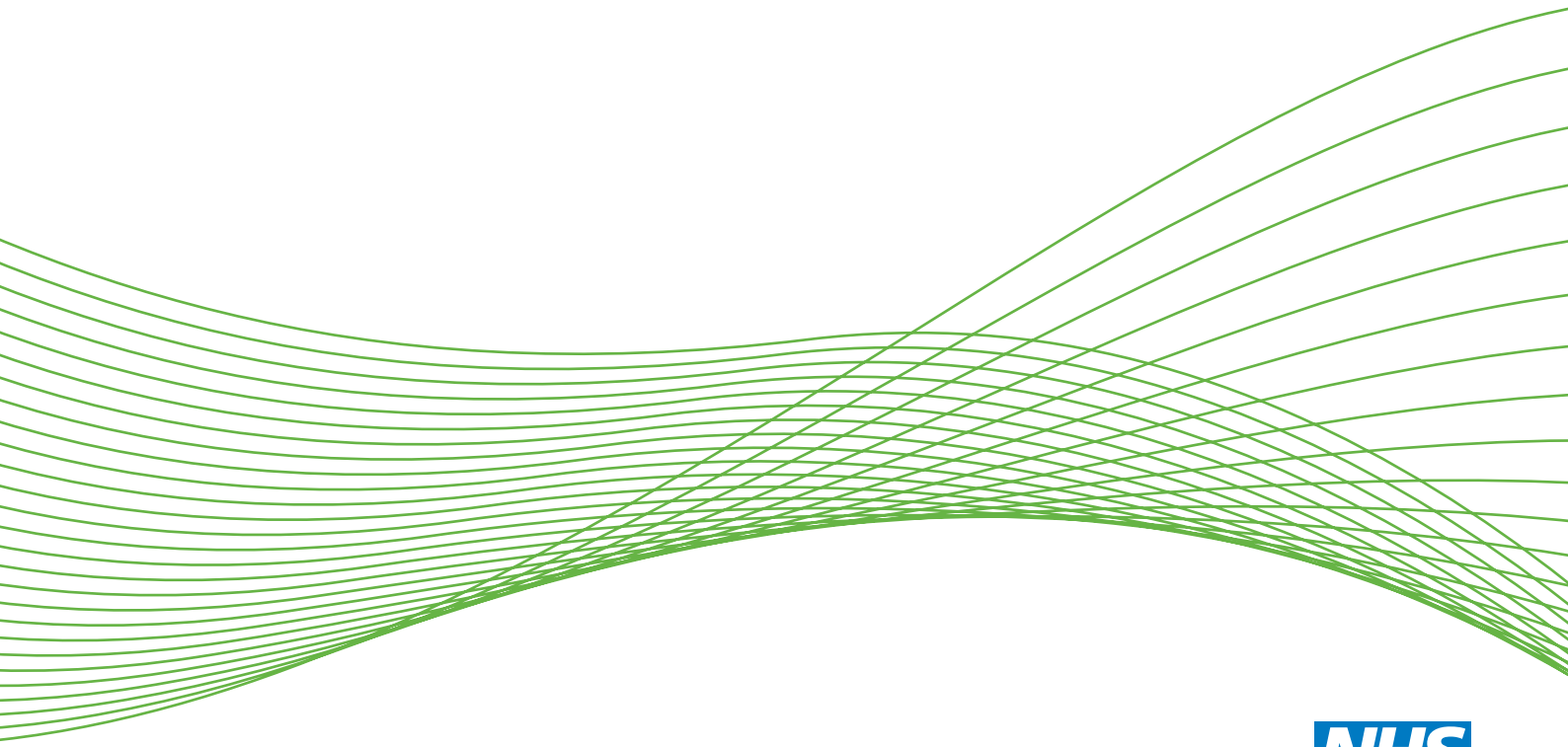

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A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis

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Abstract

A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis

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Background: Severe allergic rhinitis uncontrolled by conventional medication can substantially affect quality of life. Immunotherapy involves administering increasing doses of a specific allergen, with the aim of reducing sensitivity and symptomatic reactions. Recent meta-analyses have concluded that both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are more effective than placebo in reducing symptoms. It is uncertain which route of administration is more effective and whether or not treatment is cost-effective.

Objective: To determine the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal allergic rhinitis in adults and children.

Data sources: Electronic databases {MEDLINE, EMBASE, The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)], NHS Economic Evaluation Database (NHS EED)} and trial registries (from inception up to April 2011).

Review methods: Standard systematic review methods were used for study selection, data extraction and quality assessment. Double-blind randomised, placebo-controlled trials of SCIT or SLIT, or of SCIT compared with SLIT, and economic evaluations were included. Meta-analysis and indirect comparison meta-analysis and meta-regression were carried out. A new economic model was constructed to estimate cost–utility.

Results: Meta-analyses found statistically significant effects for SCIT and SLIT compared with placebo across a number of outcome measures and for the vast majority of subgroup analyses (type and amount of allergen, duration of treatment). There was less evidence for children, but some results in favour of SLIT were statistically significant. Indirect comparisons did not provide conclusive results in favour of either SCIT or SLIT. Economic modelling suggested that, when compared with symptomatic treatment (ST), both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per quality-adjusted life-year (QALY) from around 6 years, or 5 years for SCIT compared with SLIT (NHS and patient perspective).

Limitations: It is uncertain to what extent changes in the outcome measures used in the trials translate into clinically meaningful benefits. Cost-effectiveness estimates are based on a simple model, limited data and a number of assumptions, and should be seen as indicative only.

Conclusions: A benefit from both SCIT and SLIT compared with placebo has been consistently demonstrated, but the extent of this effectiveness in terms of clinical benefit is unclear. Both SCIT and SLIT may be cost-effective compared with ST from around 6 years (threshold of £20,000–30,000 per QALY). Further research is needed to establish the comparative effectiveness of SCIT compared with SLIT and to provide more robust cost-effectiveness estimates.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

A&E	accident and emergency
AE	adverse event
AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
AUC	area under the curve
BNF	*British National Formulary*
BSACI	British Society for Allergy and Clinical Immunology
CBA	cost–benefit analysis
CCA	cost–consequences analysis
CEA	cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CrI	credible interval
CUA	cost–utility analysis
DBPC	double blind, placebo controlled
DIC	deviance information criterion
EAACI	European Academy of Allergy and Clinical Immunology
EE	economic evaluation
EPS	entire pollen season
EQ-5D	European Quality of Life-5 Dimensions (EuroQol Group standardised instrument for use as a measure of health outcome)
GCSE	General Certificate of Secondary Education
GP	general practitioner
ICER	incremental cost-effectiveness ratio
ICMA	indirect comparison meta-analysis
ICMR	indirect comparison meta-regression
IgE	immunoglobulin E
IT	immunotherapy
MAC	major allergen content
MAQOL	McMaster Asthma Quality of Life Questionnaire
MCMC	Monte Carlo Markov chain
MD	mean difference
MS	medication score
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
PAR	perennial allergic rhinitis
PAT	Preventative Allergy Treatment
PPS	peak pollen season
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SAA	seasonal allergic asthma
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SCIT	subcutaneous immunotherapy
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SIGN	Scottish Intercollegiate Guidelines Network
SIT	specific (allergen) immunotherapy

SLIT	sublingual immunotherapy	SS	symptom score
SMD	standardised mean difference	ST	symptomatic treatment
SMS	combined symptom and medication score	VAS	visual analogue scale
SOCC	Standards of Care Committee	WAO	World Allergy Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Scientific summary

Background

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa following allergen exposure. The condition is often comorbid with allergic conjunctivitis and is a risk factor for asthma. AR is more common in developed countries and the prevalence of allergic sensitisation is >50% in some age groups. The high impact of AR on health-related quality of life (QoL), as well as work or educational performance results in a significant individual and economic burden. Conventional treatment involves providing symptomatic relief; however, up to two-thirds of patients report only partial or poor symptom control.

Allergen immunotherapy involves administering gradually increasing doses of a specific allergen, or part of the allergen, to an allergic subject, with the aim of reducing sensitivity and minimising future symptomatic reaction on natural exposure to the causative agent. Recent meta-analyses have concluded that both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are effective in reducing symptoms of AR when compared with placebo. In addition, the clinical benefits of both SCIT and SLIT appear to be sustained following cessation of treatment. There is some evidence that immunotherapy can prevent disease progression, development of new sensitisations and onset of asthma. However, it is unclear whether one route of administration is more effective than the other, and the long-term cost-effectiveness of the treatments is uncertain.

Objectives

To determine the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal allergic rhinitis (SAR) by (1) undertaking a systematic review of randomised controlled trials (RCTs) in order to update existing Cochrane reviews on the topic; (2) undertaking an indirect comparison of SCIT with SLIT; (3) undertaking a systematic review of existing economic evaluations (EEs); and (4) conducting an independent EE.

Review methods

Major electronic databases {e.g. MEDLINE, EMBASE, The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)] and the NHS Economic Evaluation Database (NHS EED)} and several internet sites, including trial registries, were searched from inception up to April 2011. There were no language restrictions. For the review of clinical effectiveness, double-blind randomised, placebo-controlled trials of SCIT or SLIT were included, as were direct comparisons of SCIT with SLIT. Studies were eligible if they included adults and/or children with a clinical diagnosis of moderate to severe SAR with or without asthma. For the review of EEs, any suitable evaluations (including analyses of cost-effectiveness, cost–benefit, cost–utility, cost–consequences and cost minimisation) or reviews of EEs were included, as were studies reporting data of potential use for informing an economic model, such as utilities or cost data. Standard systematic review methods were used for study selection, data extraction and quality assessment.

For the review of clinical effectiveness, analyses were limited to four patient-centred outcomes – symptom scores (SSs), medication scores (MSs), combined symptom and medication scores (SMS), and QoL – as well as any reported adverse events (AEs). With the exception of AEs, random-effect meta-analyses were conducted for all outcomes. Analyses were also conducted to explore the impact of a range of prespecified patient and trial characteristics on outcome measures. Adjusted indirect comparisons of SCIT versus SLIT

were conducted across all four patient-centred outcomes, using random-effects meta-regression and adjusting for covariates.

The EE was based on a systematic review and critical appraisal of existing EEs and a new cost-effectiveness model, based on estimates of QoL, and cost and resource use estimates derived from the literature and following consultation with clinical experts.

Results

Clinical effectiveness

Seventeen new RCTs of SCIT compared with placebo and 11 of SLIT compared with placebo were identified, which were published subsequent to the corresponding Cochrane reviews of these interventions. One small head-to-head trial of SCIT compared with SLIT was found. A further 23 ongoing, or not yet reported, RCTs were identified. Risk of bias assessment was hampered by inadequate reporting of all quality criteria. The majority of trials appeared to have low risk of bias when sufficient information to make a judgement was reported, with only very few instances of high risk of bias identified.

Of the 17 newly identified RCTs of SCIT (vs placebo) and 11 newly identified RCTs of SLIT (vs placebo), only five trials of each type of intervention reported data in a form suitable for meta-analysis. However, meta-analysis also included all previous relevant studies from the Cochrane reviews. Statistically significant results were found for both SCIT and SLIT, suggesting a moderate effect size in favour of the active treatment for all patient-centred outcomes (SS, MS, SMS, and QoL). This remained the case for the vast majority of subgroup analyses performed (e.g. for treatment duration, and type and amount of allergen used). A large amount of variability in how outcomes were scored meant that results had to be presented as standardised mean differences. Interpretation of these is difficult and the clinical significance of the results is uncertain.

There is less evidence for children, particularly for SCIT. One small SCIT trial found significantly lower SSs and MSs, and improved QoL, in the actively treated group (after 3 years of treatment). For SLIT, statistically significant results (based on nine studies) were found for SSs but not for MSs. The one study including a quality-of-life measure found a statistically significant difference in favour of SLIT.

Indirect comparisons of SCIT with SLIT were suggestive of SCIT being more beneficial for SSs and MSs, but this was associated with substantial residual heterogeneity. No statistically significant difference was found between the two interventions for combined SMSs or QoL, which could arguably be deemed more clinically useful outcomes. These findings were not substantially altered when participant age, treatment duration and type or amount of allergen were included as covariates.

Adverse events were common with both SCIT and SLIT, but the majority were local reactions at the point of administration and resolved spontaneously without treatment. Systemic reactions were less common, occurring in approximately 4.4% of injections for SCIT, and most were graded as mild or moderate in severity. However, 19% of systemic reactions following SCIT treatment were considered to be severe, compared with only 2% of systemic reactions following SLIT. Discontinuations due to AEs were similar between the interventions – 3% and 3.4% for SCIT and SLIT, respectively. No fatalities occurred in any of the trials.

Cost-effectiveness

Searches for EEs identified 14 EEs and two reviews of EEs. Overall, the studies found that both SCIT and SLIT were more beneficial than symptomatic treatment (ST), and in some cases also become less costly than ST over time. Where studies expressed results as incremental cost-effectiveness ratios (ICERs), both SCIT and SLIT were found to be cost-effective at thresholds of £20,000 per quality-adjusted life-year (QALY). However, there were issues around transparency and/or robustness of parameters for most studies. None of the cost–utility analyses were conducted by independent researchers.

A preferred Markov model was constructed for adults and children but could not be adequately populated largely owing to a lack of suitable data on transition probabilities between different health states in SAR. An alternative, simpler, model was therefore constructed, which used data on quality-of-life improvement based on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) from the direct and indirect comparison meta-analyses. Using a number of assumptions, changes in RQLQ were mapped to changes in European Quality of Life-5 Dimensions (EQ-5D), in order to express results as cost per QALY. Based on a threshold of £20,000–30,000 per QALY, results showed that immunotherapy compared with ST became cost-effective after around 6 years from the start of treatment (NHS and patient perspective; 7 years for NHS perspective only).

Subcutaneous immunotherapy was found to be cost-effective compared with SLIT after around 5 years, based on the same threshold. This is based on SCIT being both more effective and more costly than SLIT. As the difference in RQLQ was not statistically significant (the confidence interval crosses zero), there is uncertainty associated with the effectiveness estimate, which, in turn, affects the reliability of the cost-effectiveness estimate. Results overall should be seen as indicative because they are based on a very simple analysis. Sensitivity analyses were restricted to varying the time horizon and using upper and lower confidence limits for RQLQ improvement. Potential cost savings from preventing future cases of asthma were not considered in this cost-effectiveness analysis (CEA). It was not possible to undertake a CEA for children owing to a paucity of available data.

Conclusions

Based on a substantial number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than ST only, and this remains the case for the vast majority of subgroup analyses based on differences in population and treatment protocol. It is uncertain to what extent this statistical significance translates to clinically significant differences across the different types of outcome measures used. An indirect comparison is suggestive of SCIT being more beneficial than SLIT based on SSs and MSs, but no such difference could be shown for combined SMSs or QoL, and firm conclusions cannot be drawn. CEAs suggest that both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per QALY from around 6 years. However, these estimates were based on limited data and the use of a number of assumptions. Potential cost savings resulting from future cases of asthma avoided were not included in the analysis, but would likely lead to an increase in cost-effectiveness.

Recommendations for future research

Future research should focus on:

- Head-to-head RCTs comparing SCIT with SLIT, consistent with current guidelines on treatment protocols and using standardised outcome and reporting measures to enable between-study comparison. Further studies of either intervention compared with placebo are unlikely to add to the already extensive literature on this subject.
- Outcomes that (1) take into consideration that the relative effectiveness of immunotherapy compared with symptomatic medication varies depending on prevailing allergen levels and (2) could best inform EEs.
- Evaluation of long-term effectiveness from shorter courses of immunotherapy, as this places less of a burden both on the patient in terms of time and inconvenience and in terms of associated costs.
- The extent to which results of all previous primary research can be made available to independent researchers in order to inform model-based value-of-information analysis.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Seasonal allergic rhinitis

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa following allergen exposure. Symptoms include rhinorrhoea, nasal obstruction, nasal itching and sneezing. AR is often comorbid with allergic conjunctivitis and is a risk factor for asthma.[1]

Depending on the nature of the triggering allergen, AR has traditionally been categorised as either seasonal allergic rhinitis (SAR, e.g. induced by pollen) or perennial allergic rhinitis (PAR, e.g. induced by animals, dust mites, etc.). More recently, an alternative classification of either intermittent or persistent AR has been proposed [Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update].[1] The disease can further be categorised as either 'mild' or 'moderate/severe', depending on the severity of symptoms and impact on quality of life (QoL).[1] 'Hay fever' is the common name classically given to SAR or rhinoconjunctivitis.

Diagnosis is based on symptom history and examination, and could include investigations such as peak nasal inspiratory flow or nasal endoscopy. Skin prick tests should be carried out routinely in order to determine whether rhinitis is allergic or non-allergic.[2]

Epidemiology and natural history

Allergic rhinitis is a global health problem and affects patients from all ethnic groups, all socioeconomic conditions and all ages; in many countries the prevalence of allergic sensitisation is >50% in some age groups.[1] It is more common in developed countries. The prevalence of AR based on questionnaire studies has been found to range from 1% to 40% worldwide and between 3% and 29% in the UK (18%, 14.9%, 3%, 11.9%, 29%, 16.5% and 18.9%, based on sample sizes of between 813 and >12,000, including adults and children).[1] A clinical definition is difficult to use in surveys of large populations, and a questionnaire-only approach may therefore overestimate or underestimate the prevalence of AR. In a study using the ARIA definition of AR,[3] the prevalence of clinically confirmable AR in the UK was found to be 26% in adults [95% confidence interval (CI) 20.3% to 31.7%]. A 2009 report[4] estimated that SAR affected approximately 16 million people in the UK, with grass pollen allergy the most common form, affecting around 95% of sufferers, followed by sensitivity to tree pollen (25%), weed pollen (20%) and fungal spores. Many people are sensitised to more than one allergen. A large international survey in children[5] found a UK prevalence of AR of around 10% in 6- to 7-year-olds and 15–19% in 13- to 14-year-olds. Although rates of AR are increasing in countries with low prevalence, rates may be plateauing or decreasing in countries with high prevalence.[1] However, based on climate change predictions, the prevalence of SAR is likely to increase, with general practitioner (GP) consultations for SAR forecast to rise by 30–40% by 2020.[4]

There are few data on the prognosis of AR, although symptoms tend to become milder with age, and allergic skin reactivity decreases in the elderly.[1] Some studies have investigated the incidence and remission of AR in the same general population; a Danish study[6] found that remission from symptoms was relatively infrequent and remission from both symptoms and IgE sensitisation was rare; a Swedish study[7] found that overall prevalence increased over an 8-year period (from 12.4% to 15.0%), whereas in a proportion of cases (23%) symptoms ceased to be reported.

Allergic rhinitis and asthma are frequently comorbid conditions. Both disorders affect the mucosal lining of the respiratory tract and are linked by common underlying cellular processes and, thus, may be considered

as part of the same allergic disease ('united airways' approach).[8] There is now widespread evidence to suggest that AR in children often predicts development of asthma. A large longitudinal study[9] ($n = 8275$) found that childhood AR was associated with a significant two- to sevenfold increased risk of incident asthma later in life.

Burden of disease

The burden on primary and secondary care from allergic diseases, particularly asthma, is high, as are the associated costs. A 2004 review[10] of UK databases found that:

- Six per cent of all GP consultations were for allergic disease, with allergic rhinoconjunctivitis being the third most common reason for consultation after eczema and asthma (1991 data).
- Eleven per cent of community prescriptions were for asthma and other allergic problems, including nasal allergy (4.3 million prescriptions in 2000–1 for nasal allergy).
- Most hospital admissions for allergic conditions were due to asthma (87% or 92.5/100,000 in 2000–1); 1.6 per 100,000 admissions were for AR (2000–1).
- Cost estimates for GP consultations for allergic problems range from £211M to £311M per year.
- Asthma and other allergic diseases accounted for 11% (£0.7B) of all primary care prescribing costs.
- Allergic problems are responsible for over 183,000 bed-days each year, with an estimated cost of £68M per year (sensitivity analysis limits £56–83M).

Conventional treatment

Conventional treatment of SAR includes oral or topical antihistamines and intranasal corticosteroids as required, with the goal of treatment being symptomatic relief. Occasionally, systemic corticosteroids are prescribed (see *Current guidelines*). However, some patients are unable to tolerate pharmacotherapy and a substantial number – up to two-thirds in a UK study of patients in 16 general practices[11] – report only partial or poor symptom control, particularly of systemic symptoms. Pharmacotherapy has no enduring effect following discontinuation and is not thought to influence the course of disease.

Allergen immunotherapy

Allergen immunotherapy (IT) involves administering gradually increasing doses of a specific allergen, or part of the allergen, to an allergic subject, with the aim of reducing sensitivity and minimising future symptomatic reaction on natural exposure to the causative agent.[12] Delivery of specific allergen immunotherapy (SIT) has traditionally been by subcutaneous injection.[13] A number of other routes of administration have now been investigated, but only subcutaneous and sublingual administration are currently in general use.[13]

The mechanisms by which allergen-specific IT modulates the immune response have not been fully elucidated; however, IT has been shown to increase serum levels of allergen-specific IgG, which correlates closely with an IgE-blocking activity and may be partly responsible for the therapeutic effect.[14] IT also appears to alter the balance of helper T-cells, consequently decreasing production of proallergenic cytokines.[14]

In contrast with the use of conventional symptom relief medication, the clinical benefits of both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) appear to be sustained following cessation of treatment. An uncontrolled cross-sectional study[15] of SIT for Japanese cedar pollinosis (mean treatment duration 3.6 years; $n = 485$) reported duration of effect at 10 years post completion, with 42% of patients remaining symptom free even in the year with the highest pollen count.

A small prospective, open, controlled study[16] (treatment duration 3 years; $n = 28$) recorded ongoing clinical benefit 12 years after discontinuation of treatment. However, this study was not randomised, with treatment allocation based on patient or parent preference.

Few studies have conducted long-term follow-up while maintaining double-blind conditions. One study[17] of SCIT for grass pollen allergy demonstrated that, following 3–4 years of treatment, clinical benefits were maintained over the next three allergy seasons, and did not differ from a continued active treatment arm. A 3-year trial of SLIT for grass pollen allergy with 2 years of blinded follow-up has also shown sustained effects of IT for all clinical and patient-reported outcomes measured.[18]

Subcutaneous IT must be delivered in a clinical setting owing the increased risk of severe allergic reactions. Full resuscitation facilities must be available and, in the UK, a minimum of 60 minutes post-injection supervision is required.[19,20] SCIT thus requires a considerable time commitment from patients, as well as substantial use of clinical resources. SLIT appears to be safe even at very high doses (up to 500 times the usual monthly subcutaneous dose) and is associated with fewer adverse events (AEs).[21] Thus, SLIT can normally be self-administered outside of a clinical setting, and is therefore more time efficient for the patient, as well as reducing resource utilisation. It should be noted, however, that maintenance doses for SLIT generally range from 20 to 200 times the dose used in SCIT, with implications for treatment cost.[21]

Treatment schedule

Owing to the risk of adverse reactions to allergen injection in sensitised patients, conventional SCIT treatment schedules involve a gradual increase in the allergen content of injections, usually involving one or two injections per week over a 3- to 6-month period.[22] Once a prespecified maximum treatment dose has been achieved, or the maximum tolerated dose for any given patient attained, treatment continues with this maintenance dose at regular intervals, usually monthly, for the duration of therapy.[21] Optimal maintenance dosing for a given product is often prespecified by the manufacturer, although substantial evidence suggests that a maintenance dose in the range of 5–20μg of major allergen per injection is associated with significant clinical improvement.[23] However, the maximum tolerated dose varies between individual patients and may be lower than the target therapeutic dose.

A number of studies have investigated accelerated updosing schedules for SCIT. For example, rush IT involves administering increasing doses of allergen at intervals of between 15 and 60 minutes over a 1- to 3-day period, until the target therapeutic dose is achieved.[22] An alternative form of accelerated schedule is cluster IT, whereby two to three incremental doses are administered on non-consecutive days. Maintenance dose is usually reached at between 4 and 8 weeks.[22]

In contrast, treatment schedules for SLIT may or may not include an updosing period, and following initial treatment administration under medical supervision, maintenance dosing is undertaken by the patient in a non-clinical setting. Typically, dosing continues daily for the period of treatment – up to 3 years. However, studies[21,24–26] have shown that shorter treatment periods, with SLIT administered for a few months before and during the pollen season, or during the pollen season only, may be as effective as year-round treatment, in terms of symptom and medication reduction and improved QoL.

Optimal treatment schedules for SLIT have yet to be definitely established, and a wide variety of practices are used.[19] Updosing may or may not be necessary, and maintenance schedules ranging from once per day to once per week have been used,[19] although daily dosing is the most common.

More recently, rush or cluster regimens for SLIT have been used. A recent meta-analysis[27] of individual patient data (IPD) from three open, prospective studies of high-dose SLIT, totalling 1052 adult and paediatric pollen-allergic patients, found no significant difference in rhinoconjunctivitis symptom scores (SSs) or use of rescue medication between perennial or coseasonal schedules, or standard or ultrarush titration. The rate of AEs was also similar between the different treatment schedules. Thus, the major benefit of accelerated IT schedules appears to be in terms of patient convenience. As inconvenience is one

of the major reasons for treatment discontinuation,[28] accelerated schedules may increase both adherence and therapy uptake.[22]

A recent review[29] found that accelerated schedules in SCIT may be associated with a higher risk of systemic reactions but also suggested that premedication, for example with antihistamines or corticosteroids, may result in a risk profile similar to that of conventional treatment schedules.

A number of studies[25,30,31] have reported that the clinical effects of SIT are additive over time, with increasing benefit following subsequent years of treatment. Based on evidence of sustained clinical benefits after treatment cessation following studies with 3 years of active treatment,[17,32] current guidelines recommend this duration of treatment for both SCIT and SLIT.[19] However, there are few double-blind discontinuation studies, and none comparing the long-term effects after different lengths of active treatment for SAR. One prospective controlled study[33] evaluated relapse rates following between 12 and 96 months of SCIT treatment in 40 adult and paediatric patients with house dust mite allergy. All patients were symptom free at completion of treatment, but 55% relapsed over the following 3 years. Relapse rate was significantly related to treatment duration, with 62% of those treated for 35 months or less experiencing a recurrence of symptoms, compared with 48% of those treated for >36 months ($p < 0.04$).

Specific (allergen) immunotherapy formulations

The immunomodulatory effect of SIT is specific to the allergen used. Although single-allergen IT has proven effective in reducing symptoms on exposure to the specific allergen in polysensitised patients, no additional benefit is obtained in respect of the other allergic triggers. However, there is some indication that SIT may prevent the onset of new sensitisations in monosensitised children,[16,34,35] possibly due to cross-reactivity between related allergen species. For example, there is strong reactivity between members of the Festucoideae family of grasses, which includes timothy grass (*Phleum pratense L.*), rye grass and orchard grass, and there is extensive cross-reactivity within and between a number of subfamilies of tree pollen.[21]

In contrast, mixtures of unrelated allergens have failed to show efficacy in double-blind, placebo-controlled (DBPC) trials of either SCIT or SLIT in multisensitised populations, possibly due to potential interactions between the different enzymatic components and/or dilution of individual allergen dosage.[21,36] For example, extracts from *Alternaria* species reduce the immunogenicity of timothy grass extract, and studies have shown that extracts of moulds and fungi significantly reduce the potency of grass pollens, some weeds, trees, and a number of perennial allergens when mixed together.[21] Thus, concurrent treatment of multiple sensitivities is not recommended. However, mixtures of related and cross-reacting allergens (e.g. antigens from more than one species of grass pollen) are effective, and a number of commercial products of this type are currently available.[19] It should be noted that multiallergen treatment is commonplace in the USA, where vaccines are formulated for individual use by the treating clinician, but separate vaccines may need to be given for each allergen.[37]

A number of modifications in formulation procedures have been made in recent years to improve treatment convenience and/or safety, particularly for SCIT products. The development of depot formulations by adsorption of allergen extract on to depot materials, for example aluminium hydroxide, L-tyrosine or calcium phosphate, is now common practice.[23] This results in prolonged, gradual release of the allergen at the injection site, allowing for a larger maintenance dose to be given at each injection and reducing the number and frequency of maintenance injections required. Another important modification involves chemical modification of the allergen extract with adjuvants such as glutaraldehyde or formaldehyde.[23] The resultant allergoid has reduced specific IgE-binding capacity and therefore lower allergenicity, reducing the risk of treatment-emergent AEs. The reduced allergenicity of allergoid compounds again allows for larger doses to be used, making treatment schedules more convenient. The effect of these modifications on the immunogenicity of the allergoid is unchanged and, hence, clinical efficacy is maintained. Again, this situation differs from that in the USA, where the use of unmodified aqueous allergen extracts is standard practice.[37] More recently, genetically modified allergens or allergen derivatives, or use of allergens conjugated with immunostimulatory molecules has been reported.[12,38]

Standardisation

The production of allergen extracts derived from natural allergens can result in highly variable potency of the end product to be used in SIT. Individual manufacturers have therefore developed in-house standardisation procedures for the purpose of quality control and consistency between batches.[23] In addition, European regulations now specify requirements for starting materials, production processes and quality control.[39] Nevertheless, in-house reference standards are based on units of biological activity obtained from immunological assays and/or skin prick tests in a representative population. Thus, sensitivity of the test population, sample size, and the immunological methodologies used may result in differences in potency between products with the same nominal activity. Further, manufacturers use a range of specific units to measure biological response and these are not readily comparable between different commercial products.[23] Given these differences, optimal dosages are product specific and cannot be generalised. Nevertheless, the degree of clinical improvement appears to be dose dependent in both SLIT and SCIT.[40] In injection IT, increased efficacy with higher doses must be balanced with increased risk of systemic reactions.[41] In contrast, a meta-analysis of 25 studies[42] in SLIT found that this route of administration did not result in a dose-dependent increase in AEs. These findings were confirmed by a 2011 report from the European Academy of Allergy and Clinical Immunology (EAACI) task force on dose–response relationships in SIT.[40]

It has been recommended that manufacturers state the major allergen content (MAC) of their products in mass units (g/ml),[43,44] although differences in assay methods may still limit comparability, and the variable contribution of minor allergen content to total biological potency is not accounted for. The use of recombinant allergen products may improve standardisation in the future but these are not yet widely available and few have been tested in large-scale randomised controlled trials (RCTs).[23]

Commercial products in the UK

The only aeroallergen SLIT product licensed in the UK for adults and children (5 years) is Grazax® (75,000 SQ-T oral lyophilisate; ALK-Abelló Ltd, Hørsholm, Denmark), a standardised allergen extract of grass pollen from timothy grass. Tablets (one per day) are placed under the tongue and allowed to disperse. Treatment is ideally initiated 4 months before the grass pollen season and continued for a period of 3 years. Where no improvement in symptoms is observed during the first pollen season, there is no indication for continuing the treatment.[45] Grazax costs £66.77 for 30 tablets [source: *British National Formulary* (BNF) (2012)].[46]

The only SCIT product licensed in the UK is Pollinex® (Allergy Therapeutics, Worthing, UK), a standardised L-tyrosine-adsorbed allergoid of grass or tree pollens. Pollinex for grass allergy contains allergen extracts of 12 grass species plus rye, and the tree pollen vaccine contains birch, alder and hazel. Both vaccines may be prescribed to adults and children (≥6 years) and are given in six preseasonal injections.[19] An initial treatment set (three vials) and extension course treatment (one vial) of Pollinex costs £450 [source: BNF (2012)[46]].

A variety of unlicensed products may be prescribed by specialists on an individual 'named-patient' basis [see the 2011 British Society for Allergy and Clinical Immunology (BSACI) guidelines for AR[19] for an overview].

Non-standard therapies

A number of researchers have investigated highly truncated SIT schedules, including single-injection treatment[47,48] and the Rinkel method.[49,50] These are not considered to be standard IT, have proven ineffective in double-blind placebo-controlled studies[49,50] and, therefore, have not been included in this review. More recent developments in IT formulations have included the use of peptides fragments of relevant T-cell epitopes of an allergen, as opposed to whole allergens; vaccination with immunostimulatory compounds without a specific allergen attached; and the use of recombinant wild allergens or allergen fragments.[51] Genetically engineered allergens have the potential to reduce allergenicity while maintaining immunogenicity[52,53] and are thus a promising avenue for future research. However, these products are

generally in the early stages of development and are therefore not currently used in standard practice. These therapies have also not been included in this review.

The role of specific (allergen) immunotherapy in asthma prevention

As well as treating symptoms of AR (and allergic asthma), there is evidence that SIT can prevent disease progression, development of new sensitisations, and onset of asthma.[8,19] The review by Fiocchi and Fox[8] identifies a number of studies[54–56] demonstrating the preventative effect of SIT, including the Preventative Allergy Treatment (PAT) study. The PAT study[54–56] was an open-label RCT ($n = 205$) of SCIT compared with control, which followed children aged 6–14 years for up to 7 years after a 3-year treatment period. Symptomatic rescue medication was allowed in both treatment arms. At 10 years, the number of patients who had developed asthma was 16 out of 64 (25%) in the SCIT group and 24 out of 53 (45%, control OR = 2.5, 95% CI 1.1 to 5.9; *p*-value not reported) in the control group.[54] Loss to follow-up at this point was 23% in the SCIT and 33% in the control group. When adjusted for bronchial hyper-responsiveness and asthma status at baseline, the treatment effect was found to be statistically significant (OR for no asthma = 4.6, 95% CI 1.5 to 13.7; $p = 0.0075$).

Fiocchi and Fox[8] identify a number of additional studies that support these findings. Overall, they showed that SCIT or SLIT is beneficial compared with medication only in the prevention of new asthma cases and/or new sensitisations, or for reducing asthma severity or the number of asthma cases. The studies included in the review are mainly open-label RCTs or use non-randomised designs, so are likely to be subject to greater bias than blinded RCTs, which, in turn, may influence the effect size. Loss to follow-up may also be an issue in those studies with long follow-up periods and fairly small numbers of patients.

Three studies[54–58] report on the preventative effect of SIT in the development of new asthma cases; these are summarised in *Table 1*.

An ongoing RCT, which may be able to further substantiate these findings, is the Grazax Asthma Prevention (GAP) RCT,[59] which commenced in 2010 and is due to finish in 2015. It randomised children aged 6–12 years with grass pollen-induced AR and no asthma to receive SLIT with Grazax or a placebo tablet. The primary outcome measure is the evaluation of allergy and asthma symptoms.

TABLE 1 Preventative effect of SIT in asthma development

Study	Participants	Study design	Outcome
Novembre 2004[57]	Children ($n = 113$, aged 5–14 years) with AR (grass) and fewer than three episodes of asthma per season	Open-label RCT, 3 years of SLIT or medication only	At 3 years, asthma development less frequent in active group (OR = 3.8, 95% CI 1.5 to 10)
Polosa 2004[58]	Adults ($n = 30$, aged 20–54 years) with AR (grass) and no asthma	Double-blind RCT, 3 years of SCIT or placebo	At 3 years, 7/15 (47%) in the placebo group developed asthma symptoms compared with 2/14 (14%) in the SCIT group ($p = 0.0056$)
PAT study[54–56] (2002, 2006, 2007)	Children ($n = 205$, aged 6–14 years) with AR (grass/birch) and no asthma needing daily treatment	Open-label RCT, 3 years of SCIT or medication only, follow-up up to 10 years	For those with no asthma at baseline, lower incidence of new asthma in SCIT group at 3, 5 and 10 years: • 3 years: OR = 2.5 (95% CI 1.3 to 5.1) • 5 years: OR = 2.7 (95% CI 1.3 to 5.7) • 10 years: OR = 2.5 (95% CI 1.1 to 5.9)

Current guidelines

Guidance for the management of patients with AR and non-allergic rhinitis prepared by the Standards of Care Committee (SOCC) of BSACI in 2008[2] can be summarised as follows. Following diagnosis, first-line treatment of AR is allergen avoidance (where possible and practicable). The nature and severity of symptoms determines the type of medication offered; if symptoms are mild, a non-sedating oral or topical H_1-antihistamine is given. Where symptoms are moderate to severe, first-line therapy is with a topical intranasal steroid. If these treatments fail, further agents may be added according to the troublesome symptom: ipratropium for watery rhinorrhoea, a non-sedating H_1-antihistamine for itch or sneeze, or a leukotriene-receptor antagonist for catarrh if asthmatic. Blockage of the nose may require a decongestant, oral corticosteroids or a long-acting non-sedating H_1-antihistamine.

If there is further treatment failure, and if the symptoms are predominantly due to one allergen, then IT may be considered. Specific guidelines from BSACI on the use of allergen IT for AR,[19] published in 2011, conclude that both injection and SLIT are effective in patients with IgE-mediated seasonal pollen-induced rhinitis and/or conjunctivitis whose symptoms respond inadequately to usual therapy, although the relative efficacy of SCIT and SLIT has still to be determined. The BSACI highlights the need for both head-to-head trials of SCIT compared with SLIT, and for long-term studies that include pharmacoeconomic evaluation comparing SIT with antiallergic drugs.[19] The 2011 BSACI guidelines also update the position on the use of SIT in asthmatic patients. SIT has been shown to improve symptoms in atopic, asthmatic adults and children clinically sensitised to seasonal and perennial allergens, and treatment is generally considered safe in patients with pollen-induced seasonal allergic asthma (SAA), provided any updosing is conducted out of season.[19] However, owing to the slightly elevated risk of severe systemic reactions in asthmatic patients, perennial, unstable or uncontrolled asthma is still considered a relative contraindication for SIT.

The ARIA guidelines (2010 revision)[60] on the role of SIT in the treatment of AR make the following recommendations (a summary is shown in *Table 2*). The guidelines suggest that both SLIT and SCIT can

TABLE 2 Summary of ARIA recommendations (2010 revision)[60] for the treatment of AR with SIT

Treatment	Recommendation	Underlying values/preferences
SCIT for adults with AR and without asthma	Suggest use in adults with seasonal AR (moderate-quality evidence) and persistent AR caused by house dust mites (low-quality evidence)	Relatively high value placed on symptom relief; relatively low value placed on avoidance of AEs and resource expenditure
SCIT for children with AR and without asthma	Suggest use in children (low-quality evidence)	Relatively high value placed on probable reduction in symptoms and potential prevention of development of asthma; relatively low value placed on avoidance of AEs and resource expenditure
SLIT for adults with AR and without asthma	Suggest use in adults with rhinitis caused by pollen (moderate-quality evidence) or house dust mites (low-quality evidence)	Relatively high value placed on symptom relief; relatively low value placed on avoidance of AEs and resource expenditure Local AEs are relatively frequent (around 35%)
SLIT for children with AR and without asthma	Suggest use in children with rhinitis caused by pollen (moderate-quality evidence), but not in children with AR caused by house dust mites outside clinical trials (very low-quality evidence)	Relatively high value placed on symptom relief; relatively low value placed on avoidance of AEs and resource expenditure Local AEs are relatively frequent (around 35%)
SCIT or SLIT in patients with AR and asthma	Suggest use of SCIT or SLIT to treat asthma and/or rhinitis (moderate-quality evidence)	Relatively high value placed on symptom relief; relatively low value placed on avoidance of AEs and resource expenditure

Source: 2010 revision[60] of the ARIA guidelines.

be used in both adults and children for treating AR, but note that a higher value is placed on relieving symptoms, and a lower value on avoiding AEs and resource expenditure.

No guidelines from the National Institute for Health and Care Excellence (NICE) regarding IT for AR were identified. The British Guidelines on the Management of Asthma,[61] produced by the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (SIGN), mention IT in the context of primary prevention of asthma, but find that more studies are required to establish this role and no recommendations are made.

UK clinical practice

A 2010 report[61] from the Royal College of Physicians reported an increasing trend in the use of SLIT compared with figures from 2007. Sales figures for SCIT products have remained relatively unchanged over this time. The authors estimate that approximately 2000 patients per year are receiving each treatment.

One possible explanation for the relatively low uptake of SIT is the perception of risk associated with the practice following reports of serious AEs in early studies of SCIT.[62,63] Consequently, outside of specialist centres, there remains an unwillingness to utilise SIT in clinical practice. Knowledge of safety improvements in SCIT preparations and the relatively favourable safety profile of SLIT remains lacking.[62] In addition, primary care trust funding for SIT is still uncommon, leading to wide geographic variations in treatment access. The shortage of trained specialists and the absence of clinical guidelines from NICE may be compounding factors in this matter.[62]

With increasing evidence that SIT may result in the prevention of new sensitisations and incidence of asthma, the uptake of SIT in paediatric allergy sufferers is likely to have long-term clinical and economic impacts. However, although children attending specialist centres are more likely to be treated with SIT than those in non-specialist practices,[62,64] a recent audit of NHS paediatricians offering pollen IT in England and Wales[65] identified only 20 centres, all of which were in England, with three located in London. Further, absolute numbers of children treated with SIT were still low, although the trend was for increasing numbers over time. Approximately twice as many children had been treated with SLIT ($n = 363$ courses) than with SCIT ($n = 165$ cycles) over the 10-year audit period. The most commonly used SCIT products were Pollinex Quattro (Allergy Therapeutics, 53%), Pollinex (Allergy Therapeutics, 32%), Allergovit® (Allergopharma, Reinbek, Germany, 8%) and Alutard SQ® *P. pratense* (ALK-Abelló, 8%). Only two SLIT products were used in these centres: Staloral® (Stallergènes, Antony Cedex, France) made up the majority of treatment courses (70%), with the remainder accounted for by Grazax®.[65] Despite earlier guidelines that asthma was a contraindication for SIT in children,[2] 49% of children receiving SCIT and 58% of those receiving SLIT had a diagnosis of asthma. Of these, nearly three-quarters had perennial asthma (126/174, 72%),[65] which remains a contraindication to SIT in the updated BSACI guidelines.[19]

Patient perspective

A survey was conducted in 2005 by Allergy UK, in conjunction with the General Practice Airways Group;[66] 1000 individuals with AR were asked about their symptoms and the impact of SAR on their lives. It should be noted that there were no details on how patients were sampled and it is unclear whether or not patients across the whole of the severity spectrum are represented. The results are shown in *Table 3*.

The same survey[66] found that over half of those patients taking medication felt that their symptoms were not fully controlled, and that one in four patients had tried more than five different oral antihistamines.

Another UK report[67] found that students who have AR symptoms are 40% more likely to drop a grade in their General Certificate of Secondary Education (GCSE) examinations, with the figure rising to 70% if they

TABLE 3 Impact of AR symptoms (Allergy UK survey[66])

Impact	Percentage
AR symptoms for >2 months/year	92
AR symptoms for >10 years	73
AR symptoms affect school/work moderately to severely	49
AR symptoms affect how social/leisure time is spent	80
AR symptoms disrupt sleep	85
Disrupted sleep affects school/work	56
Disrupted sleep affects planned social activities	33

were taking antihistamines. Onset of hay fever peaks in adolescence and GCSE examinations run from mid-May to the end of June, coinciding with the height of the grass pollen season.

For this report, a patient representative, Lynne Deason (LD), shared her experiences of living with hay fever and other allergies, and receiving treatment with SCIT at Birmingham Heartlands Hospital, Birmingham, UK. These are summarised below.

Patient experience

Lynne Deason developed allergies to different moulds and dog dander in her mid-teens. In her mid-20s she also suffered increasingly with SAR (mainly birch) and allergic reactions to fruit (oral allergy syndrome). In addition, she regularly experienced episodes of anaphylaxis, for which she sought help on several occasions from the accident and emergency (A&E) department; the allergen responsible for these episodes has to date not been identified. No treatment was initiated as a result of visits to the A&E department. As a teenager, LD's parents had paid for her to have private allergy testing and standard medication was recommended (antihistamines and nasal sprays). LD 'managed' her anaphylaxis by quickly taking antihistamines whenever signs appeared that an episode was imminent, such as an itching sensation in her ears. More recently, conventional medication provided reasonable relief for SAR, although this still impacted negatively on daily activities, particularly work. Symptoms from both SAR and the oral allergies included puffy eyes, not being able to see very clearly, changes in voice quality, looking like 'someone had punched me in the face', feeling 'groggy' and an itchy throat; these symptoms made giving presentations at work difficult.

After seeing a nurse at her local GP practice and describing her history of oral allergies, SAR and regular anaphylaxis, LD was referred to hospital and was eventually placed under consultant care for treatment. The nurse expressed disbelief that there had been no earlier referral. Treatment with SCIT was time intensive as it initially involved weekly 2-hour appointments, which then decreased to monthly appointments for approximately 3 years. It also involved a travelling distance of around 25 miles to the hospital. Undergoing treatment was facilitated by having an employer willing to allow time off work. LD did not experience the treatment itself as being particularly unpleasant and felt that professional members of staff who provided good explanations of the procedure were a positive aspect of treatment. LD stated that treatment would be more difficult to incorporate into daily life for parents, as it would involve additional childcare. Additional positive aspects of undergoing SCIT included meeting people with similar experiences at hospital, sharing tips on managing symptoms, feeling less isolated and feeling that people were being empathic. LD also started carrying an EpiPen® (Mylan Speciality L.P., Basking Ridge, NJ, USA) for the first time.

Subcutaneous IT significantly improved LD's SAR symptoms, which became both milder and less frequent. Four years after completing the treatment, significant improvement is still noticeable, with only mild irritation experienced in response to particularly high pollen counts. Medication use also decreased and

LD now rarely takes antihistamines. No occurrences of anaphylaxis have arisen since treatment and LD no longer carries an EpiPen. The lessening of symptoms also had a positive knock-on effect on general QoL.

Side effects of the treatment included tiredness (particularly after updosing) and some fairly mild swelling and redness of the arm immediately afterwards. LD noted that other patients had more severe swellings. The treatment has had no effect on the oral allergies. A single allergen was used in the treatment (birch), and LD now knows she is also allergic to almond and hazel. LD felt that there was generally little awareness of severe allergy and treatments with SCIT or SLIT and little empathy for affected individuals. Although, in her own estimation, LD was not among the worst affected, she felt that other people might benefit even more from SCIT or SLIT, for example individuals who are confined indoors during peak allergen times.

Existing evidence for allergen immunotherapy

Subcutaneous immunotherapy

To date, the most comprehensive systematic review of SCIT for SAR is a Cochrane review,[68] with searches up to February 2006. The review identified 51 RCTs including a total of 2871 participants (1645 active, 1226 placebo), with only one study[69] including children of <12 years. There was significant heterogeneity in treatment durations (3 days to 3 years) but, on average, participants received 18 injections each. Pooled standardised mean differences (SMDs) from meta-analyses found statistically significant results in favour of active treatment across all outcomes [symptoms scores, rescue medication use, combined symptom and medication scores (SMS) and QoL]. AE reporting was highly variable, making comparisons difficult. Local reactions at site of injection were the most commonly reported event, with the majority resolving without treatment. Systemic reactions occurred in over half of studies, with more severe reactions occurring less frequently than milder reactions. No deaths were reported.

However, evidence from surveillance studies in the USA suggests that fatal reactions still occur following SCIT in clinical practice.[70] Between 1973 and 2007, 82 direct or indirect reports of fatal reactions were identified, although the frequency appears to be decreasing – only six of these deaths occurred between 2001 and 2007, presumably due to improved vaccines, protocols and safety measures. No fatalities were identified between 2008 and 2010.

A 2008 systematic review[71] of the paediatric literature included only four randomised, placebo-controlled studies[72–75] of SCIT for seasonal allergens, all of which were conducted between 1966 and 1986. Adequacy of blinding could be ascertained in only one study,[72] although this may be due to less transparent reporting practices in earlier studies. Overall, only one study[72] reported positive effects of SCIT on symptoms, but medication use was not monitored in this study. None of the other studies[73–75] reported benefits of SCIT on either SSs, or, when reported, medication scores (MSs). The authors concluded that there was insufficient good-quality evidence to draw conclusions regarding the effectiveness of SCIT in this patient group.

Sublingual immunotherapy

A number of systematic reviews evaluating the effectiveness of SLIT for SAR have been published,[71,76–82] the largest and most recent of which was the Cochrane review of SLIT for AR.[83] Although this review included studies in both SAR and PAR, subgroup analysis was performed for both types of allergen. The review identified 39 studies[24,26,35,84–119] conducted in patients with SAR, comprising a total of 4084 participants (2081 active, 2003 placebo). Meta-analysis of both symptom and MS data suggested a moderate effect size in favour of SLIT, with similar results reported for MS outcomes. Subgroup analyses were conducted in adults or children; short-, medium- and long-term duration; low, medium and high levels of MAC; and type of allergen. All of the subgroup analyses included studies of both SAR and PAR, but all reported pooled effect sizes favouring the active treatment. The majority of these findings were statistically significant, although a few were not: MSs in children, SSs in studies using IT with <5μg MAC, MSs in studies with >20μg MAC and MSs in ragweed pollen. QoL was reported in only two studies,[102,112] both involving seasonal allergens, and combined SMD was in favour of SLIT. As for SCIT, AEs for SLIT are

reported quite variably between studies. The majority of systemic reactions were of mild to moderate severity; none required administration of adrenaline and no fatalities were reported. Discontinuations due to AE were rare and more often associated with unpleasant local side effects than with systemic reactions.

One recent meta-analysis[77] has been conducted for studies of SLIT for SAR only, specifically grass pollen AR. This meta-analysis included 19 RCTs (compared with 23 studies in grass allergen in the Cochrane review) and produced almost identical results. Subgroup analysis by age showed that effect sizes were greater in adult populations than in children, with neither symptom nor MSs reaching statistical significance in the five included paediatric studies.

Several reviews of the paediatric literature have been published.[71,78–80,82] Although all included both SAR and PAR, results are often separable for the two types of allergen. The most recent, and inclusive, of these (Larenas-Linneman 2009)[78] included 10[84–89,120–122] double-blind studies of SLIT in children with SAR (as well as three with SAA), which reported clinical outcomes. All of these studies were identified in the 2010 Cochrane review.[83] Interestingly, earlier studies deemed to be of high quality[84,89] (total $n = 192$) failed to report statistically significant effects of SLIT on rhinitis outcomes, whereas studies deemed to be of lower quality[86,88,121,122] (total $n = 158$) favoured SLIT. In contrast, three[26,85,90] of the four studies conducted since 2006 (total $n = 560$)[26,84,85,90] reported significant improvements in both SSs and MSs with active treatment. It is not clear whether this change was due to improvement in SLIT treatments over time or to the larger study sizes. One recent study[87] ($n = 168$) did not find an advantage for SLIT treatment in grass allergy. However, this study[87] was conducted in a primary care setting, inclusion criteria did not specify objective diagnosis of AR, and dropout rates were high (44%).

Sublingual immunotherapy has a good safety profile. One report, based on 41 studies, identified 1047 AEs in an estimated 386,149 doses, equivalent to 2.7 AEs per 1000 doses.[123] Based on 49 studies, approximately 12% (529/4378) patients experienced at least one AE, although most of these were local reactions in the oral cavity or gastrointestinal symptoms, also considered a local reaction in SLIT.[124] Systemic reactions occurred in 169 of 314,959 doses, or 0.54 per 1000 doses. Only 14 treatment-related serious adverse events (SAEs) were recorded in 5377 treatment-years, mostly involving asthma or gastrointestinal symptoms, equivalent to one SAE per 384 treatment-years. A 2010 Cochrane review[83] reported no occurrences of anaphylaxis in six trials reporting this outcome ($n = 579$) and no reports of adrenaline use for systemic reactions following active treatment. Again, the vast majority of AEs were of mild to moderate severity, and gastrointestinal symptoms were the only systemic reactions reported more frequently in patients receiving active treatment than in placebo (88 events in 630 patients vs 10 events in 561 patients, respectively). Discontinuations due to AEs were more often associated with unpleasant local side effects than with systemic reactions, and were reported in 5% of active patients (41/824) in 15 studies.

Outcome measures in randomised controlled trials of specific (allergen) immunotherapy

Outcome measures used in trials of SIT are highly variable. SSs are the most widely used, and often the only outcome measure used in older trials. Although no individual scoring system has been thoroughly validated for clinical trials,[64] the vast majority of RCTs conducted in the last 20 years utilise a four-point scoring scale for describing symptom severity, ranging from a score of '0' to indicate absence of symptoms to a score of '3' representing severe symptoms that interfere with activities of daily living. Despite this common system of measuring symptom severity, there is significant heterogeneity in the actual number of symptoms that are scored in any given trial, meaning that maximum possible scores vary between studies. Indeed, the six major European manufacturers (ALK-Abelló, Allergopharma, Allergy Therapeutics, HAL Allergy, Leiden, the Netherlands, Laboratorios LETI/Novartis, Barcelona, Spain, and Stallergènes) all use different systems.[125] There are also differences in the way that SS data are reported, for example as mean daily score, cumulative score over 1 week or an entire season, differences from baseline, or area under the curve (AUC). In addition, some studies record outcomes over an entire pollen season (EPS), whereas

others use values for a 1- or 2-week period around the peak recorded pollen value. These differences make comparisons between studies very difficult.

One limitation of the use of SSs as the sole outcome measure is that most trials allow the use of rescue medication on an as-needed basis, under varying conditions of stringency. As placebo patients might be expected to use more rescue medication, the use of SSs alone may underestimate the effects of treatment.[125] Reporting of MSs, a measure of rescue medication use, is intended to address this problem. However, although a 2008 report[126] from the World Allergy Organization (WAO) taskforce on standardisation of clinical trials suggested a three-point scoring system for anti-allergy medications, scoring of this outcome remains somewhat arbitrary and highly variable between trials. As with SSs, methods for reporting MSs also vary. In addition, the use of separate SSs and MSs does not account for the interdependence of these two measures.[125]

Thus, the WAO taskforce also recommended that weighted SSs and MSs be combined into a SMS, and that this combined score should be used as the primary outcome in clinical trials.[126] Indeed, an increasing number of recent trials have reported SMSs (15 out of 28 trials in this report). Further, the 'Allergy-Control-SCORE©', a combined symptom and MS, has recently been formally evaluated, and was found to be a valid and reliable tool for assessing and monitoring allergy severity.[127] However, there is currently no standardised method for calculating SMSs, and the methods used are frequently not reported. As with SSs and MSs, the units of statistical analysis of SMS differ between studies, and are often not stated explicitly. Again, the six major European manufacturers of IT products use different protocols and scoring systems for usage of rescue medication, and different methods of weight symptom and MSs into a combined measure.[125] Thus, despite the increasing convergence in outcome measurements used in clinical trials, between-trial comparison is still problematic.

Other outcomes that have been recommended by the WAO[126] and European Medicines Agency (EMA)[64] include responder analysis – the percentage of patients with a combined SMS below a prespecified level, visual analogue scales (VASs) for long-term treatment outcomes, number of 'well-days' – i.e. SSs below a predefined threshold and no requirement for rescue medication, and patient-reported outcomes, such as overall impact on health-related QoL, which may provide more useful information on the impact of treatment than measuring organ-specific SSs. However, data on these outcomes are available in only a small proportion of the SIT literature.

It has been argued in an ARIA-GA(2)LEN statement[128] that RCTs in IT cannot be interpreted in the same way as RCTs in drug treatment. One of the factors that has been criticised in SIT RCTs is the relatively low level of efficacy compared with medications, which may prevent regulatory bodies from recommending SIT. One of the reasons for this apparently lower efficacy may be that exposure to allergens varies over the pollen season, yet the averaged score is presented for the whole season. It is for this reason that the concept of 'worst-days',[129] i.e. days with severe symptoms as an outcome measure, has been introduced, as it may better reflect the impact of IT compared with placebo on days when pollen counts are high and symptoms are severe.

The majority of studies reporting on QoL have used the validated disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[130–132] although there are a number of different versions of this instrument. A few studies have used more global measures, such as the Short Form questionnaire-36 items (SF-36). Generic tools are broad and are likely to be less sensitive to measuring changes in AR, where disease-specific instruments may be more appropriate.[125] QoL is a difficult parameter to be measured in trials of IT: patients do not have impaired QoL at inclusion, but this will deteriorate during the course of the trial. The difference in QoL between IT and placebo groups will depend on the pollen exposure on the day(s) that QoL is measured. If pollen exposure is low then QoL in the placebo group may appear relatively high compared with that of the IT group.[128]

Even within a single trial, results may be difficult to interpret clinically. So, for example, a difference in reduction in symptoms scores may be statistically significant but not necessarily clinically significant. Malling has proposed ranges of improvement in SSs or MSs to discriminate between effective and non-effective therapy (no effect, improvement of <30%; little effect, improvement of 30–44%; moderate effect, improvement of 45–59%; strong effect, improvement of ≥60%).[133] This outcome is not at present reported consistently. In contrast, an expert group[134] has estimated that an improvement of 20% is clinically relevant given that SIT trials may show relatively lower effectiveness (than drug trials) given the reasons outlined above. There is no consensus on a minimum meaningful difference.

Chapter 2 Aim of the review

The aim of this systematic review and cost-effectiveness analysis (CEA) was to:

- update the Cochrane review[68] on the clinical effectiveness of SCIT based on double-blind RCTs of SCIT compared with placebo
- update the Cochrane review[83] on the clinical effectiveness of SLIT based on double-blind RCTs of SLIT compared with placebo
- more specifically, to update the meta-analyses (including those for prespecified subgroups including adults and children) undertaken in the Cochrane reviews in order to provide up-to-date summary estimates
- evaluate the clinical effectiveness of SCIT compared with SLIT using both direct and indirect comparisons
- undertake a systematic review and critical appraisal of existing economic evaluations (EEs) of SCIT or SLIT compared with placebo or SCIT compared with SLIT
- develop a de novo cost-effectiveness model, based where possible on clinical data from this report
- estimate cost-effectiveness separately for SCIT compared with placebo, SLIT compared with placebo, SCIT compared with SLIT, and for adults and children.

This report did not aim to address questions relating to the optimum dosing schedules (e.g. rush or cluster compared with conventional dosing) or optimum length of treatment of SCIT or SLIT. It also did not address other methods of administration, such as epicutaneous or intralymphatic IT.

Chapter 3 Clinical effectiveness

Methods

The original protocol can be found in *Appendix 1*.

Searches

Randomised controlled trials of SCIT compared with placebo and SLIT compared with placebo were sought, as were any existing RCTs of head-to-head comparisons (SCIT vs SLIT). A sensitive search strategy, based broadly on those employed in the Cochrane reviews, but with no restriction on routes of IT administration or dates, was used in order to cover both the update and the search for head-to-head trials. There were no language restrictions. Appropriate filters for study design were used where possible. Searches were carried out during April 2011. See *Appendix 2* for full details of the search strategies.

The following resources were searched:

- bibliographic databases: MEDLINE (Ovid) 1948–April week 2 2011; EMBASE (Ovid) 1980–April week 15 2011; The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)] 2011 Issue 1; Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO*host*) 1982–2011; Science Citation Index (Web of Knowledge) 1900–2011. Searches were based on index and text words that encompassed the population and intervention (e.g. 'seasonal allergic rhinitis', 'immunotherapy')
- ClinicalTrials.gov, UK Clinical Research Network Portfolio Database and metaRegister of Current Controlled Trials (*m*RCT) (http://controlled-trials.com) were searched for ongoing studies, as well as the lists of ongoing trials identified in the Cochrane reviews
- references lists of relevant reviews and included studies
- consultation with clinical advisors
- selected websites.

Study selection

The following inclusion and exclusion criteria were used (*Table 4*). These are broadly consistent with those listed in the Cochrane reviews.

The brief specified adults and children (examined separately) with *severe hay fever, which does not respond to conventional treatment*. We anticipated that not all trials would provide this information, or that they would use different classifications for 'severe' or 'not responding to conventional treatment'. We therefore did not restrict inclusion by severity. We did restrict inclusion to treatment-naive patients; where this was not explicitly stated we noted this but included the study.

Titles and abstracts of retrieved studies underwent an initial screen by one reviewer, and studies that were clearly not relevant were excluded. The remaining studies were independently screened for inclusion by two reviewers. Where it was unclear whether or not studies met the inclusion criteria on the basis of title and abstract, full copies were obtained for assessment. Any discrepancy between reviewers was resolved through discussion or referral to a third reviewer. Reference Manager software, version 11 (Thompson ResearchSoft, San Francisco, CA, USA) was used to track and record study selection decisions and reasons for exclusion. Foreign-language papers were translated, where necessary, by the authors or colleagues.

Assessment of trial validity

Cochrane collaboration guidelines were followed for risk of bias assessment.[135] The following criteria were considered: adequate sequence generation, concealment of allocation, blinding of patients and personnel, completeness of outcome data, selective reporting of outcomes and IT treatment history. This

TABLE 4 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Study design	
Double-blind RCTs of SCIT compared with placebo, or SLIT compared with placebo or SCIT compared with SLIT	Single-blind or open-label RCTs. Any other study design
Population	
Treatment-naive adults or children with a confirmed diagnosis and symptoms of SAR (hay fever). Patients with comorbidities such as (seasonal allergic) asthma will be included. All or majority (≥90%) of included patients (adults or children) with SAR	Adults or children with a different allergic disease (e.g. food allergy, perennial rhinitis). Population (or >10%) with SAA only
Intervention	
Allergen-specific subcutaneous (injection) or SLIT in any setting. Any allergen responsible for inducing SAR (e.g. grass, tree). No restrictions regarding a particular dose or dosing regimen	Any other route of administration [e.g. oral (swallowed rather than sublingual), nasal, epicutaneous, intralymphatic]; specific allergen IT with other allergens (e.g. house dust mite, cat dander). Non-standard therapy protocols or products, e.g. Rinkel method, peptide IT
Comparator	
Placebo [with or without conventional (rescue) medication], SCIT or SLIT	Any other route of administration (e.g. oral, nasal). Studies comparing different doses or schedules of IT that did not include a placebo arm
Outcomes	
At least one of the following: symptom severity, medication use, combined SMSs, frequency of exacerbations, QoL, AEs, the prevention of new asthma cases	RCTs not reporting any of the listed outcomes (e.g. laboratory parameters, such as IgE levels only). Studies evaluating clinical effectiveness without natural exposure (e.g. allergen chamber)

last point is relevant as it is known that SIT can have long-lasting effects. Blinding of outcome assessors was not assessed, as outcomes were largely patient reported. Each item was classified as having a low risk of bias, high risk of bias or unclear risk of bias. Assessment of trial validity was at study level rather than outcome level.

Data extraction

Data extraction, including quality assessment, was conducted by one reviewer and checked by another using a standard, piloted, extraction form. There were no discrepancies that could not be resolved through discussion. Data were extracted on main study characteristics, main patient characteristics, study quality and all included outcomes. Data previously reported in the Cochrane reviews and included in this report were not checked.

Analysis

Where possible, we updated the meta-analyses, including subgroup analyses, from the existing Cochrane reviews. Meta-analysis assumes similarity between trials, and this was explored for both population and study characteristics in the newer studies identified. Studies included in meta-analyses in the Cochrane reviews were assumed to satisfy the similarity criteria.

Meta-analysis was limited to the following outcomes that were consistently reported across a high proportion of trials, and where data suitable for use in meta-analysis were provided or calculable: SSs, MSs, combined SMS and QoL scores. Where not reported, standard deviations (SDs) were calculated from other appropriate measures of variance (e.g. standard error, 95% CIs) according to Cochrane guidelines.[136] Results not suitable for meta-analyses were tabulated and described.

All meta-analyses were undertaken in RevMan software version 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) using a random-effects model. SMDs were presented, as there was little overlap between outcome measures across trials. So, for example, although AR symptoms were frequently measured, the number of symptoms measured was different across trials, as was the maximum score that could be achieved. As a rule of thumb, SMDs (effect sizes) can be described as small (<0.4), moderate (0.4–0.7) or large (>0.7).[137]

In studies with more than one active intervention arm receiving different dosage IT, data for the group receiving the highest dose were used in meta-analysis, consistent with the Cochrane reviews. Where data were reported at different time points, data for the longest treatment duration were used. Outcome values were sometimes reported both for peak pollen season (PPS) and averaged over an EPS. Consistent with the Cochrane review, the mean values for the EPS were used when available.

Indirect comparison meta-analysis (ICMA) and indirect comparison meta-regression (ICMR) were used to compare the efficacy of SCIT and SLIT for each of the four outcomes (SSs, MSs, combined SMSs and QoL). Similarity of trial and population characteristics within (1) SCIT compared with placebo and (2) SLIT compared with placebo trials was assessed qualitatively and statistically (to test the assumption of homogeneity[138]); similarity between population and trial characteristics between SCIT compared with placebo and SLIT compared with placebo trials was also assessed (to test the assumption of similarity[138]). Possible sources of heterogeneity were explored and adjusted for using meta-regression, with a number of trial, population and reporting characteristics being used as covariates; specifically, these comprised participant age (adult/child), treatment duration, MAC of IT product and type of allergen (covariates as prespecified in subgroup analyses in the Cochrane review). We also conducted a post hoc exploration using year of publication and number of separate symptoms for which outcome data had been obtained as covariates. Improvement in model fit was expressed using the deviance information criterion (DIC), a compound measure of model fit and complexity, and extent of residual variation was monitored. As scores were measured on different scales, standardised score differences were calculated, except for RQLQ scores. Analyses were conducted in WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, UK).[139] Full methodological details for the indirect comparison can be found in *Appendix 3*.

Results

Quantity of evidence (subcutaneous immunotherapy versus placebo studies)

Searches identified 84 publications of DBPC RCTs of SCIT (see PRISMA flow diagram in *Appendix 4*). Of these, 48 were included in the relevant Cochrane review.[68] Of the remaining 36 publications, 10 pre-dated the Cochrane searches but were not included in that review, and a further four had been excluded by the Cochrane review, despite appearing to meet the inclusion criteria. Details of excluded studies are presented in *Appendix 5*. The remaining 22 publications,[30,140–160] reporting on 18 distinct RCTs, post-dated the final search date listed in the Cochrane review (February 2006). Two[151,156] of these publications provided additional data relating to the trial reported in Frew *et al*. in 2006,[161] which was included in the Cochrane review. Thus, 20 publications[30,140–150,152–155,157–160] relating to 17 new RCTs were identified. As the purpose of this report was to update, rather than repeat, the Cochrane review, results are presented only for those 17 trials initially published from 2006 onwards. However, all relevant studies have been included in the meta-analyses.

Main study characteristics and risk of bias (subcutaneous immunotherapy versus placebo studies)

The main study and population characteristics, and assessment of risk of bias are detailed for each of the 17 newly identified RCTs[30,142–146,148–150,152–155,157–160] in *Appendix 5*. All studies were DBPC RCTs. Approximately half of the studies (nine trials[30,142–144,146,148,152,158,160]) involved fewer than 65 participants, but the remaining trials included at least 100 patients, and the largest[145] represented over 1000 participants. Skin prick tests were performed in all patients to demonstrate specific sensitivity. Allergy symptoms were described

as moderate to severe in 2 out of 17 trials,[145,146] whereas level of severity was not stated in 15 out of 17.[30,142–144,148–150,152–155,157–160] Ten studies[30,142,143,148–150,152,154,155,160] stated that some patients also had asthma symptoms. Patients with previous IT were excluded in five studies,[30,142,152,154,160] four trials[143,145,157,159] allowed patients who had not received SIT in the last 3–5 years or 'recently', and previous treatment status was unclear in eight trials.[144,146,148–150,153,155,157] Outcomes included SSs, MSs, combined symptom and medication scores, QoL and AEs (note: only outcomes consistent with the inclusion criteria for this report have been listed). Approximately half of the studies (9[30,145,148,149,152,153,155,157,160] out of 17[13,30,142–146,148–150,152–155,157,159,160]) reported a combined score, either alone or in addition to individual SSs and MSs. Although SSs were consistently reported across trials, the number and types of symptom assessed varied widely (see *Appendix 7* – SSs across studies). Similarly, there were differences in how SMSs were calculated.

Tree and mixed-grass allergens were the most commonly investigated (eight[30,142,148,149,154,155,158,160] and three trials,[145,150,157] respectively), followed by two trials each of timothy grass (*P. pratense*)[146,153] and ragweed,[144,159] one trial in *Alternaria*[142] and one in Russian thistle[143] (*Salsola kali L.*). The main study characteristics are summarised in *Table 5*.

Similarity between trials was explored for a range of study and population characteristics. Trial duration and type and amount of allergen used varied between trials; however, this was explored as a source of heterogeneity in subgroup analyses. Where reported, inclusion criteria were very similar across trials, with the majority stipulating a minimum of 2 years' clinical history of moderate to severe SAR, incompletely controlled by standard medication, and no prior experience of SIT. Rates of asthma across trials were largely consistent, comprising between one-quarter and one-third of participants. Prevalence of asthma was higher in one paediatric trial[122] (38 out of 50 patients). All studies excluded patients with severe or perennial asthma.

Results of the risk of bias assessment are summarised in *Table 6*. Full details are given in *Appendix 5*.

The risk of bias was low in three or more areas of potential bias for 12[30,142–146,148,152,154,158,160] out of 17 studies. A lack of detail in the published reports, most notably for those reported in abstract form only, meant that the risk of bias was unclear in many cases. Lack of detail related most often to allocation concealment, sequence generation and whether or not patients were treatment naive. In all studies, apart from those reported as abstracts, there were details on blinding. Study authors were not contacted and an 'unclear' rating may be due to a lack of reporting rather than a reflection of poor trial quality. There were only two instances for which a high risk of bias was identified, in the area of data completeness. Only one[114] of these studies contributed to any meta-analyses (QoL data); owing to its small sample size ($n = 25$) it is unlikely to have a large influence on overall results. It should be noted that a certain degree of subjectivity remains in assigning a rating of low/high/unclear risk of bias.

Effectiveness of subcutaneous immunotherapy compared with placebo

Of the 17 newly identified RCTs, only five[142–144,152,154] reported data in a form suitable for meta-analyses. Of these, three studies provided new SS and MS data,[142,152,154] and two provided QoL data[143,144] (*Table 7*).

Symptom scores

Of the 15 studies[91,162–174] included in the Cochrane review meta-analysis, one[162] was excluded from this study as patients were not treatment naive. Searches for this report identified 10 new studies[142–144,148,152,154,155,157,158,160] reporting this outcome, of which only three[142,152,154] provided data suitable for inclusion in meta-analysis. Thus, a total of 17 studies, comprising 659 active and 525 placebo patients, were included (*Figure 1*).

The combined SMD was –0.65 (95% CI –0.85 to –0.45; $p < 0.00001$) favouring SCIT, with evidence of moderate heterogeneity, similar to the findings of the Cochrane review[68] (SMD –0.73, 95% CI –0.97 to –0.50; $p < 0.00001$, based on 15 trials).

TABLE 5 Main study characteristics: newly identified SCIT vs placebo studies

Study ID	Size	Previous SIT	Stated that symptoms moderate to severe	Patients with asthma allowed/ included	Type of allergen	Administration schedule	Outcomes
Casale 2006[159]	$n = 159$	Not 'recently' but 19.5% had previous SIT	No details on severity	No (patients with asthma excluded)	Ragweed	Pretreatment with active/placebo omalizumab, rush IT (six injections over 3–5 hours), 4 weeks updosing, 8 weeks maintenance; coseasonal	AEs
Ceuppens 2009[160]	$n = 62$	No	No details on severity	Yes (mild only)	Birch	Weekly, then fortnightly induction doses, followed by monthly maintenance dose, total of 18–22 months	SMSs, SSs, MSs, AEs
Chakraborty 2006[30]	$n = 35$	No	No details on severity	Yes	Sugar date palm	Weekly induction phase for 24 weeks, maintenance phase for 18 months at 2-weekly intervals. Dose reduced 20–40% in symptomatic patients during pollen season	SMSs, global measure of severity, spirometry, AEs
Charpin 2007[142]	$n = 40$	No	No details on severity	Yes	Cypress	Induction phase with fortnightly injections followed by maintenance phase at maximum tolerated dose for 15 months (frequency not reported), covering two pollen seasons	SSs, MSs, days with asthma, AEs, QoL
Colas 2006[143]	$n = 63$	Not in last 4 years	No details on severity	Yes	Russian thistle	Cluster schedule: first day: 0.1, 0.25 and 0.5 ml × 450 g extract/ml; 1 week later, 0.1, 0.25 and 0.5 ml × 450 g/ml; then starting 1 month later one injection per month totalling 12 maintenance doses 0.5 ml × 450 g/ml	SSs, MSs, QoL, global assessment of health, AEs
Creticos 2006[144]	$n = 25$	Unclear	No details on severity	No details	Ragweed	Preseasonal, six weekly injections	SS, QoL, AE
DuBuske 2011[145]	$n = 1028$	Not in last 3 years	Yes	No details	Thirteen grass mix (Grass MATA MPL Pollinex Quattro)	Ultrashort course SCIT: four increasing dose injections given at approximately weekly intervals preseason	SMSs, number of well-days, number of bad-days, number of well patients, AEs
Francis 2008[146]	$n = 18$	Unclear	Yes, with poor symptom control	No details	Timothy grass (Alutard SQ)	Modified cluster regimen: weekly visits for 2 months, with two injections per visit in increasing dosage. Maintenance dose monthly up to 1 year	Overall clinical assessment, AEs

continued

TABLE 5 Main study characteristics: newly identified SCIT vs placebo studies (*continued*)

Study ID	Size	Previous SIT	Stated that symptoms moderate to severe	Patients with asthma allowed/ included	Type of allergen	Administration schedule	Outcomes
Hoiby 2010[148]	*n* = 61	Unclear	No details on severity	Yes	Birch (Depigoid®, Laboratorios LETI SL, Barcelona, Spain)	Updosing at 7-day intervals, maintenance dose every 6 weeks for 18 months	SMSs, SSs, MSs, AEs, QoL
Kettner 2007[149] (A)	*n* = 211	Unclear	No details on severity	Yes	Birch	Updosing then maintenance for 1.5 years (frequency of injections not stated)	SMSs, AEs
Klimek 2010[150] (A)	*n* = 148	Unclear	No details on severity	Yes	Grasses and rye (Alutard SQ)	Coseasonal. Updosing with six injections with one to three injection intervals then two injections after 14 and 28 days	AEs
Kuna 2011[152]	*n* = 50	No	No details on severity	Yes	*Alternaria*	Updosing: 14 injections weekly or fortnightly. Maintenance dose every 4–6 weeks for up to 3 years	SMSs, SSs, MSs, AEs, QoL
Ljorring 2009[153] (A)	*n* = 162	Unclear	No details on severity	No details	Grass (Alutard SQ)	One year. No further details on treatment schedule.	SMSs
Pauli 2008[154]	*n* = 147	No	No details on severity	Yes	Birch	Build up starting 6 months before pollen season by weekly injections. Maintenance dose reached at least 7 weeks before pollen season then given monthly for 2 years	SSs, MSs, AEs
Pfaar 2010[155]	*n* = 184	Unclear	No details on severity	Yes	Birch, hazel, alder (Depigoid)	Updosing at 7-day intervals. Maintenance dose every 6 weeks for 18 months	SSs, MSs, SMSs, responder analysis, AEs
Sahin 2011[157] (A)	*n* = 121	Not in last 5 years	No details on severity	No details	Grass and rye	Two injections/day for initiation phase (cluster schedule) then once/month for maintenance (length of treatment not clear)	SMSs, symptom-free day, global evaluation by patients, AEs
Ventura 2009[158]	*n* = 20	Unclear	No details on severity	No details	Cypress	Twelve-week induction phase with weekly injections and maintenance phase of 9 months with monthly injections	SSs

(A), abstract.

TABLE 6 Risk of bias assessment: newly identified SCIT studies

Study	Sequence generation	Allocation concealment	Blinding	Data completeness	Selective reporting	Patients treatment naive
Casale 2006[159]	?	?	+	+	+	?
Ceuppens 2009[160]	?	?	+	+	+	+
Chakraborty 2006[30]	?	?	+	+	+	+
Charpin 2007[142]	+	?	+	?	+	+
Colas 2006[143]	?	?	+	+	+	?
Creticos 2006[144]	+	+	+	–	?	?
DuBuske 2011[145]	+	+	+	+	+	+
Francis 2008[146]	?	?	+	+	+	?
Hoiby 2010[148]	+	?	+	?	+	?
Kettner 2007[149] (A)	?	?	?	?	?	?
Klimek 2010[150] (A)	?	?	?	?	+	?
Kuna 2011[152]	+	+	+	?	+	+
Ljorring 2009[153] (A)	?	?	?	?	+	?
Pauli 2008[154]	?	?	+	+	+	+
Pfaar 2010[155]	?	?	+	–	+	?
Sahin 2011[157] (A)	?	?	?	?	+	?
Ventura 2009[158]	+	?	+	+	+	?

+, low risk; –, high risk; ?, unclear; (A), abstract.

Subgroup analyses were conducted by age, study duration, MAC and type of allergen. All favoured the active treatment and were statistically significant. Results of subgroup analyses are shown in *Table 8*. Forest plots of all subgroup analyses are shown in *Appendix 7*. Note that the Cochrane review of SCIT did not include subgroup analyses, but that studies identified in that review are included in subgroup analyses here.

Sixteen[142,154,161,163–174] of the 17 studies were conducted in an adult population and the results did not differ from those of the entire sample. Only one study[152] involved a paediatric population. In this study,[152] rhinitis, conjunctivitis and asthma SSs were all significantly lower following 3 years of active treatment than with placebo.

Analysis by treatment duration found that studies of ≥6 months in duration resulted in similar effect sizes to the sample as a whole. All three[142,152,154] of the more recent trials lasted for >12 months. Shorter studies gave a larger effect size; this was associated with a high degree of between-study heterogeneity.

In line with current guidelines, all three of the newer studies[142,152,154] used vaccines with between 5 and 20 μg MAC. Subgroup analyses (see *Appendix 7*, *Figures 31–95*) suggest that effectiveness increases with increasing MAC; this finding should be interpreted cautiously, as it is not based on a randomised comparison.

Immunotherapy with grass allergens made up the largest subgroup (47% total sample). Combined effect size was similar to that of the entire sample, with a moderate degree of heterogeneity. Similar effect sizes

TABLE 7 Outcome measures in recent SCIT RCTs

Study ID	Not in meta-analyses	In meta-analyses
Casale 2006[159]	AEs	None
Ceuppens 2009[160]	SSs, MSs, SMSs, AEs	None
Chakraborty 2006[30]	SMSs, global measure, spirometry, AEs	None
Charpin 2007[142]	Days with asthma, AEs, QoL	SSs, MSs
Colas 2006[143]	SSs, MSs, global assessment, AEs	QoL
Creticos 2006[144]	SSs, AEs	QoL
DuBuske 2011[145]	SMSs, well-days, bad-days, well patients, AEs	None
Francis 2008[146]	Overall clinical assessment, AEs	None
Hoiby 2010[148]	SMSs, SSs, MSs, AEs, QoL	None
Kettner 2007[149] (A)	SMSs, AEs	None
Klimek 2010[150] (A)	AEs	None
Kuna 2011[152]	SMSs, AEs, QoL	SSs, MSs
Ljorring 2009[153] (A)	SMSs	None
Pauli 2008[154]	AEs	SSs, MSs
Pfaar 2010[155]	SSs, MSs, SMSs, responder analysis, AEs	None
Sahin 2011[157] (A)	SMSs, symptom-free days, global evaluation, AEs	None
Ventura 2009[158]	SSs	None

(A), abstract.

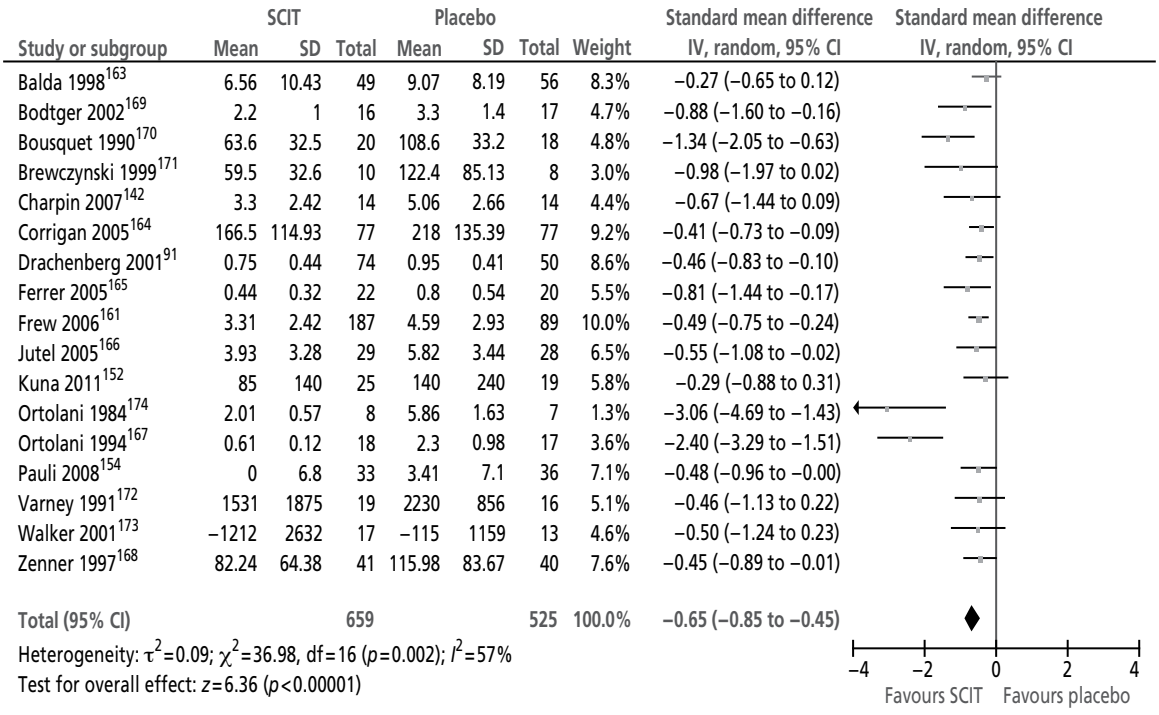

FIGURE 1 Subcutaneous immunotherapy vs placebo: SSs.

TABLE 8 Subcutaneous immunotherapy vs placebo, subgroup analyses: SSs

Subgroup	No. of studies	Total *n*	SMD (IV, random 95% CI)
Age			
Adults	16	1140	–0.68 (–0.89 to –0.47)
Duration (months)			
<6	5	274	–1.29 (–2.10 to –0.49)
6–12	2	309	–0.54 (–0.78 to –0.29)
>12	8	442	–0.51 (–0.70 to –0.32)
MAC			
<5μg	3	228	–0.43 (–0.69 to –0.16)
5–20μg	5	231	–0.54 (–0.80 to –0.27)
>20μg	3	341	–1.06 (–2.08 to –0.05)
Allergen			
Grass	9	552	–0.64 (–0.91 to –0.37)
Parietaria	3	353	–1.15 (–2.09 to –0.21)
Tree	4	235	–0.46 (–0.72 to –0.20)

IV, inverse variance.

were found for tree pollen allergy. Only three studies involved *Parietaria* pollen.[161,165,167] Combined effect size was quite large, but was associated with wide CIs and a high degree of heterogeneity. None of the studies conducted in ragweed that were identified in the Cochrane review were suitable for meta-analysis, and no new studies were found. Only one study[152] was conducted in *Alternaria*.

Details of SS data from the seven studies not included in the meta-analysis[143,144,148,155,157,158,160] are presented in *Table 9*. All favoured the active treatment over placebo.

Medication scores

Medication scores suitable for meta-analysis were available in 16 studies (13 from the Cochrane review,[91,161,163–166,169–173,175,176] three[142,152,154] more recent), which together included 621 active and 483 placebo patients. The combined SMD was –0.55 (95% CI –0.75 to –0.34; $p<0.00001$); this was very similar to that reported in the Cochrane review (SMD –0.57, 95% CI –0.82 to –0.33; $p<0.00001$). Heterogeneity was reduced slightly, but remained statistically significant (*Figure 2*).

Subgroup analyses were conducted by age, study duration, MAC and type of allergen. All favoured the active treatment and, with the exception of studies using a <5μg MAC, were statistically significant. However, this non-significant result was based on only two trials[163,165] totalling 147 patients. Results of the subgroup analyses are shown in *Table 10*.

Fifteen[91,126,142,154,161,163–166,169–173,176] of the 16 trials[91,126,142,152,154,161,163–166,169–173,176] reporting MSs were conducted in adults, and the results did not differ greatly from the sample as a whole. Only one study[152] was conducted in children, and also reported that active treatment resulted in statistically improved MSs compared with placebo.

Nine[126,142,152,154,164–166,171,173] of the 14 studies[126,142,152,154,161,163–166,169–171,173,176] in the meta-analysis for which treatment duration could be determined lasted for >12 months. All subgroups favoured active treatment and were statistically significant, although effect size appeared to increase with treatment duration.

TABLE 9 Subcutaneous immunotherapy SSs: studies not in meta-analysis

Study ID	Results
Ceuppens 2009[160]	Median nasal SSs (IQR) 0.3 (0.1–0.6) vs 0.7 (0.5–1.1) in the active and placebo groups, respectively ($p = 0.041$)
Colas 2006[143]	Over the EPS, median (IQR) TSSs were 4.3 (3.4–4.6) and 6.4 (4.0–8.4) in the IT and placebo groups, respectively ($p < 0.001$)
Creticos 2006[144]	During the first ragweed season post treatment, mean rhinitis visual analogue score was 13.8 in the AIC-treated group, vs 35.1 in the placebo group ($p = 0.01$). Daily nasal SSs were also lower in the active group ($p = 0.03$)
Hoiby 2010[148]	Median SS was not significantly different between treatment groups ($p = 0.375$), despite a reduction of 25% in the SCIT group compared with placebo
Pfaar 2010[155]	Median SSs were 0.54 (IQR 0.27–0.77) for Depigoid-treated patients completing the study and 0.61 (IQR 0.48–0.75) for placebo [median difference –0.1 (95% CI –0.20 to –0.02); $p < 0.01$]
Sahin 2011[157] (A)	Compared with placebo, the overall SS in the active group was significantly reduced by 36% ($p = 0.006$)
Ventura 2009[158]	Not possible to extract data from graphs. Clinical improvements were noted with active treatment compared with placebo

(A), abstract; AIC, Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate; IQR, interquartile range; TSS, total symptom score.

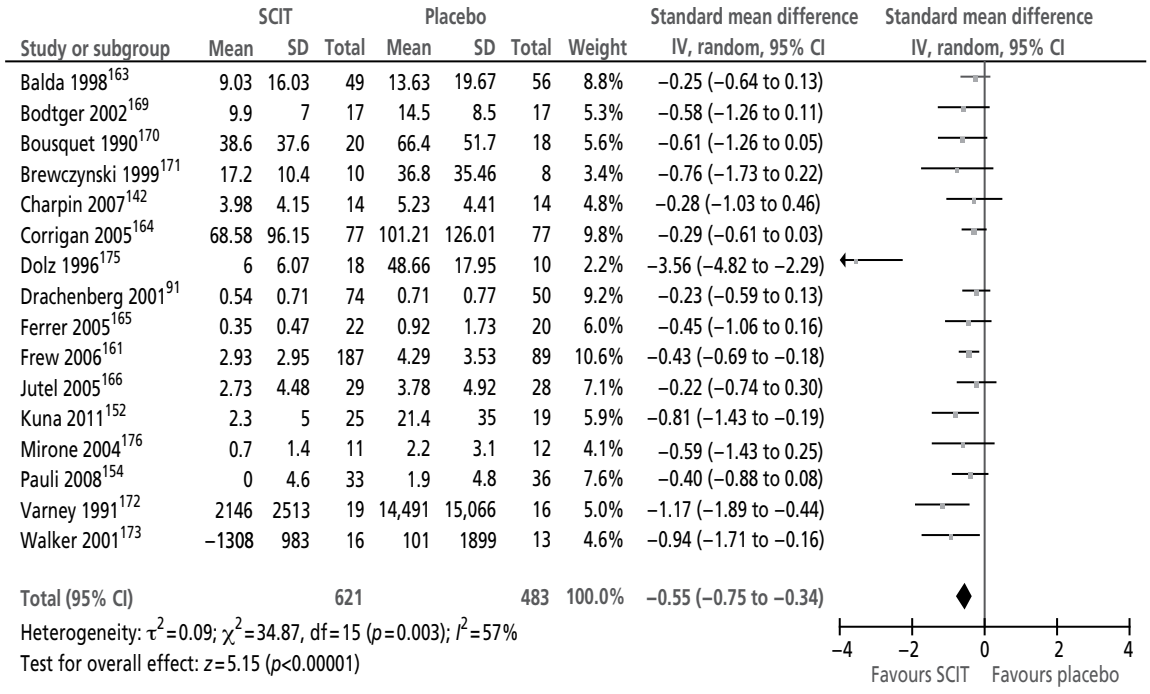

FIGURE 2 Subcutaneous immunotherapy vs placebo: MSs.

TABLE 10 Subcutaneous immunotherapy vs placebo, subgroup analyses: MSs

Subgroup	No. of studies	Total *n*	SMD (IV, random 95% CI)
Age			
Adults	15	1059	–0.53 (–0.75 to –0.32)
Duration (months)			
<6	2	143	–0.34 (–0.68 to –0.01)
6–12	3	332	–0.46 (–0.69 to –0.23)
>12	9	469	–0.67 (–1.06 to –0.29)
MAC			
<5μg	2	147	–0.31 (–0.63 to 0.02)
5–20μg	6	254	–0.45 (–0.70 to –0.20)
>20μg	2	305	–0.55 (–0.96 to –0.13)
Allergen			
Grass	8	483	–0.77 (–1.22 to –0.33)
Parietaria	2	318	–0.43 (–0.67 to –0.20)
Tree	4	235	–0.34 (–0.60 to –0.09)

IV, inverse variance.

Six[142,152,154,166,169,176] of the 10 included studies,[142,152,154,161,163,165,166,169,173,176] including all three of the recent trials, utilised vaccines with between 5 and 20μg MAC. Again, combined SMD increased with increasing dosage. Improvements in MS in the lowest dosage group were not significantly better than placebo, but this finding was based on only two studies[163,165] (total $n = 147$).

The most commonly investigated allergen was grass pollen, representing 483 subjects across eight trials,[91,126,164,166,170–173] and this was associated with the largest effect size, but also with a high degree of between-study heterogeneity. Tree pollen allergy was studied in four trials,[142,154,163,169] and *Parietaria* (a plant of the nettle family) in two trials.[161,165] Combined SMD favoured active treatment and were statistically significant in all allergen subgroups. Only one study[152] was performed in *Alternaria* (a fungus) and thus meta-analysis was not possible. No studies in ragweed reported MSs suitable for meta-analysis.

Medication score results from five recent studies[143,148,155,157,160] were not suitable for inclusion in meta-analysis, and details are shown in *Table 11*. Two studies reported quite large reductions in MSs in actively treated patients (43%[157] and 52%[148]); however, three studies[143,155,160] reported no significant difference between the groups. These contrasting results cannot be explained by differences in sample size, treatment duration, MAC or type of allergen.

Symptom and medication scores

Only the eight studies[91,163–168] (total $n = 617$) previously reported in the Cochrane review reported this outcome in a manner suitable for meta-analysis. Thus, the combined effect size calculated in that review remains valid (SMD –0.48; 95% CI –0.67 to –0.29; $p < 0.00001$) (*Figure 3*).[68] However, it was possible to conduct a number of subgroup analyses on this sample.

TABLE 11 Subcutaneous immunotherapy MSs: studies not in meta-analysis

Study ID	Results
Ceuppens 2009[160]	No significant differences between groups ($p = 0.155$)
Colas 2006[143]	Over the EPS, median (IQR) MSs were 0.8 (0.7–0.8) and 0.9 (0.5–1.1) in the IT and placebo groups, respectively ($p = 0.115$)
Hoiby 2010[148]	Median MS were significantly different between treatment groups after 18 months: median (IQR) 2.1 (0.6–3.7) in the SCIT group and 4.4 (1.9–14.0) in the placebo group ($p = 0.016$), a reduction of 51.9% in the SCIT group compared with placebo
Pfaar 2010[155]	Median MSs were 1.36 (IQR 0.4–2.9) for Depigoid-treated patients completing the study and 2.95 (IQR 1.7–3.9) for placebo [median difference –1.3 (95% CI –1.87 to –0.34); $p = 0.09$]
Sahin 2011[157] (A)	Compared with placebo, the overall MS in the verum group was significantly reduced by 43% ($p = 0.002$)

(A), abstract; IQR, interquartile range.

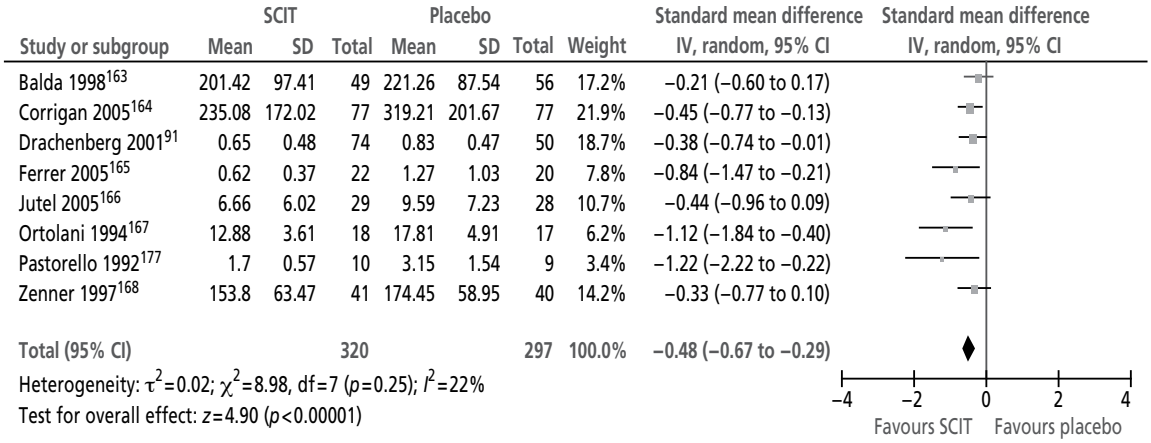

FIGURE 3 Subcutaneous immunotherapy vs placebo: SMSs.

All of the eight included studies[91,163–169] were conducted in adults. Thus, subgroup analyses were conducted for study duration, MAC and type of allergen. All favoured the active treatment and were statistically significant. Results of subgroup analyses are shown in *Table 12*.

Treatment duration could not be determined for two studies.[91,177] Three of the included studies[164–166] were of <6 months' duration. Combined effect size was similar to that in the overall sample, although significantly more heterogeneity was indicated in this subgroup ($I^2 = 59\%$ vs 22%). A further three studies[163,167,168] lasted over 12 months, and effect sizes were again similar. However, these studies[163,167,168] were more homogeneous ($I^2 = 0\%$). None of the studies reporting this outcome lasted between 6 and 12 months in length.

Major allergen content could not be determined for three studies.[91,164,177] Three studies[163,165,168] utilised a dose of <5 μg major allergen. Effect size was a little smaller than for the sample as a whole but remained significant. Only one study each used a vaccine with 5–20 μg[166] and >20 μg[167] major allergen, and thus meta-analysis was not possible in these subgroups.

TABLE 12 Subcutaneous immunotherapy vs placebo, subgroup analyses: SMSs

Subgroup	No. of studies	Total *n*	SMD (IV, random, 95% CI)
Duration (months)			
<6	3	221	–0.47 (–0.91 to –0.02)
>12	3	253	–0.51 (–0.76 to –0.25)
MAC			
<5μg	3	228	–0.39 (–0.70 to –0.07)
Allergen			
Grass	5	435	–0.43 (–0.62 to –0.24)
Parietaria	2	77	–0.96 (–1.44 to –0.49)

IV, inverse variance.

Again, the largest subgroup of studies was for grass pollen: five studies,[91,164,166,168,177] (total $n = 435$) resulted in a moderate effect size in favour of active treatment. Two studies[165,167] were conducted with *Parietaria* allergen, with the combined effect size strongly favouring the active treatment. Only one study[164] was conducted with tree allergen and meta-analysis was therefore not possible.

None of the nine newer studies[30,145,148,149,152,153,155,157,160] reporting combined SMSs was suitable for meta-analysis. Results from all nine studies[30,145,148,149,152,153,155,157,160] favoured active SCIT; details of the data from these studies are shown in *Table 13*. Studies that involved >1 year of treatment reported that the effect size increased with each year of active treatment.

Quality of life

Quality-of-life data suitable for meta-analysis were available for eight RCTs (five from the Cochrane review,[161,164–166,173] three more recent;[143,144,146] *Figure 4*). The addition of the three newer studies resulted in a nearly 70% increase in sample size for this outcome (total $n = 955$). Nevertheless, the results (SMD –0.53, 95% CI –0.66 to –0.39; $p < 0.00001$) were almost identical to those reported in the Cochrane review (SMD –0.52, 95% CI –0.69 to –0.34; $p < 0.00001$). No heterogeneity between studies was found.

Where subgroup analyses were possible, treatment duration, MAC and type of allergen did not appear to affect the outcome (*Table 14*). All of the studies included in the meta-analysis were conducted in adults and thus analysis by participant age was not possible. However, based on results from one paediatric study,[152] SCIT appears to be effective for the improvement of QoL in children and adolescents when used long term.

As all eight of the included studies[143,144,156,161,164–166,173] assessed QoL using the Juniper RQLQ, an additional meta-analysis was conducted to calculate weighted mean difference (MD) (*Figure 5*). Active treatment had a significant positive effect on QoL, equivalent to a 0.74 unit reduction in RQLQ score compared with placebo.

Three new studies[142,148,152] reported QoL data in a manner not suitable for inclusion in meta-analysis. Details of data from these studies[142,148,152] are shown in *Table 15*. The smallest[142] of the three studies (total $n = 28$) found no difference in overall QoL between treatment groups using SF–36. The other two studies[148,152] used disease-specific instruments (age-appropriate versions of the RQLQ) and both reported clinically significant improvements in QoL in active- but not placebo-treated subjects. However, in the 3-year paediatric study,[152] improvements became statistically significant only in later years of treatment.

TABLE 13 Subcutaneous immunotherapy SMSs: studies not in meta-analysis

Study ID	Results
Chakraborty 2006[30]	The SIT group had a 33.5% ($p<0.01$) and 57% ($p<0.001$) decrease in the SMS during the first and second treatment seasons of 2000 and 2001 when compared with the baseline peak month. There were no significant changes in the control group
Ceuppens 2009[160]	Clinical index score (a combined score of symptoms and medication use) was reduced in the verum group by 24% compared with placebo [median (IQR) 0.5721 (0.2759–1.2830) vs 1.0322 (0.5882–1.6080), respectively; $p = 0.055$]
DuBuske 2011[145]	Median (SD) combined SMS during the four peak weeks of the grass pollen season was 6.00 (5.57) in the Grass MATA MPL-treated subjects and 7.06 (5.57) in the placebo-treated subjects. In the ITT analysis ($n = 1028$), the least squares mean combined SMS was reduced by 13.4% with Grass MATA MPL compared with placebo ($p = 0.0038$). Similar differences were seen during the EPS
Hoiby 2010[148]	After 18 months, the median (IQR) combined SMS of the SCIT and placebo groups were 8.0 (5.8–10.3) and 12.6 (8.6–16.2), respectively ($p = 0.004$) – a 36.5% reduction in the SCIT group compared with the placebo
Kettner 2007[149] (A)	After 1.5 years of therapy, a highly significant and clinically relevant reduction in the median AUC of the SMS from 389.6 to 207.8 in the active group compared with the placebo group (from 382.5 to 306.5; $p = 0.0137$) was observed in the full analysis set
Kuna 2011[152]	Reductions in combined SMS after therapy, compared with placebo, were 10.8%, 38.7%, and 63.5% after the first, second, and third years of SIT, respectively ($p = 0.73$, 0.102, <0.001 and <0.001 for baseline, 1, 2 and 3 years of SIT, respectively, active therapy vs placebo, one-way ANOVA test)
Ljorring 2009[153] (A)	The estimated treatment effect on combined SMS over peak season was –4.45 (95% CI –6.84 to –2.06) in favour of active treatment. (Abstract; patient numbers in each group not reported)
Pfaar 2010[155]	At 18 months, the median AUC for the combined SMS was 2.3 (IQR 0.9–3.2) for the actively treated patients and 2.6 (IQR 2.2–4.4) for placebo-treated patients [median difference –0.4 (95% CI –1.22 to –0.03); $p<0.04$] for the ITT population
Sahin 2011[157] (A)	There was a significant reduction in total combined scores in the active group compared with the placebo group ($p = 0.005$)

(A), abstract; ANOVA, analysis of variance; IQR, interquartile range; ITT, intention to treat; MATA MPL, modified allergen tyrosine adsorbate monophosphoryl lipid A.

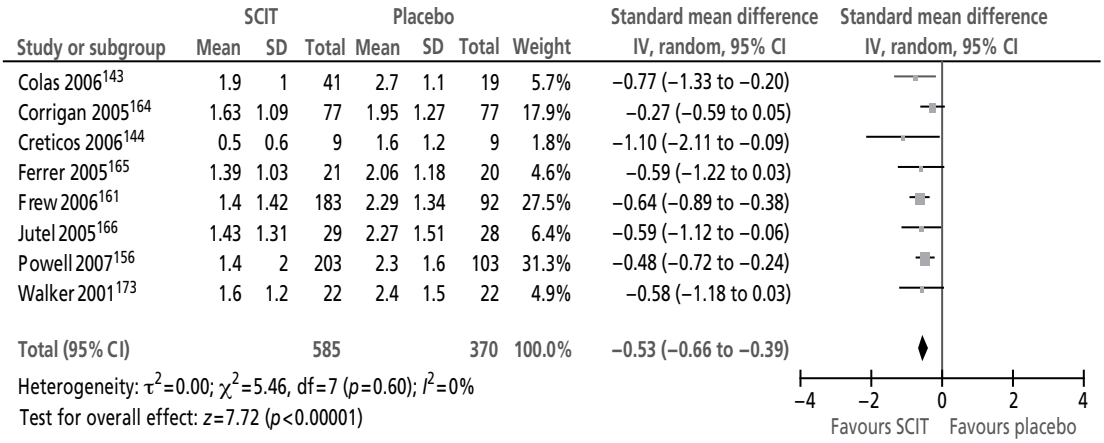

FIGURE 4 Subcutaneous immunotherapy vs placebo: QoL.

TABLE 14 Subcutaneous immunotherapy vs placebo, subgroup analyses: QoL

Subgroup	No. of studies	Total *n*	SMD (IV, random, 95% CI)
Duration (months)			
>12	6	662	–0.47 (–0.63 to –0.31)
MAC (μg)			
5–20	3	381	–0.52 (–0.74 to –0.31)
>20	3	379	–0.65 (–0.87 to –0.43)
Allergen			
Grass	4	561	–0.44 (–0.61 to –0.26)
Parietaria	2	316	–0.63 (–0.87 to –0.39)

IV, inverse variance.

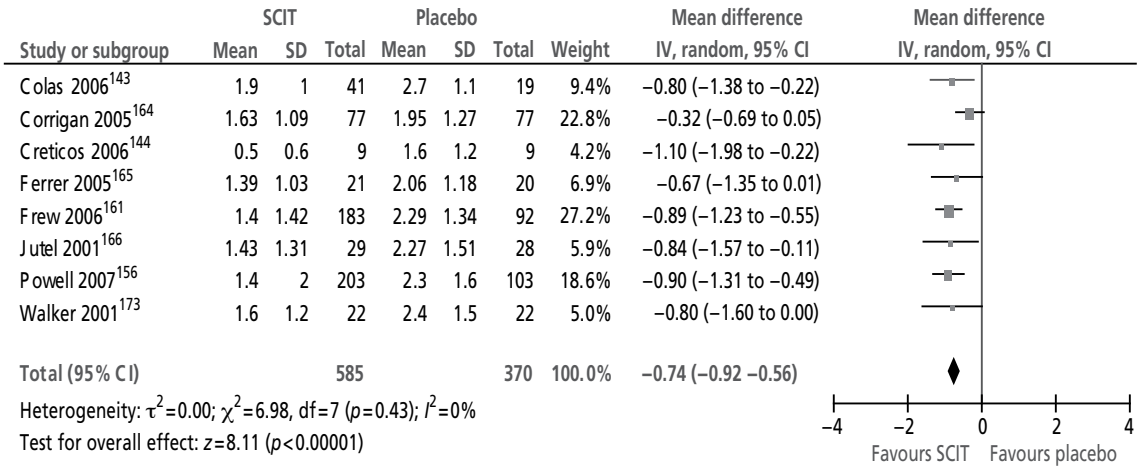

FIGURE 5 Subcutaneous immunotherapy vs placebo: QoL (RQLQ scores).

TABLE 15 Subcutaneous immunotherapy QoL scores: studies not in meta-analysis

Study ID	Results
Charpin 2007[142]	Assessment measure was SF–36. There was no significant difference between the two treatment groups except for variations in social function after the first season
Hoiby 2010[148]	At baseline, there was a statistically significant difference between the two treatment groups in the mean RQLQ (SCIT: 2.58; placebo: 2.7; $p<0.0001$). During the study, RQLQ improved in both groups. The change in mean RQLQ between baseline and assessment during pollen season 2005 after 6 months of treatment was significantly different between the two groups (SCIT –3.8; placebo –0.1; $p<0.0001$)
Kuna 2011[152]	Active treatment was associated with an improvement in QoL for children (up to 12 years of age) with rhinoconjunctivitis. The mean baseline RQLQ score was 1.7 and decreased significantly in consecutive years of therapy to 1.4, 1.0, and 0.7 ($p = 0.009$, 0.008 and 0.003 after the first, second and third years of SIT, respectively). In the comparable group of children receiving placebo, the baseline QoL score was 2.0 and increased in consecutive years of therapy to 2.3, 2.3 and 2.7 ($p = 0.08$, 0.09 and 0.019, respectively). The group of adolescents who received active treatment also showed significant improvements in QoL: a baseline QoL score of 2.7 decreased significantly in consecutive years of therapy to 2.0, 1.4 and 0.9 ($p = 0.0018$, 0.0006 and 0.0006, respectively). The comparable placebo group showed no change during the entire study, with a baseline mean QoL score of 2.0, and scores of 1.9, 1.9 and 2.2 after the first, second, and third years, respectively ($p = 0.034$, 0.5 and 0.68, respectively). Comparisons of the actively treated and placebo groups showed statistically significant differences for children after the second and third years of SIT ($p = 0.015$ and 0.001, respectively) and for adolescents after the third year of SIT ($p = 0.03$)

Other clinical outcomes

Recent guidelines[64,134] have recommended the use of a number of secondary efficacy outcomes, including patient-reported assessments of improvement, symptom control (well-/bad-days) and responder analysis. Seven of the recent SCIT studies[30,142,143,145,146,155,157] reported additional clinical outcomes, all of which favoured the active treatment (*Table 16*). No studies reported on the development of new asthma cases.

TABLE 16 Subcutaneous immunotherapy: other clinical outcomes

Study ID	Results
Chakraborty 2006[30]	*Pulmonary function tests*: After 2 years of treatment, % predicted FEV_1 during pollen season in patients with both AR and asthma ($n = 8$ active, $n = 6$ placebo) was better in patients receiving active treatment, and was also significantly better than baseline values in patients receiving SCIT ($p < 0.001$) but not the control group ($p > 0.05$) *New sensitivities*: During the 2-year treatment period, two patients in the placebo group and none in the active group developed new allergic sensitivities
Charpin 2007[142]	*Days with asthma*: Six active and four placebo patients suffered with comorbid asthma. During the first pollen season after commencement of treatment, patients receiving active SCIT experienced 0.4 days with asthma symptoms vs 2 days for placebo patients. During the second pollen season, the figures were 0.8 days vs 4 days, respectively. These differences were not statistically significant
Colas 2006[143]	*SMFDs*: During the EPS, 368/1230 (29.9%) patient-days were symptom and medication free in patients receiving active treatment, compared with 50/570 (8.7%) patient-days in patients receiving placebo ($p < 0.01$). Similar results were reported for the active group during the PPS but fewer SMFD were reported in the placebo group (29.1% vs 1.4%; $p < 0.01$) *Visual scale of health situation related to symptomatology* (100 mm VAS, from 'very poor' to 'very good'): No differences in scores between active and placebo groups were apparent before or after the pollen season – median (cm) (IQR) 9.00 (8.20–9.30) vs 8.75 (6.80–9.58) and 9.35 (8.50–10.00) vs 8.20 (7.10–9.25), respectively; both $p > 0.05$. During the pollen season, scores decreased in both groups, but were significantly better in the active group compared with placebo – 7.00 (6.50–7.70) vs 4.30 (3.43–4.90), respectively; $p < 0.001$
DuBuske 2011[145]	*No. of well-days* (days without rescue medication and low TSS): Maximum TSS = 24. Total $n = 491$ active, 499 placebo TSS ≤2: 78% more well-days in active group – median 16 days vs 9 days *n* active and placebo, respectively; $p = 0.007$ TSS ≤3: 28% more well-days in active group – median 32 days vs 25 days; $p = 0.008$ TSS ≤4: 22% more well-days in active group – median 39 days vs 32 days; $p = 0.004$ *No. of bad-days* (combined SMS ≥8 or 10): SMS ≥8: 35% fewer bad-days in active group – median 20 days vs 27 days in active and placebo, respectively; $p = 0.008$ SMS ≥10: 86% fewer bad-days in active group – median 7 days vs 13 days; $p = 0.0046$ *No. of well subjects* (overall median combined SMS ≤2 during the 4-week PPS). Total $n = 485$ active, 488 placebo 85% more well subjects in active group compared with placebo – median 78 vs 42 active and placebo subjects, respectively; $p = 0.0005$
Francis 2008[146]	*Overall assessment*: On completion of 1-year treatment, subjects answered question 'How has your hay fever been this year compared with previous years?' on a numerical scale of –3, a lot worse, to +3, a lot better; mean (standard error) 2.42 (0.22) in active group vs 1.50 (0.34) in placebo group; $p < 0.05$
Pfaar 2010[155]	*Responder analysis*: Based on receiver operating curves, responders were defined as those subjects with AUC of at least 30% less than median AUC for placebo group during the pollen season; 64% (87/137) of the active group were defined as treatment responders compared with 32% (15/47) of the placebo group; $p < 0.01$
Sahin 2011[157] (A)	*Well-days* (symptom-free days): Significantly more well-days in active group than placebo group *Global evaluation*: 85% active SCIT group improved ($p = 0.002$), and 91% were satisfied with the treatment ($p < 0.001$)

(A), abstract; FEV_1, forced expiratory volume in one second; IQR, interquartile range; SMFD, symptom- and medication-free day; TSS, total symptom score.

Adverse events

Adverse event data were available from 15 of the newly identified trials.[30,142–146,148–150,152,154,155,157,159,160] Comparison of AE data between trials was not straightforward as methods of reporting varied considerably. Most studies reported only the number of patients experiencing events rather than the number of events; some only counted patients once, by their worst-case event, whereas others counted all events; and some studies only reported events considered to be treatment related. In addition, the amount of information regarding AEs varied greatly between trials, from brief narrative reports to detailed analyses of events. The following results are based on both newly identified trials and those in the Cochrane review.[68]

At least one AE was experienced by 79% (667 out of 849) of patients receiving active injections, compared with 57% (418 out of 729) of patients receiving placebo in the nine trials that reported this outcome.[30,142–145,148,154,155,159]

Incidence of local reactions was reported in eight trials,[30,142,143,148,152,154,155,160] comprising 352 SCIT and 222 placebo patients in total. The active and control groups experienced a total of 138 and 39 localised AEs, respectively. Where actual number of injections delivered was reported, the rates of injection site reactions were 2.8% (67 events in 2428 injections),[155] 1.1% (11 events in 987 active injections),[152] 0.5% (29 events in 1672 injections)[160] and 0.02% (five events in 2095 injections).[30] In the four trials[143,144,148,152] (total $n = 116$ active, 80 placebo) that reported on treatment of local reactions, 103 local reactions occurred after active treatment, compared with 84 after placebo, none of which required treatment.

Systemic AEs were relatively uncommon, with 129 events occurring after 2909 injections (4.4%) in six trials that reported this statistic.[155,166,178–181] Six trials[30,143,144,148,155,157] gave some indication of the event severity (*Table 17*). The majority (81%) were of mild or moderate intensity. However, severe AEs constituted 19% of the total. Three per cent of patients receiving active treatment withdrew owing to AEs.

In addition, eight trials[142,146,148,152,154,155,159,160] reported systemic reactions by type of event. *Table 18* shows systemic events reported in more than one trial. Thirteen studies ($n = 557$)[23,161,164–167,175,176,178,182–185] reported using adrenalin after 19 of 14,085 injections (0.13%).

Post-injection anaphylaxis was reported in one trial,[159] and was experienced in 10 patients receiving active SCIT ($n = 39$), with eight requiring administration of adrenaline, and in one patient receiving placebo ($n = 37$).

TABLE 17 Systemic AEs in SCIT: severity and withdrawals

Severity of reaction	No. studies reporting	SCIT		Placebo	
		n	No. of events	*n*	No. of events
Mild	4	227	38	113	8
Moderate	4	227	25	113	25
Severe	6[a]	302	12	183	11
AE leading to study withdrawal	2	536	15	532	4

a One trial (Sahin *et al.*[157]) reported only severe AEs that were considered to be treatment related, with no instances occurring.

TABLE 18 Systemic AEs in SCIT: type of event

Type of reaction	No. studies reporting	SCIT		Placebo	
		n	No. of events	*n*	No. of events
Wheezing/asthma	6	271	9	169	7
Urticaria/oedema	5	241	19	138	2
Rhinitis	4	223	44	131	22
Conjunctivitis	4	223	25	131	17
Headache	3	91	18	81	8
Flushing	3	91	16	73	51
Light-headedness	2	69	8	68	2

Occurrence of SAEs was reported by seven studies.[142,144,148–150,155,159] Sixteen SAEs occurred in 770 patients, none of which was considered treatment related. Treatment of AEs was not widely reported. Eleven trials[126,143,144,148,152,163,168,169,186–188] (total active $n = 324$) reported 21 local reactions that required treatment. In contrast, 28 trials (total active $n = 1023$) reported 936 local reactions that did not require any treatment. Approximately one-third of systemic reactions (69 out of 206 events, based on 20 studies, $n = 558$) required treatment, with antihistamines, bronchodilators and glucocorticoids being the most commonly used. Administration of adrenaline is reported above.

Summary of findings: subcutaneous immunotherapy

A summary is shown below in *Box 1*.

BOX 1 Summary of findings: SCIT

- Treatment with SCIT resulted in a statistically significant reduction in SSs, MSs and combined SMSs compared with placebo. Moderate effect sizes were observed in most cases, and these were largely unrelated to treatment duration and type of allergen. All but one[152] trials were conducted in adults; the one small ($n = 50$) trial[122] in children found a statistically significant reduction in SSs and MSs with SCIT after 3 years of treatment. Larger effect sizes observed in some analyses were always associated with wide CIs and a very high degree of between-study heterogeneity. Subgroup analyses suggested an increased benefit with greater allergen content
- Subcutaneous immunotherapy treatment had a moderate effect on QoL scores, independent of treatment duration, MAC or type of allergen. Results from the one trial in children[152] are suggestive of a benefit from SCIT in the long term
- A range of other clinical outcomes were reported in a number of trials, and all favoured the active treatment
- The majority of AEs were local injection site reactions and were more prevalent in participants receiving active treatment. Local reactions occurred in between 0.02% and 2.8% of injections (based on four studies[30,152,155,160])
- Most (81%) of systemic reactions were graded as mild or moderate; however, one-fifth were classified as severe
- Discontinuation rates due to AEs were around 3% (reported in two trials, total $n = 1068$)
- Post-injection anaphylaxis was reported in only one small trial[159] (total $n = 76$) but was considerably more frequent following active treatment, occurring in approximately 10 of 39 patients (compared with 1 of 37 receiving placebo); 8 of the 10 patients were treated with adrenaline

Quantity of evidence (sublingual immunotherapy vs placebo studies)

Searches identified 85 publications of DBPC RCTs of SLIT (see PRISMA flow diagram in *Appendix 4*). Of these, 52 publications relating to 44 RCTs were already included in the relevant Cochrane review[83] (note: the other RCTs in the Cochrane review related to dust mites or animal dander). Of the remaining 33 publications, 15 were within the Cochrane search period but appear not to have been identified and two had been excluded from the Cochrane review despite apparently meeting the inclusion criteria. Details of the excluded studies are presented in *Appendix 5*. Sixteen publications[25,32,158,188–199] post-dated the Cochrane searches; thirteen[25,158,188–199] of these related to 11 new RCTs, three were updates of trials previously included in the Cochrane review: two[32,200] related to the Dahl *et al.* (GT–08) trial[201] and one[202] provided additional data from the trial described in Didier *et al*.[24] As the purpose of this report was to update, rather than repeat, the Cochrane review, results are presented for only the 11 studies[25,158,189–199] published from 2009 onwards, although all relevant studies were included in the meta-analyses.

Main study characteristics and risk of bias (sublingual immunotherapy compared with placebo studies)

The main study and population characteristics, and assessment of risk of bias, are detailed for each of the 11 new studies[25,158,189–199] in *Appendix 6*. All studies were double-blind placebo-controlled RCTs. The largest four trials[25,189,192,195] had between 276 and 633 participants, with the number of participants in the smaller trials ranging from 20 to 115. Skin prick tests were performed in all patients to demonstrate specific sensitivity. Allergy symptoms were described as moderate to severe in 6 out of 11 trials,[189–191,195–197] with no indication of severity given in 5 out of 11 trials.[25,158,192–194] Seven studies[25,189,190,192,193,195,197] stated that some patients also had asthma symptoms. Two trials specified that patients were treatment naive,[190,191] four reported no details,[25,158,189,197] and in five trials[192–196] it was stated that patients had not received SIT within the last 3–5 years, although it was unclear if any patients had ever been treated with SIT. This may be important, as it is known that SIT can have long-term effects. Outcomes included SSs, MSs, combined SMSs, QoL and AEs (note: only outcomes consistent with the inclusion criteria of this report have been listed). Six[25,189–192,196] of the eleven studies reported SMSs compared with none of the studies in the Cochrane review. As for SCIT compared with placebo trials, the number and types of symptom assessed varied widely (see *Appendix 7* – SSs across studies).

The most commonly tested allergen was timothy grass (*P. pratense*), investigated in four trials,[174,177–179] followed by tree pollen (three trials),[158,191,197] a mix of several grasses (two trials),[25,194] one trial[196] with ragweed and one[190] with *Alternaria*. Length of treatment varied between 8 and 10 weeks and over three pollen seasons, and there was also variation in treatment schedules (e.g. daily or weekly dosing). One study[189] was in children and adolescents, one[190] in both children and adults, with the remaining studies all conducted in adults. The main study characteristics are summarised in *Table 19*.

Similarity between trials was explored for a range of study and population characteristics. Trial duration and type and amount of allergen used varied between trials; however, this was explored as a source of heterogeneity in subgroup analyses. Where reported, inclusion criteria were very similar across trials, with the majority stipulating a minimum of 2 years' clinical history of moderate to severe SAR, incompletely controlled by standard medication; actual SAR history of included patients ranged from approximately 5 to 18 years. Four studies[158,191,194,196] did not report whether or not patients with previous SIT were included. Rates of asthma across trials were largely consistent, with none greater than one-quarter (range 7–26%). All studies excluded patients with severe or perennial asthma.

Results of the risk of bias assessment are summarised in *Table 20* (full details are given in *Appendix 5*).

Overall, the risk of bias was low for three or more areas of potential bias in most of the studies, although a lack of detail in the published reports meant that risk of bias was unclear in many cases. Study authors were not contacted, and an 'unclear' rating may be due to lack of reporting rather than a reflection of poor trial quality. All but one study[191] indicated that endeavours were made to maintain blinding. There were only two instances[191,197] in which a high risk of bias was identified; neither of these studies

TABLE 19 Main study characteristics: newly identified SLIT vs placebo studies

Study	Size	Previous SIT	Stated that symptoms moderate to severe	Patients with asthma allowed/ included	Type of allergen	Administration schedule	Outcomes
Blaiss 2011[189]	$n = 345$	Unclear	Yes	Yes	Timothy grass (Grazax)	Once-daily tablet for 23 weeks; pre-and coseasonal	SSs, MSs, SMSs, QoL, AEs, effects on asthma
Cortellini 2010[190]	$n = 27$	No	Yes	Yes	*Alternaria* (seasonal mould)	Fifteen days build-up phase (one to five drops daily); five drops every other day for 10 months; pre-, co- and post-seasonal	SSs, MSs, SMSs, AEs
Didier 2011[25]	$n = 633$	Unclear	No details on severity	Yes	Five-grass mix	Once-daily tablet, 2 or 4 months preseasonal then over three consecutive pollen seasons	SMSs, SSs, MSs, SMFDs, QoL, AEs
Fujimura 2011[191]	$n = 103$	No	Yes	No details on asthma	Tree (cedar)	Approximately 3-week build-up phase (unclear from report), followed by 18 months of maintenance with once-weekly dosing of 1 ml 2000 JAU/ml drops	SMSs, AEs, QoL
Nelson 2011[192]	$n = 438$	Not in last 5 years	No details on severity	Yes	Timothy grass	Once-daily tablet for 23–24 weeks; pre-and coseasonal	SS, MS, SMS, QoL, AEs, effects on asthma
Panizo 2010[193]	$n = 78$	Not in last 5 years	No details on severity	Yes	Timothy grass (Grazax)	Once daily tablet for approximately 22 weeks; pre-and coseasonal	AEs
Pfaar 2011[194]	$n = 80$	Not in last 3 years	No details on severity	No details on asthma	Twelve-grass mix	High-dose group: dose escalation to maximum 19.04 μg Phl p1/dose + 52.5 μg MPL; daily dosing with 0.21 ml sublingual drops for a total of 11 weeks	AEs
Reich 2011[180]	$n = 276$	Not in last 5 years	Yes	Yes	Timothy grass (Grazax)	Once-daily tablet (active or placebo) for 8–10 weeks; treatment initiated during pollen season and administered coseasonally	Days with medication, AEs, global evaluation, spirometry
Skoner 2010[196]	$n = 115$	Not in last 3 years	Yes	No details on asthma	Ragweed	Once-daily tablet for 14–20 weeks; pre- and coseasonal	SSs, MSs, SMSs, AEs
Ventura 2009[158]	$n = 20$	Unclear	No details on severity	No details on asthma	Tree (juniper)	30-day induction, then drops given three times per week for 11 months	SSs
Voltolini 2010[197]	$n = 24$	Unclear	Yes	Yes	Tree (birch)	Induction over 11 days then daily drops 300 IR over 4 months	SSs, AEs, asthma days/ severity

IR, index of reactivity; JAU, Japanese allergy unit; MPL, monophosphoryl lipid; SMFD, symptom- and medication-free day.

TABLE 20 Risk of bias assessment: newly identified SLIT studies

Study	Sequence generation	Allocation concealment	Blinding	Data completeness	Selective reporting	Patients treatment naive
Blaiss 2011[189]	+	+	+	?	+	?
Cortellini 2010[190]	+	?	+	+	+	+
Didier 2011[25]	?	?	+	?	+	?
Fujimura 2011[191]	+	+	?	+[a]	+	+
				–[b]		
Nelson 2011[192]	+	+	+	+	+	?
Panizo 2010[193]	?	?	+	+	+	?
Pfaar 2011[194]	?	?	+	+	+	?
Reich 2011[195]	+	+	+	+	+	?
Skoner 2010[196]	+	+	+	?	+	?
Ventura 2009[158]	+	?	+	+	+	?
Voltolini 2010[197]	+	?	+	+	–	?

+, low risk; –, high risk; ?, unclear.
a For SMS data.
b For QoL data.

contributed to any meta-analyses. It should be noted that a certain degree of subjectivity remains in assigning a rating of low/unclear/high.

Effectiveness of sublingual immunotherapy compared with placebo

Of the 11 newly identified RCTs,[25,158,189–197] only five reported data in a form suitable for meta-analysis.[25,189,190,192,196] All five studies provided SS, MS and combined SMS data,[25,189,190,192,196] and three additionally provided QoL data[25,189,192] (*Table 21*).

TABLE 21 Outcome measures in recent SLIT RCTs

Study ID	Not in meta-analyses	In meta-analyses
Blaiss 2011[189]	AEs, effects on asthma	SSs, MSs, SMSs, QoL
Cortellini 2010[190]	AEs	SSs, MSs, SMSs
Didier 2011[25]	SMFDs, AEs	SSs, MSs, SMSs, QoL
Fujimura 2011[191]	SMSs, AEs, QoL	None
Nelson 2011[192]	AEs, effects on asthma	SSs, MSs, SMSs, QoL
Panizo 2010[193]	AEs	None
Pfaar 2011[194]	AEs	None
Reich 2011[195]	Days with medication, AEs, global evaluation, spirometry	None
Skoner 2010[196]	AEs	SSs, MSs, SMSs
Ventura 2009[158]	SSs	None
Voltolini 2010[197]	SSs, AEs, asthma days/severity	None

Symptom scores

A total of 39 SAR studies[24,26,38,84–91,94–118,197,200] were included in the meta-analysis in the Cochrane review. Of these, two were excluded by this review,[35,92] one[92] reported combined results for patients with SAR and SAA, and one[35] was restricted to patients with SAA. Further, 3-year results of the GT–08 trial[200] superseded the 1-year results reported by Dahl,[93] which was consequently removed from the meta-analysis. Searches for this review identified eight[25,158,189–191,196,197,200] new studies reporting this outcome, of which six[25,189,190,192,196,200] were included in the meta-analysis. In total, 2440 active (SLIT) and 2379 patients receiving placebo were included in 42 studies.

The combined SMD following SLIT was –0.33 (95% CI –0.42 to –0.25; $p < 0.00001$) favouring active treatment (*Figure 6*). This result is very similar to that found in the Cochrane review (SMD –0.34, 95% CI –0.44 to –0.25; $p < 0.00001$). Heterogeneity was also similar to the earlier review.

Subgroup analyses in this report were limited to studies in SAR, whereas data from the earlier Cochrane review included studies of SLIT for the treatment of PAR. Small to moderate effect sizes favouring active SLIT were found in all subgroup analyses, and these did not differ significantly with age, study duration, MAC or type of allergen. All were statistically significant, with the exception of the four studies in *Parietaria* allergy;[99,110,115,125] however, this was based on a total of only 124 participants. Results of subgroup analyses are shown below in *Table 22*. Forest plots of all subgroup analyses are shown in *Appendix 6*.

Compared with the Cochrane review, subgroup analysis by age resulted in very similar effect sizes in adult participants but a much smaller effect in children (SMD –0.24 compared with –0.52 in the Cochrane review), although this remained statistically significant. Although only nine paediatric studies have been included here,[26,84–90,189] compared with 15 in the Cochrane review,[26,35,84–90,92,203–207] total participant numbers were very similar (1343 vs 1392 children, respectively) and heterogeneity was significantly reduced ($I^2 = 0\%$, compared with 92% in the Cochrane review).

Analysis by treatment duration found reduced effect sizes in trials lasting < 6 months and over 12 months (the latter associated with a 69% increase in sample size) compared with the Cochrane review, but all remained statistically significant.

Few differences were found compared with the earlier review in subgroup analysis by allergen content, with the exception of studies using < 5 μg of major allergen.[88,99,111,116,190] Despite a small reduction in both study number and total sample size, effect size was larger in the present review (SMD –0.53, compared with SMD –0.32 in the Cochrane review), and became statistically significant. There was no apparent dose–response relationship for SLIT.

Subgroup analysis by allergen type gave effect sizes very similar to those in the earlier review, despite a 34% rise in sample size in the grass allergen subgroup. This latter was associated with a reduction in heterogeneity, which became non-significant. Effect size decreased slightly in *Parietaria* allergen, becoming non-significant, but total participant numbers were small (total $n = 124$ in present review).

Two studies[158,197] reported results in a manner not suitable for meta-analysis and details are shown in *Table 23*. Data could be extracted from only one study,[197] which showed a significant improvement in SSs compared with placebo.

Medication scores

A total of 32 SAR studies[26,35,84–86,88–109, 111,114,116,117,197] were included in the meta-analysis in the Cochrane review. Of these, two[35,92] were excluded by this review, as described above. Further 3-year results of the GT–08 trial[200] superseded the 1-year results reported by Dahl *et al.*,[93] which was consequently removed from the meta-analysis. Six new studies[25,189,190,192,196,200] reported this outcome and were included in the meta-analysis.

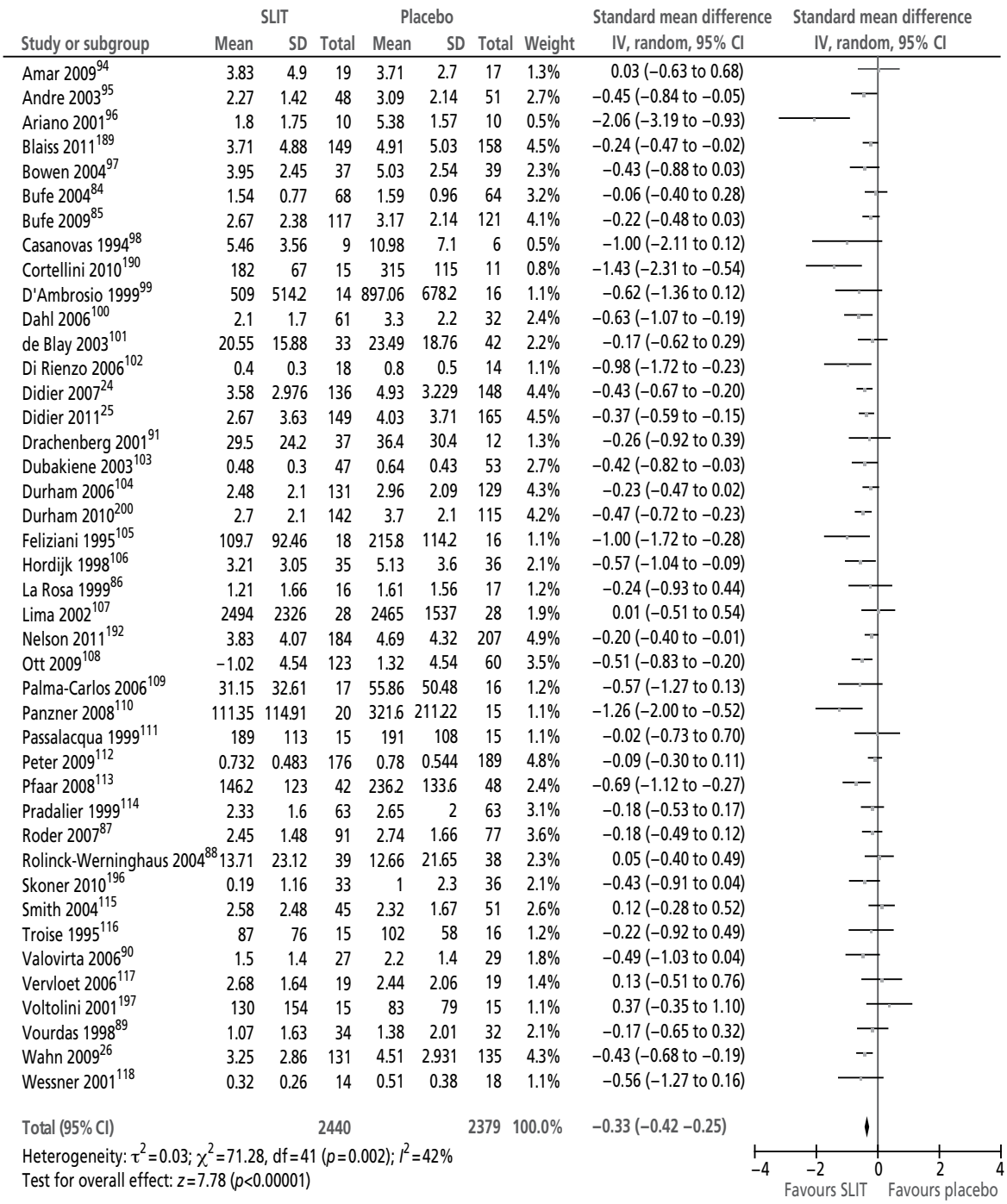

FIGURE 6 Sublingual immunotherapy vs placebo: SSs.

TABLE 22 Sublingual immunotherapy vs placebo, subgroup analyses: SSs

Subgroup	No. of studies	Total *n*	SMD (IV, random, 95% CI)	Comparison with CR
Age group				
Adults	33	3476	–0.38 (–0.49 to –0.27)	Similar
Children	9	1343	–0.24 (–0.35 to –0.13)	ES smaller, but remained statistically significant
Duration (months)				
<6	15	1882	–0.34 (–0.47 to –0.20)	ES smaller, but remained statistically significant
6–12	15	1539	–0.31 (–0.47 to –0.16)	Similar
>12	12	1398	–0.35 (–0.52 to –0.18)	ES smaller, but remained statistically significant
MAC				
<5μg	6	229	–0.53 (–1.03 to –0.03)	ES larger; becomes statistically significant
5–20μg	13	2287	–0.29 (–0.37 to –0.20)	Similar
>20μg	12	1088	–0.33 (–0.48 to –0.18)	Similar
Allergen				
Grass	25	4042	–0.31 (–0.39 to –0.24)	34% increase *n*; ES similar
Ragweed	3	244	–0.44 (–0.69 to –0.18)	Similar
Parietaria	4	124	–0.27 (–0.62 to 0.09)	ES smaller and became non-significant
Tree	9	380	–0.42 (–0.77 to 0.06)	Data as per Cochrane review

CR, Cochrane review; ES, effect size; IV, inverse variance.

TABLE 23 Symptom score results: studies not in meta-analysis

Study ID	Results
Ventura 2009[158]	Not possible to extract data from graphs. Clinical improvements were noted with active treatment compared with placebo
Voltolini 2010[197]	Median baseline rhinorrhoea score in both groups was 2 (5–95 percentiles: 1–3); after 1 year IT median scores were 1 (5–95 percentiles: 0–2) with active SLIT and 1.5 (5–95 percentiles: 0–2) with placebo ($p<0.05$)

In total, 1934 active and 1845 placebo patients were included in 35 studies.[25,26,84–86,88–91,94–109,111,114,116,117,189,190,192,196,197,200] The combined SMD was –0.27 (95% CI –0.37 to –0.17; $p<0.00001$) favouring active treatment (*Figure 7*). This result is very similar to that found in the Cochrane review (–0.30, 95% CI –0.41 to –0.19; $p<0.00001$). Heterogeneity was also similar to the earlier review.

Small to moderate effect sizes favouring active SLIT were found in all subgroup analyses. MSs in children were not significantly better than with placebo treatment. This finding was consistent with that of the earlier Cochrane review, and effect size was decreased further with the addition of the more recent studies. Of the eight included studies,[26,84–86,88–90,93] only one favouring placebo treatment was statistically significant. All others favoured active SLIT, but did not reach significance either alone or when combined. All other subgroup analyses were statistically significant, and most did not differ greatly from effect sizes reported in the earlier review, despite sometimes large increases in participant numbers (e.g. 31% increase in grass allergen; 69% increase in studies with duration of >12 months). Analyses in two subgroups – >20μg

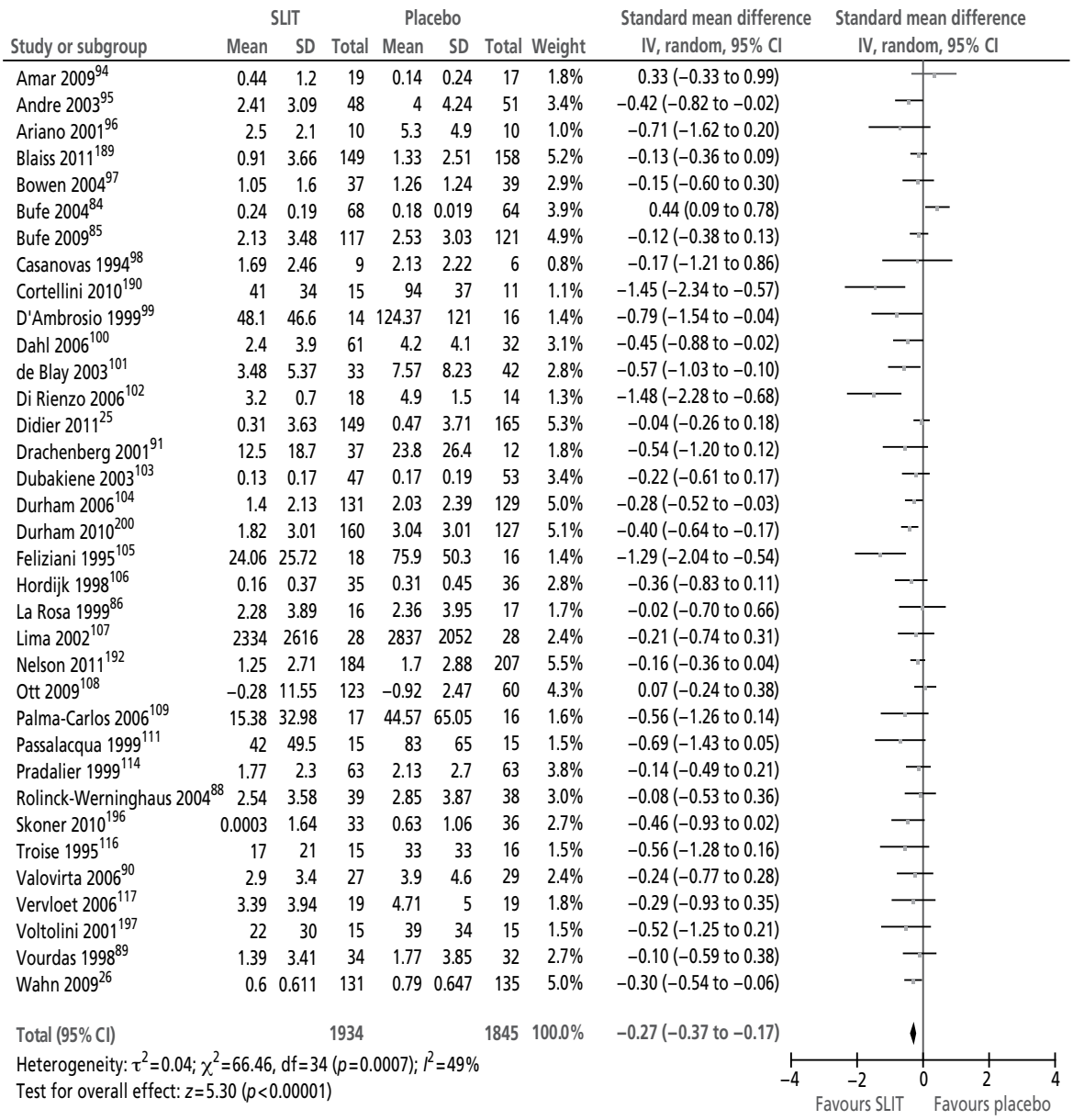

FIGURE 7 Sublingual immunotherapy vs placebo: MSs.

major allergen and ragweed pollen SLIT – became statistically significant in the present review. Results of subgroup analyses are shown in *Table 24*.

Symptom and medication scores

The Cochrane review did not report on this outcome. We identified seven new studies[25,189–192,196,200] that reported combined SMS, of which six[25,189,190,192,196,200] were suitable for meta-analysis. Details of the remaining study[191] are shown in *Table 25*. Although inadequate reporting means the results are difficult to interpret, active treatment appeared to result in improved outcomes in the second year of treatment.

The six studies[25,189,190,192,196,200] included in the meta-analysis represented a total of 690 patients who received active treatment and 704 receiving placebo (*Figure 8*). Combined SMD was –0.40 (95% CI –0.55 to –0.25; $p<0.00001$) in favour of SLIT. Some heterogeneity between studies was indicated, but this was not statistically significant.

TABLE 24 Sublingual immunotherapy vs placebo, subgroup analyses: MSs

Subgroup	No. of	Total *n*	SMD (IV, random, 95% CI)	Comparison with CR
Age group				
Adults	27	2604	–0.35 (–0.47 to –0.23)	Similar
Children	8	1175	–0.08 (–0.25 to 0.08)	ES smaller; remained non-significant
Duration (months)				
<6	14	1517	–0.33 (–0.47 to –0.19)	Similar
6–12	13	1223	–0.31 (–0.53 to –0.08)	Similar
>12	8	1039	–0.16 (–0.31 to –0.01)	69% increase *n*; ES smaller, but remained significant
MAC				
<5μg	5	194	–0.63 (–1.08 to –0.18)	Similar
5–20μg	12	2285	–0.18 (–0.30 to –0.05)	Similar
>20μg	10	708	–0.26 (–0.47 to –0.06)	ES similar; however, became statistically significant
Allergen				
Grass	19	3028	–0.20 (–0.32 to –0.08)	31% increase in *n*; ES similar
Ragweed	3	244	–0.34 (–0.60 to –0.09)	ES similar; however, became statistically significant
Parietaria	4	124	–0.49 (–0.85 to –0.13)	No new studies; one study from CR excluded;[34] ES smaller, but remained statistically significant
Tree	9	380	–0.38 (–0.62 to –0.13)	Data as per CR

CR, Cochrane review; ES, effect size; IV, inverse variance.

TABLE 25 Symptom and medication score results: studies not in meta-analysis

Study ID	Results
Fujimura 2011[191]	Data presented in graphical form only; summary statistic used unclear. No apparent difference in scores between treatment groups during first pollen season, but in second season better scores were reported in the active group

Moderate effect sizes favouring active SLIT were found in all subgroup analyses conducted (*Table 26*), and these were similar between studies. Combined SMD in the two studies[190,191] lasting between 6 and 12 months was larger but a high degree of heterogeneity was indicated and this result was not statistically significant. Only one study[189] conducted in children ($n = 307$) reported SMS and, therefore, meta-analysis was not possible. However, SMD for this study favoured active treatment and was statistically significant. Only one study[190] was conducted using <5μg of major allergen and in *Alternaria* allergy, and only one study[196] used >20μg of major allergen and was conducted in ragweed. Meta-analyses were, therefore, not possible in these subgroups. However, both of these studies[190,196] favoured active treatment. No studies of SLIT for tree allergy reported usable data and no new studies were conducted in *Parietaria* allergy.

Quality of life

Eight studies[25,102,112,189,191,192,200,202] reported QoL data (three from Cochrane review,[102,112,200] five new[25,189,191,192,202]). All assessed QoL using versions of the disease-specific RQLQ.

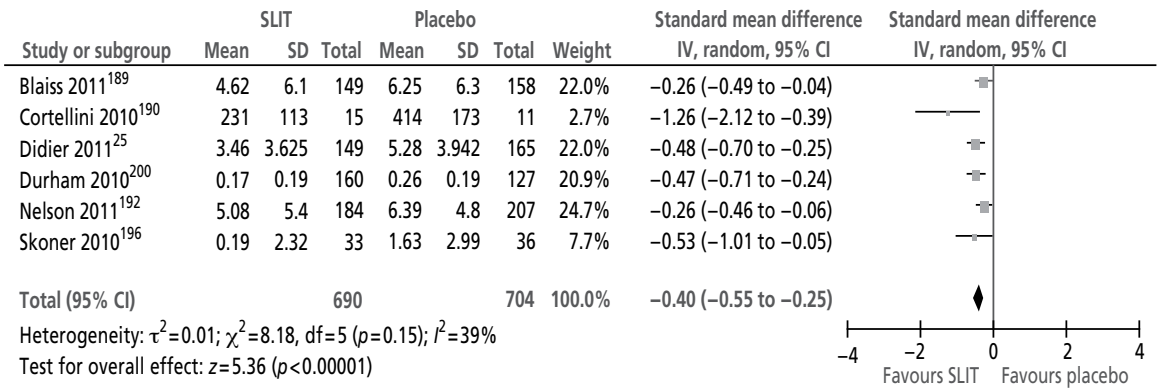

FIGURE 8 Sublingual immunotherapy vs placebo: SMSs.

TABLE 26 Sublingual immunotherapy vs placebo, subgroup analyses: SMSs

Subgroup	No. of studies	Total *n*	SMD (IV, random, 95% CI)
Age group			
Adults	5	1087	–0.44 (–0.62 to –0.27)
Duration (months)			
<6	2	376	–0.31 (–0.51 to –0.11)
6–12	2	417	–0.66 (–1.63 to 0.30)
>12	2	601	–0.48 (–0.64 to –0.31)
MAC			
5–20 μg	3	985	–0.32 (–0.45 to –0.19)
Allergen			
Grass	4	1299	–0.36 (–0.48 to –0.24)

IV, inverse variance.

Seven studies[25,102,189,192,200,202] suitable for meta-analysis included 927 active and 951 placebo patients in total, a 473% increase from the Cochrane review (*Figure 9*). Nevertheless, the effect size (SMD –0.37; 95% CI –0.52 to –0.22; $p<0.00001$) was very similar to that in the earlier review (SMD –0.42; 95% CI –0.73 to –0.12; $p=0.0063$). Heterogeneity between studies was reduced, but remained significant ($\chi^2=14.62$; $p=0.02$; $I^2=59\%$).

Summary of subgroup analyses are shown in *Table 27*.

One[189] of the new studies reported the first QoL results for children and adolescents, and these were statistically significant in favour of SLIT. Subgroup analysis of the remaining six studies[25,102,112,192,200,202] did not lead to significantly different results from those reported above.

Four[102,112,189,202] of the seven studies[25,102,112,189,192,200,202] reporting QoL data lasted for <6 months. Subgroup analysis found a moderate effect size in favour of SLIT, although heterogeneity between these studies was high ($\chi^2=11.54$, $p=0.009$, $I^2=74\%$). One study[192] was of between 6 and 12 months duration and, therefore, meta-analysis of this subgroup was not performed; however, the SMD was small and failed to reach statistical significance. In contrast, two studies[25,200] presented data from trials lasting >12 months,

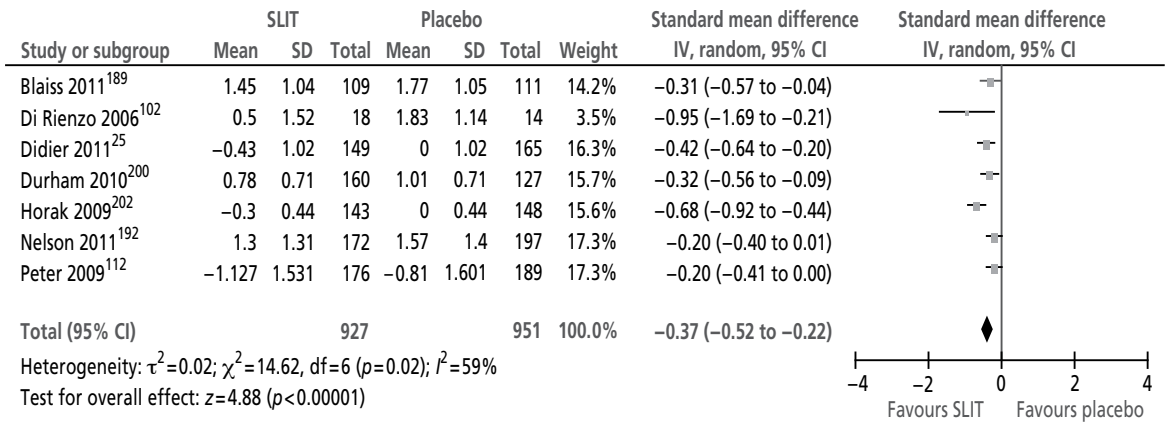

FIGURE 9 Sublingual immunotherapy vs placebo: QoL.

TABLE 27 Sublingual immunotherapy vs placebo, subgroup analyses: QoL

Subgroup	No. of studies	Total *n*	SMD (IV, random, 95% CI)
Age group			
Adults	6	1658	–0.37 (–0.52 to –0.22)
Duration (months)			
<6	4	908	–0.45 (–0.74 to –0.17)
>12	2	601	–0.37 (–0.54 to –0.21)
MAC			
5–20 μg	2	507	–0.32 (–0.49 to –0.14)
>20 μg	2	323	–0.70 (–0.93 to 0.48)

IV, inverse variance.

comprising a total of 601 participants. These longer studies[25,200] reported a moderate effect size for QoL, which was statistically significant and no between-study heterogeneity was detected ($I^2 = 0\%$).

None of the studies included in the meta-analysis used vaccines with <5 μg MAC. Two studies each used medium and high doses, and results are suggestive of a positive correlation between dose and effect size, although, given the small number of studies involved, particularly at the higher dose, these results should be interpreted with caution.

Four of the included studies[25,102,200,202] used the full version of the disease-specific RQLQ to measure QoL, and random-effect meta-analysis was conducted for these studies (*Figure 10*). Two studies[182,192] used alternate versions of the RQLQ (age-specific or standardised activities), which do not use the same scale or domains as the original, and these could therefore not be included in the meta-analysis. It was not possible to identify the instrument used in one study.[112]

Weighted MD indicated an overall reduction in RQLQ scores of 0.34 units in the active SLIT group, indicating a positive effect of treatment.

One study[191] did not present data in a manner suitable for meta-analysis (*Table 28*), but active treatment resulted in significantly improved QoL scores compared with placebo during the second year of treatment.

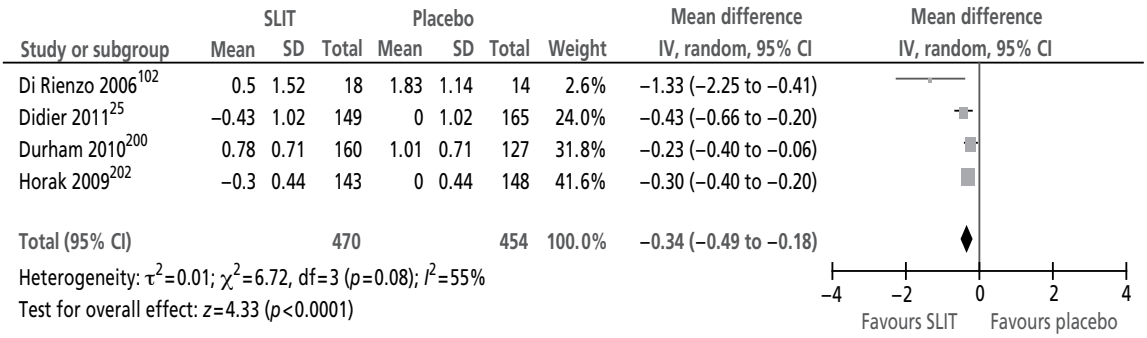

FIGURE 10 Sublingual immunotherapy vs placebo: QoL (RQLQ scores).

TABLE 28 Quality-of-life results: studies not in meta-analysis

Study ID	Results
Fujimura 2011[191]	Data presented in graphical form only; summary statistic used unclear. Total scores on the Japanese Allergic Rhinitis QoL Standard Questionnaire No. 1 were significantly better in the active group ($p<0.01$) during the second pollen season. Data are not presented for the first pollen season

Other clinical outcomes

Five of the recent SLIT studies[189,192,195,197,202] reported additional clinical outcomes, as did the updates from the GT–08[200] and Didier 2007[24] trials (*Table 29*). All trials reported that active treatment resulted in significantly better AR symptom control. Asthma SSs tended to be lower in actively treated patients, but the use of asthma medication appeared to be significantly lower in active groups. In addition, active SLIT may reduce the severity of asthma during the pollen season. One study[195] reported no significant differences between active treatment in terms of medication use, spirometry or global assessment. This trial[195] was of quite short duration, lasting only for 8–10 weeks, with treatment initiated during the pollen season. No studies reported development of new cases of asthma.

Adverse events

Again, reporting of AEs was highly variable between studies, making comparisons difficult. It should be noted that SLIT is usually self-administered outside the clinic, and thus AE reporting will depend on non-clinical judgement and patient recall.[134] Only one[158] of the 11 new RCTs did not report AE data.

Overall, the incidence of AE was quite high, with 65% (420 out of 646) of patients receiving active treatment experiencing at least one AE, compared with 42% (194/467) of patients receiving placebo in the six trials[25,189,193,195–197] that reported on AEs. The most commonly reported local reactions were itching, swelling and burning in the oral cavity. Four trials[189,190,192,194] (total $n = 890$) reported oral pruritus in 39% of active and 5% of placebo patients; two trials[189,192] (total $n = 782$) reported throat irritation in 33% of active patients compared with 4% of control patients, and mild erythema in 11% of active patients compared with 1% of control patients; and three trials[189,192,194] (total $n = 863$) reported oral paraesthesia in 10% of SLIT patients compared with 2% of placebo patients, and mouth oedema in 9% of SLIT patients compared with 1% of placebo patients. The numbers of events were generally not reported.

Six trials[88,189,192,194,195,208] reported systemic events by severity (*Table 30*). The vast majority (73%) of systemic AEs in these trials were of mild intensity, 24% were of moderate intensity and 3% were graded as severe. Anaphylaxis was reported in two trials[192,195] and occurred in 4 of 427 patients receiving active treatment and in none of 282 patients receiving placebo. Only two trials[189,192] (total $n = 782$) reported on adrenaline use. In each study, one instance of an AE in response to SLIT administration was treated with adrenaline. In both cases, the patients were receiving active treatment. Two instances of hospitalisation were reported,[88,208] both for asthma attacks.

TABLE 29 Sublingual immunotherapy: other clinical outcomes

Study ID	Results
Blaiss 2011[189]	*Effects on asthma*: Both treatment groups (asthmatic subjects: $n = 46$ active, $n = 44$ placebo) reported low mean daily asthma SSs during the pollen season – 0.86 vs 1.08, respectively, out of a maximum of 12 (21% lower in the active group). The difference was not statistically significant
Didier 2011[25]	*Proportion SMFD*: Active group ($n = 188$) experienced mean 37.9% SMFD vs 26.4% in placebo group ($n = 205$)
Durham 2010[200]/2011[129]	*Proportion SMFD*: After third treatment-year, subjects in active group experienced a mean 34.1% SMFD, compared with 24.1% in placebo group ($p = 0.0035$). This difference remained at the 1-year follow-up, with 35.2% vs 27.6% SMFD in the two groups, respectively ($p = 0.0384$) *No. of severe days*: Severe days defined as having a maximum score on at least two of four nasal SSs measured; maximum score on at least one of two ocular SSs; or an overall SS >9 out of a maximum 18. Mean number of severe days was 55.3% lower in Grazax-treated patients than in placebo; it is unclear to which time point or period this figure refers
Horak 2009[202]	*Global assessment*: Patient global assessment after first pollen season, compared with pre-treatment season, was significantly better than placebo ($p < 0.0001$). Details of assessment and absolute values not reported
Nelson 2011[192]	*Effects on asthma*: Both treatment groups (asthmatic subjects: $n = 44$ active, $n = 59$ placebo) reported low mean daily asthma SSs over the EPS – 0.84 vs 1.10, respectively, out of a maximum of 12 (24% lower in the active group, $p = 0.04$). During the PPS, the difference between the groups was not statistically significant. However, the mean daily asthma MSs were 46% lower in the active than the placebo group ($p = 0.01$). In addition, only two patients in the actively treated group required treatment for worsening asthma (defined as four or more inhalations of short-acting β_2-agonist per day, at any time) compared with 13 patients in the placebo group. The number of patients requiring initiation of treatment with inhaled corticosteroids during the pollen season was similar between the groups – six patients in the active group and five patients in the placebo group
Reich 2011[195]	*Use of rhinitis/asthma rescue medication*: Use of rescue medication was similar between treatment groups – 176 out of 219 (81%) active and 51 out of 57 (89%) placebo subjects used allergy or asthma medication. Number of days with medication during the 10-week trial were 34.9 and 37.5 days, respectively *Spirometry:* No pronounced changes in FEV_1 occurred during the trial in either group *Global evaluation*: 'Compared to your rhinoconjunctivitis symptoms in the previous grass pollen season, how have you felt overall in this grass pollen season: much worse, worse, the same, better, much better?' Results were similar between the treatment groups: 68% active and 72% placebo patients reported improvements (better/much better); no change was reported in 28% and 26% of patients, respectively; only 4% (9/219) active and 2% (1/57) placebo patients felt worse or much worse
Voltolini 2010[197]	*Days with asthma*: During the second pollen season, reduction in the median number of days with asthma from visit three to visit six was much greater in the active than placebo group – from 10 (range 0–27) to 2 (0–6) days in the active group compared with 13 (0–29) to 7 (0–15) days in the placebo group (difference between groups, $p < 0.05$) *Asthma severity*: Ten of the thirteen active patients stepped down an asthma severity grading level (GINA criteria) following treatment, compared with none of the nine placebo patients

FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; SMFD, symptom- and medication-free day.

TABLE 30 Adverse systemic events in SLIT: severity and withdrawals

Severity of reaction	No. of studies reporting	SLIT		Placebo	
		n	No. of events	*n*	No. of events
Mild	5	669	830	458	314
Moderate	5	669	253	458	129
Severe	6	744	30	498	12
AEs leading to study withdrawal	5	879	30	686	14

Five trials[25,189,192,194,195] reported a total of 20 SAEs in a total of 1565 study participants, of which only one, abdominal pain in a placebo-treated patient, was considered likely to be treatment related.

Only four small trials[107,118,175,209] (total active $n = 107$) reported on treatment of AEs. Based on this small data set, 109 out of 1000 (11%) AEs required treatment, whereas 891 out of 1000 (89%) resolved spontaneously without treatment. This includes both local and systemic reactions, which were usually not reported separately. Most reports did not specify the nature of treatment required but based on one study[209] ($n = 43$) the most commonly used treatments were salbutamol [used in 49% of cases (73 out of 149 treated AEs)] and analgesics (used in 40% of treated cases). Antiseptics, cold sore medication cold medication and glucocorticoids made up only 9% of all treatments between them. Details of adrenaline administration and hospitalisations are noted above.

Five studies[189,190,192,194,195] reported discontinuations due to AEs. Thirty patients (3.4%) out of a total of 879 receiving active treatment were withdrawn for this reason. This number is similar to the 5% withdrawal rate reported in the Cochrane review.

Summary of findings: sublingual immunotherapy

A summary is shown below in *Box 2*.

Quantity of evidence sublingual immunotherapy compared with subcutaneous immunotherapy

Searches identified only one randomised, double-blind, double-dummy comparison study[210] of SLIT with SCIT ($n = 71$). Three further studies[158,211,212] were initially identified as potentially relevant, but were subsequently excluded. One study[158] ($n = 40$) was not a double-blind, double-dummy comparison; it included a comparison of SCIT with placebo and SLIT with placebo but no adequately blinded direct comparison of SCIT with SLIT, and results for SLIT compared with SCIT were not reported (this study is included in the relevant sections on placebo-controlled studies in this report). A second study[211] ($n = 47$) compared a SLIT with a SCIT treatment arm, but there was no blinding (no treatment with placebo). Finally, a small, double-blind, double-dummy study ($n = 20$) by Quirino *et al.*[212] used 10 'matched pairs' and does not appear to have used random allocation. The three studies that reported results for SCIT

BOX 2 Summary of findings: SLIT

- Treatment with SLIT resulted in statistically significant reductions in symptom, medication and SMSs compared with placebo, and these effects were largely unrelated to participant age, treatment duration or type of allergen. SMD for SS improvement was not statistically significant in SLIT with *Parietaria* allergen, but this was based on only four studies[86,99,111,116] (total $n = 124$). MSs were not significantly improved in paediatric patients compared with placebo (eight studies,[26,84–86,88–90,174] total $n = 1175$)
- Seven trials (total $n = 1878$) reported on QoL. Overall, SLIT had a statistically significant effect on QoL. Six of these trials[25,112,190,192,200,202] were conducted in adults and there remains a shortage of paediatric QoL data; the one study[189] in children reported a statistically significant difference in favour of SLIT
- SLIT also appeared to result in better overall symptom control compared with placebo, and may reduce asthma severity and medication requirements
- AEs were relatively common and more frequent in patients receiving active treatment. Local reactions in the oral cavity were the most frequently reported event and the majority of systemic reactions were of mild or moderate severity. Only one serious AE deemed to be treatment related occurred in five trials[25,189,192,194,195] reporting this outcome (total $n = 1565$). Two trials[192,195] (total $n = 709$) reported on anaphylaxis, which occurred in 0.9% patients receiving active treatment, compared with none receiving placebo. Two trials[189,192] (total $n = 782$) reported on adrenaline use, which was required for only one treatment-related event; this event occurred in a patient receiving active SLIT. Discontinuations due to AEs occurred in 3.4% of participants receiving active treatment in five trials[189,190,192,194,195] reporting this outcome (SLIT $n = 879$)

compared with SLIT found no significant differences between the two. Results for the one study[210] meeting inclusion criteria are reported in more detail below.

Main study characteristics sublingual immunotherapy compared with subcutaneous immunotherapy

The main study and population characteristics of the included study, and the assessment of risk of bias are detailed in *Appendix 5*.

The main characteristics are summarised in *Table 31*.

Results of the risk of bias assessment are summarised in *Table 32* (full details are given in *Appendix 5*).

As in many of the placebo-controlled studies, details of randomisation and blinding are reported but a lack of detail on other aspects of quality make it difficult to judge the overall quality.

Effectiveness of subcutaneous immunotherapy compared with sublingual immunotherapy

Results were reported for SSs, MSs, QoL and AEs and are summarised below (*Box 3*). Results were not presented in a way that is consistent with most other RCTs in this area, in that absolute mean SSs or MSs post treatment are not presented; instead median changes relative to the preceding pollen season are given. Nevertheless, the findings are consistent with other studies showing a benefit in terms of symptoms and MSs with both SCIT and SLIT compared with placebo. No significant differences between SLIT and SCIT groups were identified in this small study.[210] This does not mean that such differences do not potentially exist.

Indirect comparison of subcutaneous immunotherapy with sublingual immunotherapy

Given the paucity of direct comparisons (head-to-head trials) between SCIT and SLIT, it was decided to undertake an indirect comparison of SCIT with SLIT using data from the separate meta-analyses of SCIT compared with placebo and SLIT compared with placebo. Indirect comparison analyses rely on the assumptions (explored below) that there is sufficient similarity both within the SCIT compared with placebo and the SLIT compared with placebo trials (homogeneity assumption[138]), and that the true treatment effect comparing any two interventions would be similar across all trials, irrespective of whether they included one or both of those interventions (similarity assumption[138]).

The direct (head-to-head) evidence from the one small SCIT compared with SLIT trial[210] included in this report could not be incorporated into this analysis, as the outcomes were not reported in a way that would allow this.

This section presents the most relevant results of the statistical analysis. The full list of parameter estimates and modelling approach is reported in *Appendix 3*.

Homogeneity assumption

For both SCIT compared with placebo and SLIT compared with placebo trials, heterogeneity was explored qualitatively by looking at patient and study characteristics, and statistically through meta-analysis (with I^2 giving an indication of the extent of heterogeneity). Where reported, inclusion criteria were very similar across trials and it is likely that included populations had similar severity of AR. There was also not much variation in asthma rates where these were reported. All studies excluded patients with severe or perennial asthma. There was variation between trials in trial duration and type and amount of allergen. There was statistical evidence of moderate heterogeneity in the meta-analyses for some outcome measures (I^2 of 57% for SS and MS for SCIT compared with placebo; I^2 of 59% for QoL for SLIT compared with placebo). Statistical heterogeneity was less than moderate for the other outcome measures.

TABLE 31 Main study characteristics: SLIT vs SCIT studies

Study	Size	Previous SIT	Stated that symptoms moderate to severe	Patients with asthma allowed or included	Type of allergen	Administration schedule SCIT	Administration schedule SLIT	Outcomes
Khinchi 2004[210]	$n = 71$	No SIT within last 5 years	No, but stated that rhinoconjunctivitis uncontrolled by conventional pharmacotherapy	No details	Birch	Twelve-week induction phase (weekly injections) with 0.0164μg; monthly maintenance phase 3.28μg	Thirty-day induction phase, maintenance phase 21–23 months. Drops every other day held under tongue for 2 minutes. Dose between 0.0164 and 49.2μg	SSs, MSs, QoL, AEs

TABLE 32 Risk of bias assessment: SCIT vs SLIT studies

Study	Sequence generation	Allocation concealment	Blinding	Data completeness	Selective reporting	Patients treatment naive
Khinchi 2004[210]	+	?	+	?	?	?

+, low risk; –, high risk; ?, unclear.

BOX 3 Subcutaneous immunotherapy vs SLIT: SSs and MSs

Results

Rhinoconjunctivitis SSs

Method 1: subtraction of pre-treatment values from treatment season values

Median rhinoconjunctivitis SS (0–3 scale) improved by 0.36 score points (95% CI 0.18 to 0.86) in the SLIT arm, by 0.75 score points (95% CI 0.02 to 1.31) in the SCIT arm and decreased by 0.2 score points (95% CI –1.05 to 0.22) in the placebo arm. Significant difference in change between SLIT/SCIT and placebo (both $p<0.002$). No significant difference in change between SLIT and SCIT

MSs

Method 1: subtraction of pre-treatment values from treatment season values

Median MS increased by 0.29 score points (95% CI –2.57 to 0.82) in the SLIT arm, were unchanged in the SCIT arm (95% CI –1.52 to 2.65) and increased by 1.35 score points (95% CI –4.04 to 0.12) in the placebo arm. Significant difference in change between SLIT/SCIT and placebo ($p<0.02$ and $p<0.002$, respectively). No significant difference in change between SLIT and SCIT

Rhinoconjunctivitis SSs

Method 2: values of first treatment season relative to pre-treatment season

Deterioration in SS by a factor of 1.45 (95% CI 0.87 to 2.09) in placebo group compared with an improvement in the SLIT group (by a factor of 0.78; 95% CI 0.6 to 1.06, $p<0.01$) and the SCIT group (by a factor of 0.48; 95% CI 0.28 to 1.02, $p<0.001$). No significant difference between SLIT and SCIT groups

MSs

Method 2: values of first treatment season relative to pre-treatment season

Increase in MS by a factor of 2.01 (95% CI 1.02 to 3.56) in placebo group compared with a change by a factor of 1.03 (95% CI 0.77 to 1.75; $p<0.05$) in the SLIT group and a decrease by a factor of 0.78 (95% CI 0.3 to 2.0, $p<0.02$) in the SCIT group. No significant difference between SLIT and SCIT groups

Similarity assumption

This was explored qualitatively. Overall, patient characteristics appeared to be similar between SCIT and SLIT populations (in terms of SAR history, severity, prior experience of SIT and prevalence of asthma). There was variation between trials in trial duration and type and amount of allergen. An attempt was made to assess whether placebo rates between SCIT and SLIT populations were similar. If populations are comparable, then placebo rates could also be expected to be similar. In this particular set of trials, placebo is administered in different ways (sublingual or subcutaneous) and given at different frequencies (daily for

sublingual and weekly, then monthly for subcutaneous). There is evidence from different clinical areas that placebo rates may differ according to how the placebo is administered.[213]

Although clinical opinion suggests that placebo rates between SCIT and SLIT are likely to be comparable (Stephen Durham, Imperial College London, 2 March 2012, personal communication), placebo rates could not be compared directly between SLIT and SCIT trials owing to (1) the use of different outcome measures and (2) the fact that any differences between baseline and follow-up measures are likely to differ between studies conducted at different times and in different geographical areas owing to variations in pollen count. However, failing to make this assumption would have precluded any indirect comparison analysis.

Given that there was some evidence of heterogeneity, a number of variables (treatment duration and type and amount of allergen, as well as age of participants – adults or children) were explored and adjusted for using ICMR.

A random-effects model was a better fit for the data and was therefore used in all further modelling (see *Appendix 3* for methodology and full results). Standardised score differences were calculated and indicate the difference in effect size between SCIT and SLIT; positive values favour SCIT and negative values favour SLIT. When interpreting results, the 95% credible intervals (CrIs) need to be considered,[214] with wider intervals indicating greater uncertainty. Best estimate probabilities were also presented. These show the probability of either SLIT or SCIT being the best treatment; however, the probability does not give any information on how much better one treatment is likely to be (i.e. they are not a measure of effectiveness). Note that even where there is a very high probability of one treatment being best, the 95% CrIs around the pooled standardised score differences may include zero and the results will therefore not be statistically significant.

According to the DIC measure, random-effects modelling fitted the data better than fixed-effects modelling (see *Appendix 3*), indicating a degree of unexplained heterogeneity in the data. Therefore, only results from random-effects modelling are presented in the following sections.

Symptom scores

When covariates were not included in the model (unadjusted model), the standardised score difference was 0.351 (95% CrI 0.127 to 0.586), a statistically significant result in favour of SCIT. Probabilistic analysis suggests that SCIT has a greater probability of being the best treatment compared with SLIT overall (unadjusted model) and also when participant age, study duration, MAC and type of allergen are accounted for (*Table 33*). However, not all the standardised score differences were statistically significant. For *Alternaria* allergy, the best estimate probability suggests that SLIT is the preferred treatment; however, this is based on only a single study for each intervention and a non-significant standardised score difference. Residual heterogeneity in the model could not be accounted for by participant age or type of allergen, while including MAC as a covariate reduced heterogeneity slightly (as shown by a decrease in σ^2).

The ICMR model included comparisons where there were no studies (no data) in either the SCIT or the SLIT arm (e.g. no SCIT trials for ragweed compared with three SLIT trials[95,97,196] for ragweed); here the extremely large CrIs around the standardised score difference reflect the uncertainty resulting from this absence of data.

In order to explore unexplained residual heterogeneity further, two post hoc meta-regressions were conducted. In the first analysis, year of publication was used as a covariate in the model, and a strong effect for year was identified. An improvement in the fit of the model to the data was also observed (DIC 502, compared with 508 for the null model) and the heterogeneity parameter estimate was also lower [σ^2 0.067 (95% CrI 0.017 to 0.147) compared with 0.089 (95% CrI 0.027 to 0.187), respectively].

Figure 11a shows pooled SMD point estimates for placebo-controlled trials and suggests that results from older studies show a greater benefit for SCIT, with more recent studies finding a decreasing benefit (more

TABLE 33 Indirect comparison of SSs: probabilistic analysis and random-effects meta-regression of SCIT vs SLIT under different modelling conditions

Covariate	SCIT, no.of trials (A/P)	SLIT, no. of trials (A/P)	Probability that treatment is best (%)			ICMR SCIT compared with SLIT	
			Placebo	SCIT	SLIT	Standardised score difference (95% CrI)	Heterogeneity, σ^2 (95% CrI)
None	17 (659/529)	42 (2440/2379)	00.0	99.9	00.1	0.351 (0.127 to 0.586)	0.089 (0.027 to 0.586)
Age group							
Adult	16 (634/506)	33 (1768/1708)	00.0	99.6	00.4	0.328 (0.088 to 0.579)	0.091 (0.028 to 0.192)
Child	1 (25/23)	9 (672/671)	00.9	54.9	44.2	0.059 (–0.837 to 0.966)[a]	
Trial duration (months)							
<6 months	5 (136/138)	15 (942/940)	00.0	>99	00.0	0.822 (0.379 to 1.299)	0.1112 (0.040 to 0.221)
6–12	2 (203/106)	15 (759/780)	00.0	80.1	19.9	0.252 (–0.357 to 0.862)[a]	
>12	8 (227/215)	12 (739/659)	00.0	83.4	16.6	0.187 (–0.199 to 0.577)[a]	
MAC (μg)							
<5	3 (112/116)	6 (118/111)	00.0	47.4	52.6	–0.016 (–0.516 to 0.483)[a]	0.053 (0.005 to 0.13)
5–20	5 (117/114)	13 (1163/1124)	00.0	92.0	08.0	0.262 (–0.108 to 0.634)[a]	
>20	3 (222/119)	12 (564/524)	00.0	99.7	00.3	0.582 (0.167 to 1.060)	
Type of allergen[b]							
Grass	9 (295/257)	25 (2050/1995)	00.0	99.4	00.6	0.396 (0.090 to 0.721)	0.096 (0.030 to 0.20)
Parietaria	3 (227/126)	4 (60/64)	00.0	99.1	00.9	0.775 (0.140 to 1.446)	
Ragweed	0 (0/0)	3 (118/126)	01.2	50.0	48.8	0.011 (–197.0 to 196.70)[a]	
Tree	4 (112/123)	9 (197/183)	00.0	64.3	35.7	0.092 (–0.408 to 0.597)[a]	
Alternaria	1 (25/19)	1 (15/11)	00.1	04.6	95.3	–1.133 (–2.460 to 0.199)[a]	

A, number of patients receiving active treatment; P, number of patients receiving placebo.

a Not statistically significant.

b One study[91] had separate arms for tree and grass allergens.

negative SMD values indicate a greater improvement in SSs compared with placebo). In contrast, SMD estimates for SLIT compared with placebo appear to remain more stable over time. The ICMR with year as a covariate (*Figure 11b*) finds that from approximately 2007 there is an increased probability that SLIT is more beneficial than SCIT. Note that standardised score differences at different time points are not all statistically significant (see *Appendix 3*).

Given the huge variability in symptoms recorded between trials (see *Appendix 7* for types and numbers of symptoms scored in different trials), a second post hoc analysis was conducted to explore any effect of this variable on trial outcome. It was found that increasing numbers of symptoms being measured in a trial appeared to favour SCIT over SLIT (*Figure 12*). Again, standardised score differences are not all statistically significant (see *Appendix 3*) and residual heterogeneity increases in this analysis.

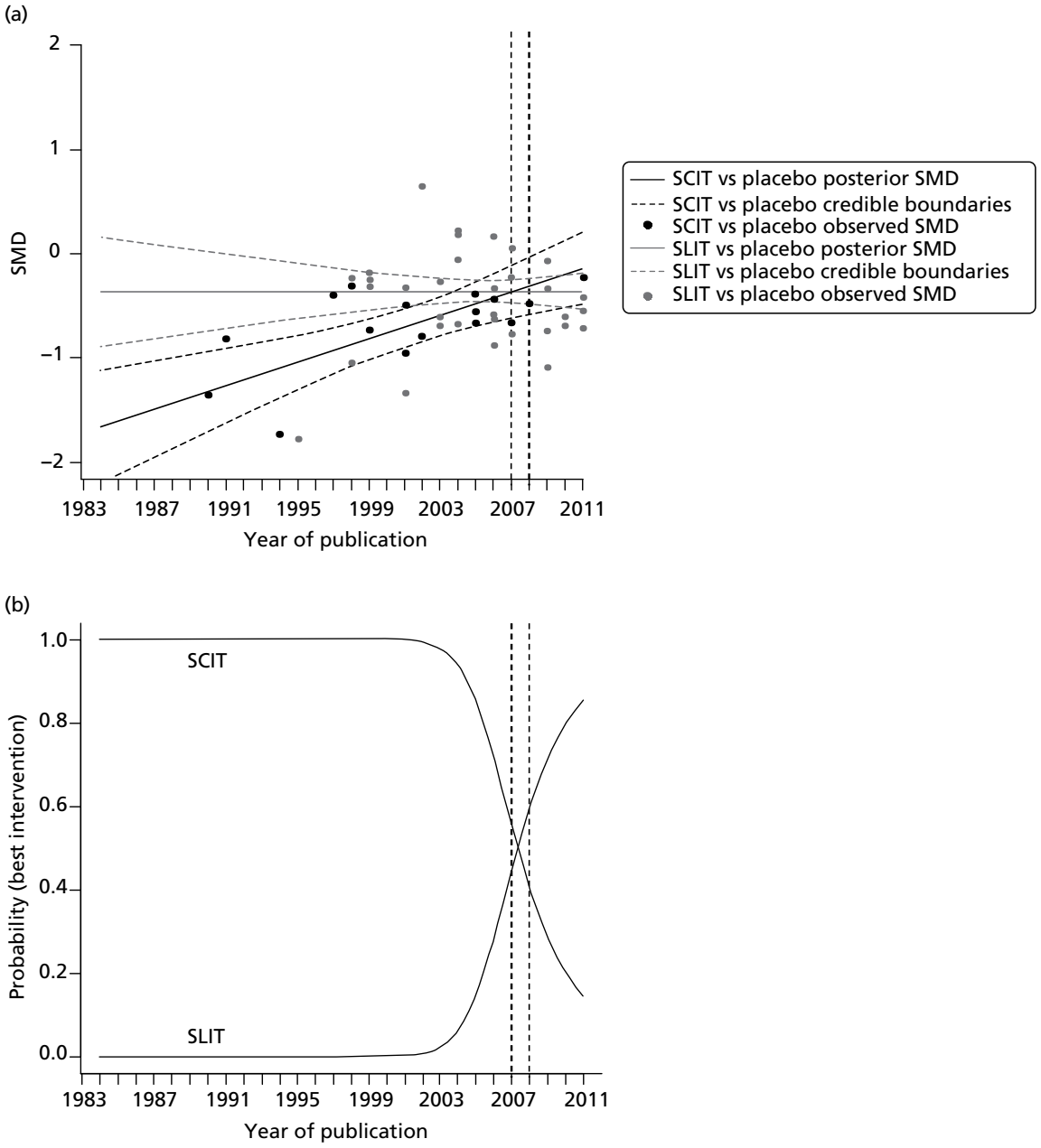

FIGURE 11 Symptoms scores: year of publication as covariate in the model. (a) theoretical and observed SMD and credible boundaries by year of publication for SCIT vs placebo and SLIT vs placebo; (b) probability of intervention being superior.

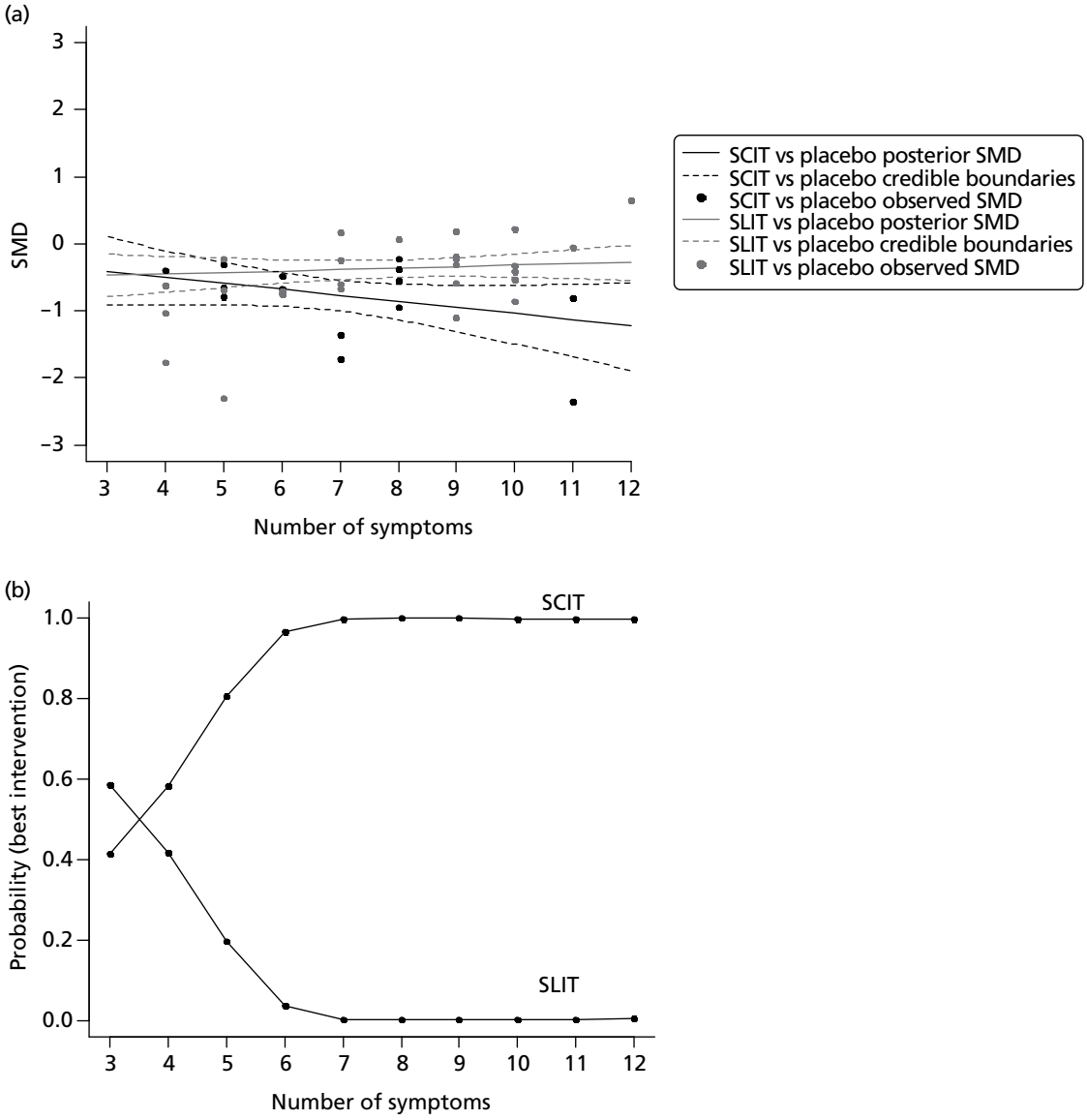

FIGURE 12 Number of symptoms measured as covariate in the model. (a) theoretical and observed SMD and credible boundaries by year of publication for SCIT vs placebo and SLIT vs placebo; (b) probability of intervention being superior.

Medication scores

The unadjusted model (no covariates included), found a standardised score difference of 0.273 (95% CrI 0.027 to 0.529) in favour of SCIT (*Table 34*). This was associated with a >99% chance of SCIT being the best treatment. Where meta-regressions resulted in standardised score differences in favour of SLIT, these were not statistically significant. It appears that some of the heterogeneity could be reduced by introducing MAC and particularly age (adult/child) as a covariate.

As for SSs above, adjusting for year of publication found changes in benefit from SCIT and SLIT over time, although the effect was not as pronounced and more difficult to interpret (*Figure 13*).

Symptom and medication scores

No significant difference between SCIT or SLIT could be shown in this analysis (*Table 35*), and this is associated with a large degree of uncertainty, as reflected in the wide CrIs. The combined SMS may be seen as a more robust outcome measure compared with the SS or MS alone, and this analysis could

TABLE 34 Indirect comparison of MSs: probabilistic analysis and random-effects meta-regression of SCIT vs SLIT under different modelling conditions

			Probability (%) that treatment is best			ICMR SCIT vs SLIT	
Covariate	SCIT, no.of trials (A/P)	SLIT, no. of trials (A/P)	Placebo	SCIT	SLIT	Standardised score difference (95% CrI)	Heterogeneity, σ^2 (95% CrI)
None	16 (621/483)	35 (1934/1845)	00.0	>99	00.0	0.273 (0.027 to 0.529)	0.099 (0.030 to 0.211)
Age group							
Adult	15 (596/464)	27 (1353/1251)	01.8	43.1	55.1	–0.009 (–0.124 to 0.106)[a]	0.002 (0.001 to 0.005)
Child	1 (25/19)	8 (581/594)	00.0	68.1	31.9	0.009 (–0.031 to 0.050)[a]	
Trial duration (months)							
<6	2 (69/74)	14 (766/751)	00.0	50.9	49.1	0.006 (–0.634 to 0.634)[a]	0.120 (0.039 to 0.255)
6–12	3 (215/118)	13 (609/614)	00.0	75.6	24.3	0.192 (–0.376 to 0.750)[a]	
>12	3 (244/225)	8 (559/480)	00.0	99.1	00.9	0.511 (0.094 to 0.950)	
MAC (μg)							
<5	2 (71/76)	5 (98/96)	00.0	15.1	84.9	–0.286 (–0.849 to 0.266)[a]	0.042 (0.006 to 0.108)
5–20	6 (129/126)	12 (1167/1118)	00.0	95.3	04.7	0.283 (–0.049 to 0.622)[a]	
>20	2 (203/102)	10 (383/325)	00.0	90.4	09.6	0.298 (–0.164 to 0.765)[a]	
Type of allergen[b]							
Grass	8 (263/220)	19 (1544/1461)	00.0	99.8	00.2	0.504 (0.169 to 0.873)	0.094 (0.024 to 0.209)
Parietaria	2 (209/109)	4 (60/64)	00.1	42.1	57.9	–0.068 (–0.761 to 0.619)[a]	
Ragweed	1 (11/12)	3 (118/126)	00.8	67.8	31.4	0.251 (–0.809 to 1.325)[a]	
Tree	4 (113/123)	8 (197/183)	00.0	43.0	57.0	–0.45 (–0.550 to 0.453)[a]	
Alternaria	1 (25/35)	1 (15/11)	00.0	18.0	82.0	–0.608 (–1.933 to 0.710)[a]	

A, number of patients receiving active treatment; P, number of patients receiving placebo.

a Not statistically significant.

b One study[91] had separate arms for tree and grass allergens.

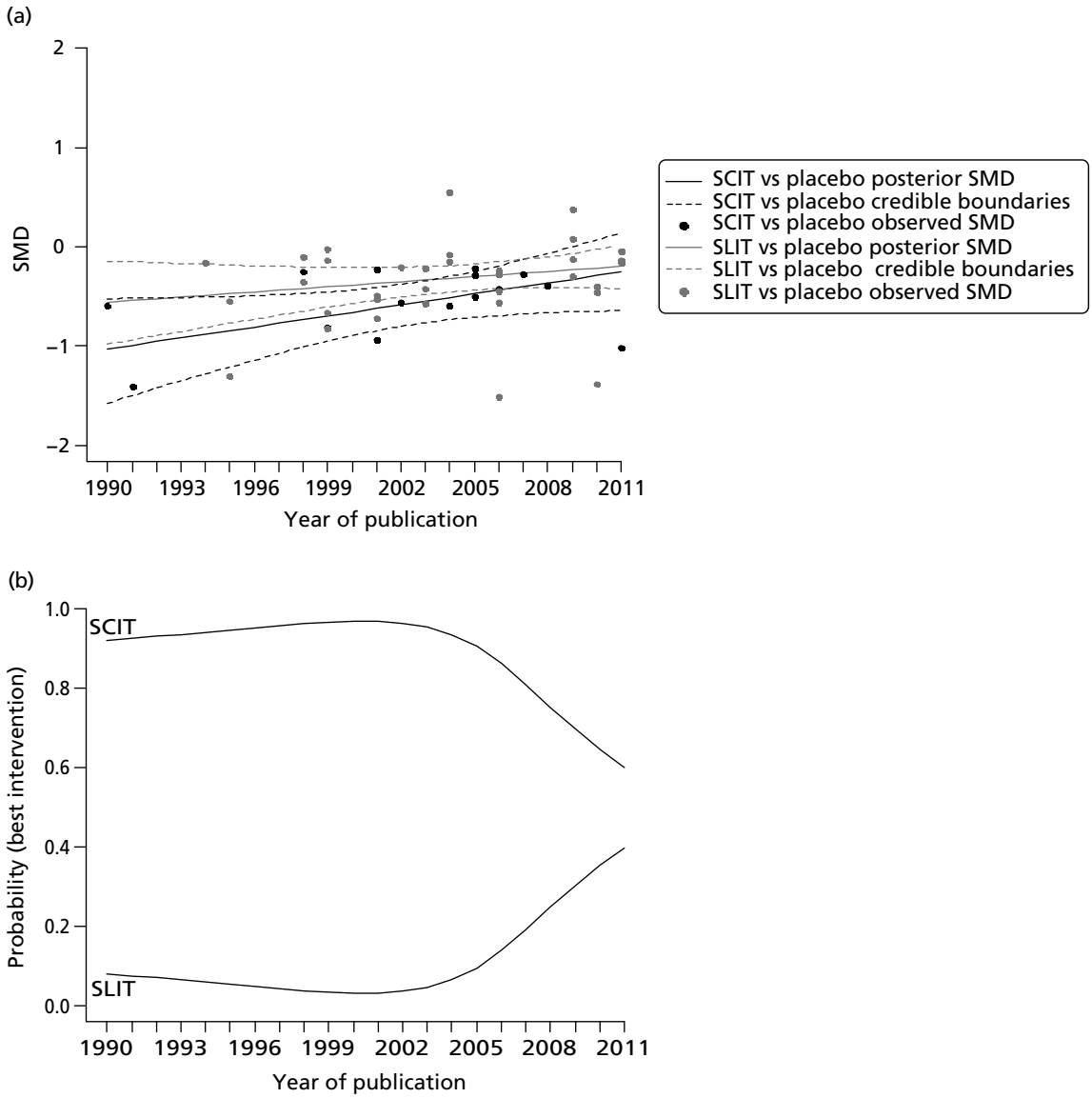

FIGURE 13 Medication scores: year of publication as covariate in the model. (a) theoretical and observed SMD and credible boundaries by year of publication for SCIT vs placebo and SLIT vs placebo; (b) probability of intervention being superior.

arguably be given more weight. Heterogeneity is lower for this analysis (compared with SSs and MSs separately) and is further reduced when type of allergen is used as a covariate.

Quality of life

Results of adjusted indirect comparison of QoL scores find that, although there is a high probability of SCIT being the best treatment, the standardised score difference is not statistically significant and is associated with a high degree of heterogeneity (*Table 36*). None of the adjusted standardised score differences are statistically significant. The analysis was repeated with trials using only the RQLQ for measuring QoL, and the result is therefore expressed as a difference in RQLQ units (*Table 37*). The results are very similar.

Discussion of the indirect comparisons

There was some evidence of heterogeneity within trials of SCIT or SLIT compared with placebo and between placebo-controlled trials. Therefore, possible sources of heterogeneity were explored through ICMR. No substantial reduction in heterogeneity when adjusting for type of allergen, allergen content

TABLE 35 Indirect comparison of SMSs: probabilistic analysis and random-effects meta-regression of SCIT vs SLIT under different modelling conditions

Covariate	SCIT, no. of trials (A/P)	SLIT, no. of trials (A/P)	Probability (%) that treatment is best			ICMR SCIT vs SLIT	
			Placebo	SCIT	SLIT	Standardised score difference (95% CrI)	Heterogeneity, σ^2 (95% CrI)
None	8 (320/297)	6 (690/704)	00.0	50.2	49.8	0.313 (–195.80 to 194.10)[a]	0.017 (0.0 to 0.086)[a]
Age group							
Adult	8 (320/297)	5 (541/546)	00.0	50.2	49.8	0.307 (–196.40 to 196.70)[a]	0.019 (0.0 to 0.097)[a]
Child	0 (0/0)	1 (159/158)	02.9	47.1	50.0	0.089 (–277.30 to 274.70)[a]	
Trial duration (months)							
<6	3 (108/113)	2 (182/194)	00.1	50.2	49.7	0.676 (–195.70 to 198.10)[a]	0.037 (0.0 to 0.210)[a]
6–12	0 (0/0)	2 (199/218)	00.5	49.8	49.8	0.583 (–274.60 to 279.40)[a]	
>12	3 (128/125)	2 (309/292)	00.0	50.4	49.6	0.874 (–276.10 to 279.20)[a]	
MAC (μg)							
<5	3 (112/116)	1 (15/11)	00.2	50.0	49.9	0.505 (–196.90 to 198.40)[a]	0.061 (0.0 to 0.338)[a]
5–20	1 (29/28)	3 (493/492)	00.7	49.2	50.0	0.148 (–278.0 to 277.80)[a]	
>20	1 (18/17)	1 (33/36)	00.2	49.8	50.0	0.843 (–276.50 to 280.90)[a]	
Type of allergen[b]							
Grass	5 (231/204)	4 (642/657)	00.0	50.3	49.7	0.623 (–194.90 to 195.70)[a]	0.011 (0.0 to 0.059)[a]
Parietaria	2 (40/37)	0 (0/0)	00.0	50.4	49.6	1.568 (–275.70 to 277.10)[a]	
Ragweed	0 (0/0)	1 (33/36)	01.0	49.5	49.5	1.189 (–278.60 to 278.40)[a]	
Tree	1 (49/56)	1 (51/37)	00.7	49.5	49.8	0.633 (–277.90 to 278.20)[a]	
Alternaria	0 (0/0)	1 (15/11)	00.1	50.3	49.7	1.341 (–274.70 to 278.70)[a]	

A, number of patients receiving active treatment; P, number of patients receiving placebo.

a Not statistically significant.

b One study[91] had separate arms for tree and grass allergens.

TABLE 36 Indirect comparison of QoL scores: probabilistic analysis and random-effects meta-regression of SCIT vs SLIT under different modelling conditions

			Probability (%) that treatment is best			ICMR SCIT vs SLIT	
Covariate	SCIT, no. of trials (A/P)	SLIT, no. of trials (A/P)	Placebo	SCIT	SLIT	Standardised score difference (95% CrI)	Heterogeneity, σ^2 (95% CrI)
None	8 (583/370)	7 (927/951)	00.0	96.4	03.6	0.383 (–0.042 to 0.804)[a]	0.132 (0.041 to 0.342)
Age group							
Adult	8 (583/370)	6 (818/840)	00.0	95.9	04.1	0.402 (–0.062 to 0.864)[a]	0.149 (0.043 to 0.402)
Child	0 (0/0)	1 (109/111)	10.5	50.0	39.5	0.161 (–196.0 to 196.40)[a]	
Trial duration (months)							
<6	1 (9/9)	4 (446/462)	01.3	92.6	06.1	0.983 (–0.363 to 2.288)[a]	0.197 (0.045 to 0.612)
6–12	1 (183/92)	1 (172/197)	02.6	76.1	21.3	0.436 (–0.872 to 1.742)[a]	
>12	6 (393/269)	2 (309/292)	00.2	66.8	33.0	0.152 (–0.617 to 0.925)[a]	
MAC (μg)							
<5	1 (21/20)	0 (0/0)	10.9	68.3	20.9	37.220 (–60.470 to 136.0)[a]	0.260 (0.015 to 1.0)
5–20	3 (241/140)	3 (269/238)	00.6	83.3	16.2	0.375 (–0.508 to 1.315)[a]	
>20	3 (246/133)	2 (161/162)	01.2	91.3	07.5	0.718 (–0.393 to 1.670)[a]	
Type of allergen[b]							
Grass	4 (331/230)	6 (909/937)	00.5	90.2	09.3	0.334 (–0.197 to 0.868)[a]	0.143 (0.038 to 0.420)
Parietaria	2 (204/112)	0 (0/0)	01.2	49.1	49.8	0.597 (–194.80 to 195.30)[a]	
Ragweed	1 (9/9)	0 (0/0)	01.5	48.9	49.6	0.933 (–194.70 to 198.0)[a]	
Tree	0 (0/0)	1 (18/14)	01.5	49.7	48.8	–0.875 (–196.70 to 194.80)[a]	
S. kali	1 (41/19)	0 (0/0)	02.5	47.8	49.7	0.622 (–195.10 to 196.60)[a]	
Alternaria	0 (0/0)	0 (0/0)	25.0	37.4	37.6	–0.283 (–275.80 to 277.0)[a]	

A, number of patients receiving active treatment; P, number of patients receiving placebo.

a Not statistically significant.

b One study[91] had separate arms for tree and grass allergens.

TABLE 37 Indirect comparison of RQLQ scores: probabilistic analysis and random-effects meta-regression of SCIT vs SLIT under different modelling conditions

			Probability (%) that treatment is best			ICMR SCIT vs SLIT	
Covariate	SCIT, no. of trials (A/P)	SLIT, no. of trials (A/P)	Placebo	SCIT	SLIT	Standardised score difference (95% CrI)	Heterogeneity, σ^2 (95% CrI)
None	8 (585/370)	4 (470/454)	00.0	96.2	03.8	0.517 (–0.071 to 1.045)[a]	0.155 (0.033 to 0.494)
Age group							
Adult	8 (585/370)	4 (470/454)	00.0	96.0	04.0	0.517 (–0.085 to 1.051)[a]	0.158 (0.033 to 0.506)
Child	0 (0/0)	0 (0/0)	24.7	37.8	37.5	0.493 (–276.0 to 278.70)[a]	
Trial duration (months)							
<6	1 (9/9)	2 (161/162)	01.5	88.9	09.6	0.950 (–0.686 to 2.364)[a]	0.226 (0.006 to 0.946)
6–12	1 (183/92)	0 (0/0)	01.9	48.3	49.8	0.536 (–194.3 to 195.2)[a]	
>12	6 (393/269)	2 (309/292)	00.1	85.8	14.0	0.374 (–0.454 to 1.228)[a]	
MAC (μg)							
<5	1 (21/20)	0 (0/0)	24.9	37.7	37.4	0.375 (–195.10 to 196.20)[a]	0.467 (0.003 to 2.323)
5–20	3 (241/140)	2 (178/141)	00.9	86.3	12.8	0.692 (–0.046 to 1.281)[a]	
>20	3 (246/133)	1 (143/148)	00.8	85.0	14.2	1.015 (–337.90 to 341.10)[a]	
Type of allergen[b]							
Grass	4 (331/230)	3 (452/440)	00.3	94.7	04.9	0.576 (–0.154 to 1.316)[a]	0.196 (0.032 to 0.771)
Parietaria	2 (204/112)	0 (0/0)	00.9	49.6	49.5	1.407 (–194.60 to 196.6)[a]	
Ragweed	1 (9/9)	0 (0/0)	01.9	48.4	49.7	0.852 (–194.50 to 195.5)[a]	
Tree	0 (0/0)	1 (18/14)	01.0	49.7	49.3	–0.518 (–196.60 to 195.3)[a]	
S. kali	1 (41/19)	0 (0/0)	03.0	47.3	49.8	0.440 (–195.70 to 195.2)[a]	
Alternaria	0 (0/0)	0 (0/0)	24.8	37.9	37.3	1.001 (–276.20 to 276.1)[a]	

A, number of patients receiving active treatment; P, number of patients receiving placebo.

a Not statistically significant.

b One study[91] had separate arms for tree and grass allergens.

or duration of treatment in the analyses for SSs, MSs or QoL scores was found. A smaller amount of heterogeneity was evident in the analysis for combined SMSs [σ^2 of 0.017 (95% CrI 0.0 to 0.086), no covariates included], and this was further reduced when type of allergen was introduced as a covariate [σ^2 of 0.011 (95% CrI 0.000 to 0.059)]. It should be noted that this is based on a smaller number of studies compared with the SS and MS analyses, which may also have an effect on heterogeneity. In the indirect comparison based on combined SMSs, the standardised score difference was not statistically significant and was associated with very wide credibility intervals. This is reflected in the best estimate probability, which found that SCIT and SLIT had roughly equal probability of being the best treatment. The analysis using combined SMS is based on fewer studies compared with the SS and MS analyses, but it has been argued that it is a more appropriate outcome measure as it takes into account the relationship between symptoms and medication use. The overall results are consistent with the results from small and mainly poor-quality studies directly comparing SCIT to SLIT (see *Chapter 3*, *Effectiveness of subcutaneous immunotherapy versus sublingual immunotherapy*), which found no significant difference between the two treatments.

Unadjusted analyses (no covariates) using SSs and MSs found significant differences in standardised scores favouring SCIT but, given the high residual heterogeneity, these results need to be interpreted cautiously. Using RQLQ, the standardised score difference was non-significant and the result was associated with substantial heterogeneity.

Using 'year of publication' and 'number of symptoms recorded in a trial' as covariates in the ICMR suggested a decreasing benefit from SCIT over time (with SLIT appearing relatively more effective) and an increasing benefit from SCIT the more symptoms were measured. These covariates were not prespecified and findings should be seen as suggestive only, and interpreted very cautiously. Possible explanations for changes over time include changes in treatment protocols (e.g. use of standardised products) or reporting/publication bias. With regard to an increasing benefit for SCIT the more symptoms are measured, it could be speculated that SCIT is better at alleviating a broader range of symptoms. It is also possible that these findings are due to chance.

Owing to the differences in outcome measures used, results were expressed as standardised score differences (except for the RQLQ). As with the meta-analyses of placebo-controlled studies, these results are difficult to interpret clinically, and statistical differences may not be consistent with clinically important differences.

There are several relevant trials that have not been included in the meta-analyses or indirect comparison meta-analyses, as data were not reported in a suitable manner (see *Tables 7* and *21*). The results are therefore not based on all of the available data; the effect of this is uncertain.

It is difficult to draw firm conclusions from these results as (1) they vary depending on which outcome measure is used and (2) they are associated in some instances with substantial residual heterogeneity. A more useful data set would include studies using validated standardised outcome measures and treatment regimens.

Ongoing trials

Searches identified 22 (12 SLIT, 10 SCIT) Phase III double-blind, randomised placebo-controlled trials that are still ongoing or had recently finished but for which no published results were yet available (see *Appendix 9*). The majority of trials are being conducted in adults (some including adolescents), comprising over 4500 adult subjects in total, with only two SLIT trials ($n = 1450$) and one SCIT trial (number of participants not stated) recruiting children and adolescents specifically. We identified only one Phase II/III double-blind, double-dummy study of SLIT compared with SCIT, initiated in March 2011 and due for completion September 2014.[215] Four studies[216–219] are investigating the efficacy and safety of SCIT with recombinant allergens, of which one includes off-treatment follow-up:[216] a SCIT trial will collect data for one season after 2 years of treatment; a further trial will look at long-term allergy and asthma

outcomes over a 5-year period in 1000 children aged 5–12 years (the Grazax Asthma Prevention study[59]). However, in general, the majority of trials do not appear to differ extensively from previously published studies in terms of patients and treatment regimens. Although beyond the scope of this report, it would be of interest to investigate the type of outcome measures being used given recent recommendations in this area.

Chapter 4 Cost-effectiveness

This chapter is divided into the following sections: (1) a systematic review of published EEs on SCIT and SLIT for the treatment of SAR; (2) a description of our preferred Markov models (for adults and children separately) that were constructed to assess the cost-effectiveness of SCIT and SLIT for the treatment of SAR; (3) challenges met when trying to identify data to populate the preferred Markov models; and (4) results of an EE of SCIT and SLIT for treating SAR based on a simpler decision model.

Systematic review of existing evidence

This section reports the results of a systematic review of published EEs evaluating the costs and benefits of SCIT and/or SLIT compared with standard care [symptomatic treatment (ST)], or of SCIT compared with SLIT. The purpose of the systematic review was to (1) gain an overview of existing evidence in this area and (2) identify any suitable data (e.g. costs, utilities, transition probabilities) with which to populate a new Markov model.

Methods

Searches

Studies on costs, cost-effectiveness, modelling and QoL were sought in The Cochrane Library [NHS Economic Evaluation Database (NHS EED)] 2011 Issue 1, MEDLINE (Ovid) 1948–April week 2 2011 and EMBASE (Ovid) 1980–week 15 2011. Quality-of-life studies were sought in MEDLINE (Ovid) 1948–June week 5 2011. Reference lists of included studies were also checked. There were no language restrictions. See *Appendix 2* for full details of the search strategies.

Study selection

Inclusion and exclusion criteria were used as outlined in *Table 38*. These were slightly broader than those for clinical effectiveness in order to cover the breadth of available evidence. Titles and abstracts of retrieved studies were screened for inclusion and exclusion by one reviewer. Full texts were obtained for any potentially relevant studies. All uncertainties around study selection were resolved through discussion with two other reviewers. Reference Manager was used to track and record study selection decisions and reasons for exclusion.

Data extraction

Data extraction was performed by one reviewer using a standard extraction form and checked by a second reviewer. Data were extracted on type of EE, study population, intervention and comparator, perspective, time horizon, model structure and model assumptions if applicable, resource and cost data and main findings.

Assessment of quality of included studies

The methodology of all included EEs was critically appraised using checklists recommended by the Cochrane Collaboration, i.e. the Philips checklist[220] for model-based EEs and the Evers checklist[221] for non-model-based EEs. For the Philips checklist,[220] this involved assessment of a range of factors relating to objectives and structure of the model, the theory underpinning the model, assumptions and treatment of uncertainty as well as the appropriateness and evaluation of the data used to populate the model. The Evers checklist[221] assesses details around the interventions being compared, assumptions made when valuing costs and benefits as well as the generalisability of the results obtained. Reviews of EEs were used as a source for identifying primary studies and were not formally quality assessed.

TABLE 38 Inclusion and exclusion criteria for EEs

Inclusion criteria	Exclusion criteria
Study design	
1. Any EE (including CEAs, CBAs, CUAs, CCAs and CMAs) 2. Any study not in (1) reporting data that could potentially be used in an model-based EEs (e.g. studies reporting transition probabilities, utilities or cost data) 3. Review of EEs	Any study not including or reporting on an EE or reporting data that could potentially be used in a model-based EE
Population	
Adults or children with SAR, with or without asthma. Where populations have included some patients with PAR, the study has been included	Adults or children with a different allergic disease, such as food allergy, or with PAR or asthma only
Intervention	
Allergen-specific subcutaneous (injection) or sublingual immunotherapy in any setting. Where SIT covered both seasonal and perennial AR (e.g. dust mite allergy), the study was included	Any other route of administration [e.g. oral (swallowed rather than sublingual), nasal, epicutaneous, intralymphatic]
Comparator	
Placebo [with or without conventional (rescue) medication], SCIT or SLIT	Any other route of administration (e.g. oral, nasal)
Outcomes	
Any measure of cost, cost-effectiveness, resource use, QoL or utility associated with SCIT or SLIT	Outcomes relating to clinical effectiveness only with no cost or quality-of-life/utility data suitable for use in a model

CBA, cost–benefit analysis; CCA, cost–consequences analysis; CMA, cost minimisation analysis; CUA, cost–utility analysis.

Quantity of evidence

Searches identified 406 potentially relevant publications, of which 330 were excluded at the title/abstract stage. Of the 76 publications that were potentially relevant, full texts could not be obtained for eight. Full-text copies of 68 papers were examined, of which 52 were excluded (reasons for exclusion are detailed in *Appendix 5*). Sixteen publications were included. Of these, 14 were primary EEs and two were reviews of EE studies. In addition, three studies were identified that reported utility-based outcomes for SAR.

Main characteristics of economic evaluations

The main study characteristics and findings are shown below. Further details can be found below (see *Table 40*) and *Appendix 9*.

Type of economic studies

Different types of EEs were identified:

- four cost–consequences analyses (CCAs)[222–225]
- two CEAs[226,227]
- five cost–utility analyses (CUAs)[228–232]
- one study reported both a CEA and CUA analysis[233]
- one study reported both a CEA and cost–benefit analysis (CBA)[234]
- one study reported both a CEA and CCA analysis.[235]

The different forms of EEs differ in the way outcomes are measured and/or expressed. Results from CEAs, CBAs and CUAs are typically reported in terms of a single measure of economic benefit, the incremental

cost-effectiveness ratio (ICER), whereas results (costs and outcomes) from CCA are expressed in a disaggregated way.

Population

All of the primary studies were based on European populations, whereas the two reviews[236,237] additionally considered US populations. Sample sizes ranged from 30 to 2230 (for cohorts used in model-based analyses). Populations considered were those with SAR only (nine studies[222,224–226,228,230–233]) or SAR/PAR (five studies[223,227,229,234,235] and the two reviews[238,239]), either with or without asthma. Where patients had PAR, this related to dust mite allergy.

Routes of immunotherapy and comparators

Five studies[222,229,233–235] compared SCIT with standard care, six studies[223,226,228,230–232] compared SLIT with standard care and two studies[225,227] compared both SCIT and SLIT with standard care. One study[224] compared different forms of SCIT (short and long term and with an adjuvant) to SLIT and standard care.

Cost perspectives and costs included

Six studies[223,228,230–232,234] were undertaken from a purely societal perspective, and two[224,227] were from a health insurer perspective. Five studies considered a combination of cost perspectives: two[222,225] considered societal, health service and patient perspectives, one[226] used societal and NHS (Italy) perspectives, one used societal and third-party payer points of view,[229] and one[235] used societal, NHS (Germany) and health insurer perspectives. The perspective used was not stated in one study.[233]

Costs associated with IT were divided into direct medical costs [e.g. costs related to GP visits, hospital visits (inpatient and outpatient), drugs and specialist examinations/tests] and indirect costs (e.g. cost related to productivity losses owing to time missed from work as a result of AR, or costs associated with productivity gains through reduced number of working days lost). Most EEs included both direct and indirect costs.

Outcomes within economic evaluations

A number of effectiveness or cost-effectiveness outcomes were reported in the EEs. These are listed by type of EE below.

For studies with a CCA, outcomes included SSs,[222] number of asthma and rhinitis exacerbations and number of nursery/school days lost[223] and VAS for allergic symptoms.[233] Other outcomes were number of medical visits and health-care use,[223,225] RQLQ and symptomatic medication reduction[225] and break-even points of costs/expenses per patient.[101] One study[201] included development of asthma and new sensitisation.

The following outcomes were reported in the CEA studies: cost per number of patients improved and number of asthma cases avoided,[226] cost per well-day and symptom-free day,[233] number of additional patients free from asthma symptoms,[235] and cost per asthma case avoided.[227]

Only six studies[228–233] conducted CUAs, and therefore reported outcomes based on utility-based measures. For the four studies[228,230–232] based on the GT–08 GRAZAX trial,[93] the chosen measure of utility was the European Quality of Life-5 Dimensions (EQ-5D), which was then converted into quality-adjusted life-years (QALYs). The instrument or outcome measure on which the utilities, subsequently converted into QALYs, were based was not specified in Brüggenjürgen *et al*.[229] In the fifth CUA study,[233] QALY estimates were based on EQ-5D values mapped from RQLQ scores.

Model-based economic evaluations

Five studies[224,226,227,229,234] reported analyses based on decision-analytic models. Of these, two[224,229] used Markov models, whereas three[226,227,235] were based on decision tree models. Six main health states were considered in Brüggenjürgen *et al*.,[229] including mild AR, moderate to severe AR, severe AR and mild allergic asthma, severe AR and moderate to severe allergic asthma, no symptoms, and dead. Transition

probabilities depicting movement between these health states and annual costs were obtained from published sources. In Claes *et al.*,[224] three main health states were modelled: SAR, non-SAR and asthma. Model inputs were not clearly described, but included data based on the PAT study.[54–56] Assumptions were made for effectiveness, adherence and discontinuation rates.

Berto *et al*.[226] considered five main health states in their decision tree: improvement, stabilisation, aggravation, inadequate response and asymptomatic. Data for the model came from the Retrospective Observation Physician Panel (ROPP). The same health states were considered in Omnes *et al*.,[227] with most of the model inputs coming from a Delphi panel of 10 allergologists and one epidemiologist. In Schädlich and Brecht,[235] two main health states were considered and divided by type of intervention (ST compared with specific IT): patients without asthma symptoms and patients with asthma symptoms. Data to populate this model came from a number of sources including observational studies and epidemiological information, statutory health insurance data, Uniform Assessment Standard information and cost-of-illness studies in Germany.[238–240]

Funding sources

Ten of the 14 EEs, and all of the CUAs, were funded by a manufacturer of SIT products or had an author who was affiliated to a manufacturer. Exceptions were the studies by Ariano *et al*.,[222] Petersen *et al.*[234] and Pokladnikova *et al*.[225]

Quality of economic evaluations

Quality assessment of the EEs identified a number of methodological issues, which are outlined below (see *Appendix 10* for completed checklists and see *Table 39* for key issues for each study).

Sources of clinical effectiveness data

Some studies[222,225,228,230–232] were based on randomised trials and therefore were able to use robust resource use and outcome data. Four of the CUAs[228,230–232] were based on findings from the GT–08 trial.[93] In other studies, however, there were limitations associated with the data sources. The use of self-reported data relying on patient recall over very long periods of time introduced imprecision in the calculating of parameters; for example, the recall period was 6 years in Petersen *et al*.[234] Other studies, such as that by Omnes *et al*.,[227] did not use patient-level data but instead used expert panels to estimate efficacy and health resource use data, which could lead to biases. In the Claes *et al*. study,[224] assumptions were made regarding clinical effectiveness parameters.

Assumptions made

Some of the assumptions made in the studies did not appear realistic. In Schädlich and Brecht,[235] for instance, non-adherence to IT was not accounted for as the model assumed 100% compliance. A number of studies made the assumption that resource use would be sustained over a period of extrapolation; Bachert *et al*.,[228] for example, extrapolated 3-year outcome and resource use estimates to a 9-year period, whereas Keiding and Jørgensen 2007[233] extrapolated 1-year data to a 9-year period.

Cost data

Overall, many studies provided sufficient detail in terms of resource use and unit cost data to allow for the potential use of these data in other studies. Some costs may have been underestimated owing to the non-inclusion of certain resource use data in the estimation of both direct and indirect costs, for example costs of hospitalisations[222,223] or costs for non-allergy-related resource use.[233]

Discounting

The majority of studies discounted their costs by between 3% and 6%.

Generalisability of studies

It is unclear to what extent results (assuming that they are otherwise robust) can be generalised to wider populations. Some evaluations were based on small sample sizes[222] or restricted to a single

allergy centre.[223] Selection bias may be an issue, as in one evaluation[226] clinicians from different centres retrospectively reported data for 100 patients each. Where assumptions have been made regarding baseline and post-treatment effectiveness,[223,227] results are unlikely to be representative of real-life populations.

Reporting

Inadequate or incomplete reporting hampered analysis of the studies included in this review. For instance, parameter estimates used to populate decision tree or Markov models were either partly reported[222] or not reported at all.[229] In particular, actual EQ-5D and QALY estimates, although used in the analyses, were not reported.[228,230–232] One study[233] did not report the size of the sample analysed, making it difficult to assess the validity of the analysis. Some studies did not clearly describe the sources of the data used (e.g. sources of health-care resource data for Berto *et al*.[223]), making it difficult to comment on the appropriateness of the costs estimates. Furthermore, some studies[222,223] did not provide information on whether or not they had discounted their costs, making it difficult to ascertain the accuracy of these costs.

Sensitivity analyses

No sensitivity analyses were conducted in three studies,[222,223,233] although this would have been appropriate. Sensitivity analyses in the other 11 studies took the form of univariate deterministic sensitivity analyses, varying a number of parameters, such as costs,[224–231] disease and severity levels,[226,239] thresholds for cost-effectiveness,[228,230] cost perspectives,[226,229] IT treatment time,[229,232] excluding certain patient groups,[230] time horizon of model[224,225,231] and discount rates.[224,229] These analyses enabled the robustness of the study results to be tested. However, no probabilistic sensitivity analyses were undertaken for the model-based studies as is usual practice.[241] This, therefore, meant that uncertainty around model inputs was not accounted for in the model results.

Results of economic evaluations

Seven studies[134,223,226–228,231,232] compared SLIT with standard care, and all found that SLIT was more cost-effective. Studies reporting results of EEs based on data from randomised studies[134,222,225,228,231,232] seemed to have been the most robust. The quality of reporting for resource use and unit cost data in these trial-based studies also appeared to be adequate. Four studies[228,230–232] reported cost per QALY (*Table 39*); all were based on the same multinational trial (GT–08[93]) and included populations from different European countries in the respective analyses. All found that Grazax was cost-effective (below a threshold of £20,000), providing that annual costs of Grazax remain below £2200. The current annual cost in the UK is £814 (at £2.23 per tablet).[46] The evaluations appear to be well conducted; however, there was a general lack of detailed reporting on the outcome side, for example lack of disaggregated baseline and follow-up EQ-5D values and QALY gains. All four studies were funded by the manufacturer of Grazax.

Six studies[222,227,229,233–235] compared SCIT with standard treatment. All found that SCIT was associated with better outcomes and/or lower long-term costs. Two studies[229,233] calculated a cost per QALY for SCIT (see *Table 39*). Brüggenjürgen *et al*.[229] found a low ICER, but the robustness of this result is uncertain, as there was insufficient detail on the instrument used to derive utilities, and on cost and resource use data. The evaluation by Keiding and Jørgensen[233] found that SCIT either dominated ST or was associated with very low ICERs, although robust sensitivity analyses were not conducted.

Where SCIT and SLIT were directly compared against each other, SCIT was found to be both more effective and more cost-effective over the long term. The sample size of the only trial[225] that has directly compared the cost-effectiveness of SCIT and SLIT was, however, small ($n = 64$), and therefore more studies based on larger samples are needed. As this was a CCA, there is no combined cost-effectiveness measure. Assumptions made in the other study[224] that directly compared the two interventions were not robust enough and variations of such assumptions should ideally be tested within a sensitivity analysis.

Other useful studies

Three studies[242–244] were identified that reported utility-based outcomes for AR. Tamayama *et al*.[242] used the rating scale and time trade-off methods to estimate utility weights for four AR severity levels (mild,

TABLE 39 Incremental cost-effectiveness ratios reported in the literature for SIT vs standard care

Study	Intervention	Cost per QALY	Comments
Bachert 2007[228]	SLIT (Grazax)	Cost per QALY gained between €12,930 and €18,263 for different northern European countries, including the UK	SLIT was cost-effective at an annual cost of €2200 [tablet <€6 (£4) and based on a threshold of €29,000 (£20,000) per QALY]
Beriot-Mathiot 2007[232]	SLIT (Grazax)	Cost per QALY gained between €7894 and €47,844 for different northern European countries, including UK	WHO-recommended SLIT pattern was cost-effective if sustained effect after treatment is ≥2 years based on a threshold of €29,000 (£20,000) per QALY, whereas seasonal SLIT pattern was cost-effective regardless of time horizon with ICER of €21,829
Brüggenjürgen 2008[229]	SCIT (product not stated)	From a third-party payer's perspective, SCIT + ST is associated with a cost per QALY of €8308	From a societal point of view break-even point is reached after 10 years, after 15 years SCIT dominates ST (i.e. is cheaper and more effective)
Canonica 2007[230]	SLIT (Grazax)	Cost per QALY gained between €13,870 and €21,695 for different European countries (Spain, France, Italy and Austria)	Cost-effective at annual cost of Grazax of between €1500 and €1900
Keiding and Jørgensen 2007[233]	SCIT (Alutard SQ)	Cost per QALY gained between €9716 and €25,863 per QALY (without indirect costs)	With indirect costs included, SCIT dominates ST or has low ICERs
Nasser 2008[231]	SLIT (Grazax)	Cost per QALY gained between £4319 and £11,769 (UK only)	Cost-effective up to an annual cost of Grazax of £1850. The highest cost per QALY in sensitivity analyses was £11,769

WHO, World Health Organization.

moderate, severe and severest) based on a Japanese sample. From mild to severest, time-trade-off estimates were 0.96, 0.94, 0.89 and 0.83, respectively. The rating scale counterpart weights were 0.82, 0.71, 0.56 and 0.43. Chen *et al*.[243] collected EQ-5D data for three groups in the USA and reported the following values: 0.76 (for individuals with asthma and rhinitis), 0.76 (for those with asthma only) and 0.92 (for individuals with rhinitis only). In Wasserfallen *et al*.,[244] the responsiveness of the EQ-5D when used on asthma patients with AR was compared with that of the McMaster Asthma Quality of Life Questionnaire (MAQOL). The EQ-5D was found to be less responsive than the MAQOL.

Two abstracts[245,246] reporting EEs of Grazax based on populations of children with AR were identified at a late stage of writing this report and have thus not been formally included. A detailed appraisal was not possible, as the information was in abstract form only, but the results of these studies were consistent with those found for adults in that Grazax was found to be cost-effective compared with ST below a £20,000 threshold.

Reviews of economic evaluations

Both reviews of EEs[237,247] considered studies that applied simple cost analyses as well as full EEs from societal, health service and patient perspectives (*Table 40*).

Nine EEs[222,223,225–228,230,233,235] included in Berto *et al.*[247] were also identified in the present review. All of the EEs reported in Hankin *et al*.[237] were included in our review with the exception of Buchner and Siepe,[248] which seems to be a cost analysis rather than a CBA. Neither review presents a detailed search strategy. An additional seven EEs[224,225,229–232,234] were identified for this report.

TABLE 40 Summary of reviews of EEs

Study ID	Type of Study	Population	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Key findings	Comments
Berto 2008[247]	Review of economic studies	USA, northen and southern European Countries	SAR or PAR	SCIT, SLIT vs ST	QALYs and other unreported outcomes	Societal, NHS and patient	Direct and indirect costs	Costs per patient/year varied from €96 to €348.50. The average costs per patient for IT ranged from €288 to €1182, whereas those for pre-IT/control subjects ranged from €116 to €2672. In EEs, IT was found to be more cost-effective than ST	The search strategy used in the review was not reported in detail. One study[103] included in our systematic review was not reported in this review
Hankin 2011[237]	Review of economic studies	USA, Germany, France, Italy, Denmark and northern Europe	SAR or PAR	SCIT, SLIT vs ST	QALYs, net benefits and other natural outcomes	NHS, societal and patient	Direct and indirect costs	IT provided cost benefits ranging from $96 to $5465. Average annual costs for IT per patient ranged from US$247 to US$10,200; Average annual costs for per patient ranged from US$1335 to $24,243; mean cost of allergy medications per patient year varied from US$23 to US$37 and costs per QALY gained ranged from US$14,536 to US$38,695	The search strategy used in the review was not reported Five studies[224,225,228–230] reported in our systematic review were not included in this review

Consistent with our findings, both reviews found that IT (SCIT or SLIT) was (just) more effective or, in some cases, both more effective and cost-effective when compared with standard care. Hankin *et al.*[237] also highlighted limitations associated with the data sources used in the EEs, a finding similar to ours. In particular, there were issues around generalisability and short time horizons associated with trial-based studies, and concerns about the quality of data obtained from observational studies were also raised.

Conclusions

Economic evaluations varied widely in the type of analysis used, outcome measures, sources for cost and effectiveness data, and adequacy of reporting for different parameters (*Table 41*). They did find consistently that where either SCIT or SLIT was compared with standard therapy, IT was (just) more effective or, in some cases, both more effective and cost-effective. The most robust studies[228,230–232] found that SLIT is likely to be cost-effective at thresholds of £20,000; these studies did not, however, report all of the utility data in a disaggregated form and all were funded by a manufacturer of SIT products. SCIT was also found to be cost-effective at a threshold of £20,000 (based on two studies[229,233]); however, these results were associated with slightly greater uncertainty.

Only two studies[224,225] looked at the cost-effectiveness of SCIT compared with SLIT. Although suggestive of greater cost-effectiveness for SCIT, both studies had some methodological concerns associated with them and neither presented combined cost-effectiveness measures.

Preferred adult and child Markov models

To estimate the comparative long-term cost-effectiveness of SCIT and SLIT when used to treat SAR, two Markov models were constructed (adults and children) in TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA, USA). Both models were built to combine costs and outcomes associated with three different treatment pathways, SCIT, SLIT or standard (symptomatic) treatment.

Briefly, this entailed dividing a patient's possible course of disease progression into a number of health states with transition probabilities assigned for the movement between these states over a discrete time period (Markov cycle). Long-term costs and health outcomes are assessed by attaching estimates of resource use and health outcomes to the states in the model and then running the model over a large number of cycles to evaluate patient movement between states. Clinical advice was taken into account for the model structure (e.g. types of health states).

Adult Markov model

The long-term progress of a hypothetical cohort of AR patients moving along the three alternative pathways of care (SCIT, SLIT and ST) was to be compared. The treatment schedules for SCIT, SLIT and ST are presented in more detail in *Chapter 1* (see *Allergen immunotherapy*). Briefly, patients would receive weekly subcutaneous injections (SCIT) for 16 weeks in a clinical setting, followed by monthly injections for up to 3 years. Patients receiving SLIT would take daily tablets or drops at home, also for up to 3 years. Symptomatic treatments may be oral, topical or intranasal. Occasionally, systemic corticosteroids may be prescribed.

Patients would then follow clinical pathways designed to mirror the natural progression of the condition in the population, with health resources use for all three groups also modelled. The aim was to enable model-based predictions of costs and outcomes to be compared for the SCIT, SLIT and ST groups in a CUA from the UK NHS and patient perspectives.

Adult Markov model structure and model inputs

The structure of the adult Markov model is shown in *Figures 14–16*. Only health states for the SCIT and ST arms are presented. The health states for the SLIT arm are identical to those in the SCIT arm.

TABLE 41 Summary of EEs

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Ariano 2006[222]	CCA	Italy	SAR	SCIT vs ST	Symptom and satisfaction scores	Societal, NHS, patient	Direct costs	N/A	SCIT associated with better symptom and satisfaction scores. Net savings started at year 3 and were €623 per year at year 6	Not all relevant costs appear to have been identified, valued and discounted appropriately. There were no appropriate sensitivity analyses
Bachert 2007[228]	CUA	UK, Sweden, Germany, Netherlands, Denmark, Norway and Finland	SAR	SLIT vs ST	EQ-5D, QALYs	Societal	Direct and indirect costs	N/A	SLIT (Grazax) had more QALY gains associated with it compared with standard treatment. SLIT was cost-effective at an annual cost of €2000 and based on a threshold of €29,000 (£20,000) per QALY. Cost per QALY across seven countries was between €12,930 and €18,263	Good range of values used in sensitivity analyses. Actual EQ-5D inputs and QALY estimates were not presented, which makes it impossible to assess the robustness of these, or to apply the values in another model. Study funded by manufacturer of SIT products

continued

TABLE 41 Summary of EEs (*continued*)

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Beriot-Mathiot 2007[232]	CUA	UK, Netherlands, Denmark and Sweden	SAR	SLIT vs ST	EQ-5D, QALYs	Societal	Direct and indirect costs	N/A	SLIT (Grazax) had more QALY gains associated with it compared with standard treatment. In the seasonal scenario, SLIT was more cost-effective, regardless of time horizon, with an ICER of €21,829 In the WHO-recommended scenario, SLIT was more cost-effective than standard care (at a threshold of €29,200) if the sustained effect of treatment is over 2 years or more. The ICER decreased from €47,844 at the 1-year time horizon to €7894 at the 9-year time horizon. The WHO-recommended SLIT scenario was the most cost-effective, with a time horizon of ≥6.3 years	Limited sensitivity analysis performed. Some EQ-5D inputs were presented, but not disaggregated according to SLIT or ST. Actual QALY estimates were not presented, which makes it impossible to assess the robustness of these, or to apply the values in another model. Study funded by manufacturer of SIT products

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Berto 2005[223]	CCA	Italy	SAR or PAR	SLIT vs no SLIT control (assumed to be standard care)	Number of asthma and rhinitis exacerbations, medical visits, absence from nursery or school	Societal	Direct and indirect costs	N/A	SLIT associated with substantial reductions in the number of asthma and rhinitis exacerbations, number of school/ nursery days lost and number of medical visits (overall and in the SAR and PAR groups). Costs per patient (SAR group) were €2723 pre-SLIT and €643 during SLIT	Effectiveness and costs compared within the same group, before and during treatment with SLIT. Costs associated with the different treatment options have not been described. There were no details on funding. One of the author's affiliations was a manufacturer of SIT products
Berto 2006[226]	CEA	Italy	SAR	SLIT vs ST	No. of patients improved, number of asthma cases avoided	NHS, societal	Direct and indirect costs	Decision tree model	SLIT was more effective and cheaper than standard therapy (i.e. dominates) from both cost perspectives in terms of costs per additional improved patient and costs per additional asthma cases avoided	There was some uncertainty about representativeness and similarity of patients in different treatment arms, also a lack of details on the data used in the model. Study funded by manufacturer of SIT products

continued

TABLE 41 Summary of EEs (*continued*)

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Brüggenjürgen 2008[229]	CUA	Germany	SAR or PAR	SCIT vs ST	Utilities, QALYs	Societal, third-party payer	Direct and indirect costs	Markov model	From a societal point of view at 15 years, SCIT + ST dominates ST with break-even point reached after 10 years. From a third-party payer's perspective, SCIT + ST was associated with an ICER of €8308 per QALY (cost-effective at a threshold of £20,000)	Overall there was insufficient detail on the instrument used to derive utilities, and on cost and resource use data. Several assumptions were based on expert consensus. Study funded by manufacturer of SIT products
Canonica 2007[230]	CUA	Spain, France, Italy and Austria	SAR	SLIT vs ST	EQ-5D, QALYs	Societal	Direct and indirect costs	N/A	SLIT (Grazax) had more QALY gains and was more cost-effective than ST (at annual Grazax cost of between €1500 and €1900). Cost per QALY gained was between €13,870 and €21,695 for different European countries	Overall, this CUA seemed to be well conducted; however, no actual QALY or EQ-5D inputs for each treatment arm were given in the paper. Study funded by manufacturer of SIT products

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Claes 2009[224]	CCA	Germany	SAR	SLIT, SCIT (short and long term), ST, adjuvant-supported allergoid (allergoid + MPL)	No. of asthma cases and new sensitisations	Health insurer	Direct costs	Markov model	Three-year average direct costs for the five forms of IT were: €2584 (long-term SCIT), €4269 (SLIT), €1533 (short-term SCIT), €2523 (short-term SCIT + maintenance injections) and €2080 (short-term SCIT + MPL). The direct costs of the short-term SCIT + MPL arm, compared with those of other forms SCIT and SLIT, are higher at the beginning of therapy. Other scenarios show that, compared with other forms of IT, short-term SCIT and short-term SCIT + MPL have favourable sustainability and adherence-related outcomes. Standard therapy is the cheapest option at 3 years and the most expensive option at 15 years	There was substantial uncertainty over sources and appropriateness of data feeding into model. An assumption of 100% effectiveness for the base case was made, which seems infeasible. The study was funded by a manufacturer of SIT products

continued

TABLE 41 Summary of EEs (*continued*)

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Keiding 2007[233]	CEA and CUA	Austria, Denmark, Finland, Germany, Netherlands and Sweden	SAR	SCIT vs ST	Symptom-free days and well-days (RQLQ), VAS, EQ-5D, QALYs	Not stated	Direct and indirect costs	N/A	SCIT associated with ICERs of between €9716 and €25,863 per QALY (without indirect costs). With indirect costs, SCIT dominates ST or has low ICERs (€6458 per QALY for the Netherlands and €5024 per QALY for Sweden). SCIT also has more favourable costs per symptom-free day and costs per well-day	Overall, this CUA seemed to be well conducted, however, no sensitivity analyses were conducted so it is difficult to assess the robustness of results. Utility values were obtained by mapping RQLQ values to the EQ-5D. The study was funded by a manufacturer of SIT products
Nasser 2008[231]	CUA	UK, Germany, Netherlands, Denmark, Sweden, Spain, Italy and Austria	SAR	SLIT vs ST	EQ-5D, QALYs	Societal	Direct and indirect costs	N/A	SLIT (Grazax) had more QALY gains and was more cost-effective than ST (ICER of £4319 per QALY gained). Grazax remained cost-effective up to an annual cost of £1850. The highest cost per QALY in sensitivity analyses was £11,769	Actual EQ-5D inputs were not presented. The study was funded by a manufacturer of SIT products

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Omnes 2007[227]	CEA	France	SAR or PAR	SLIT, SCIT vs ST	No. of improved patients and number of asthma cases	Health insurers	Direct and indirect costs	Decision tree model	When compared with ST, both SCIT and SLIT were associated with favourable costs per number of improved patients and costs per number of asthma cases. ICERs for SCIT were lower than those for SLIT. Costs per asthma case avoided were €1327 (SCIT) and €1708 (SLIT)	Most of the effectiveness inputs for the model came from estimates from a Delphi panel. There were no details on funding; however, one of the author's affiliations was a manufacturer of SIT products
Petersen 2005[234]	CBA and CEA	Denmark	SAR or PAR	SCIT vs ST	Monetary benefits and measure of psychological well-being	Societal	Direct and indirect costs	N/A	SCIT was associated with an ICER of DKK 2784 per patient/year of improved well-being. From a CBA perspective, SCIT was shown to be net beneficial	Unvalidated measure of psychological well-being used and the methodology used to determine CBA estimates was not clearly described
Pokladnikova 2007[225]	CCA	Czech Republic	SAR	SLIT, SCIT vs ST	RQLQ, VAS, Symptomatic MS	Third-party payer, patient and societal	Direct and indirect costs	N/A	Clinical benefits for SLIT comparable to those for SCIT, but SCIT patients showed a slightly better improvement especially in VAS and symptomatic MSs. Compared with SCIT, SLIT was associated with lower costs (from all perspectives). No comparisons with ST	Based on small ($n = 64$) open-label trial. As CCA, no combined measure of cost-effectiveness

continued

TABLE 41 Summary of EEs (*continued*)

Study ID	Type of EE	Country	Type of AR	Intervention and comparator	Outcomes assessed	Cost perspective	Type of costs included	Type of model where applicable	Key findings	Comments
Schädlich 2000[235]	CEA and CCA	Germany	SAR or PAR	SCIT vs ST	No. of additional patients free from asthma symptoms and break-even points of costs or expenses per patient	Societal, NHS, statutory health insurance provider	Direct and indirect costs	Decision tree model	Break-even point reached between 6 and 8 years after commencement of SCIT and net savings associated with SCIT were between DM650 and DM1190 per patient after 10 years. Further, SCIT was associated with ICERs of between DM3640 and DM7410 per additional patient free from asthmatic symptoms	Some uncertainty around estimates of benefit. Study funded by manufacturers of SIT products

DKK, Danish Krone; MPL, monophosphoryl lipid; N/A, not applicable; WHO, World Health Organization.

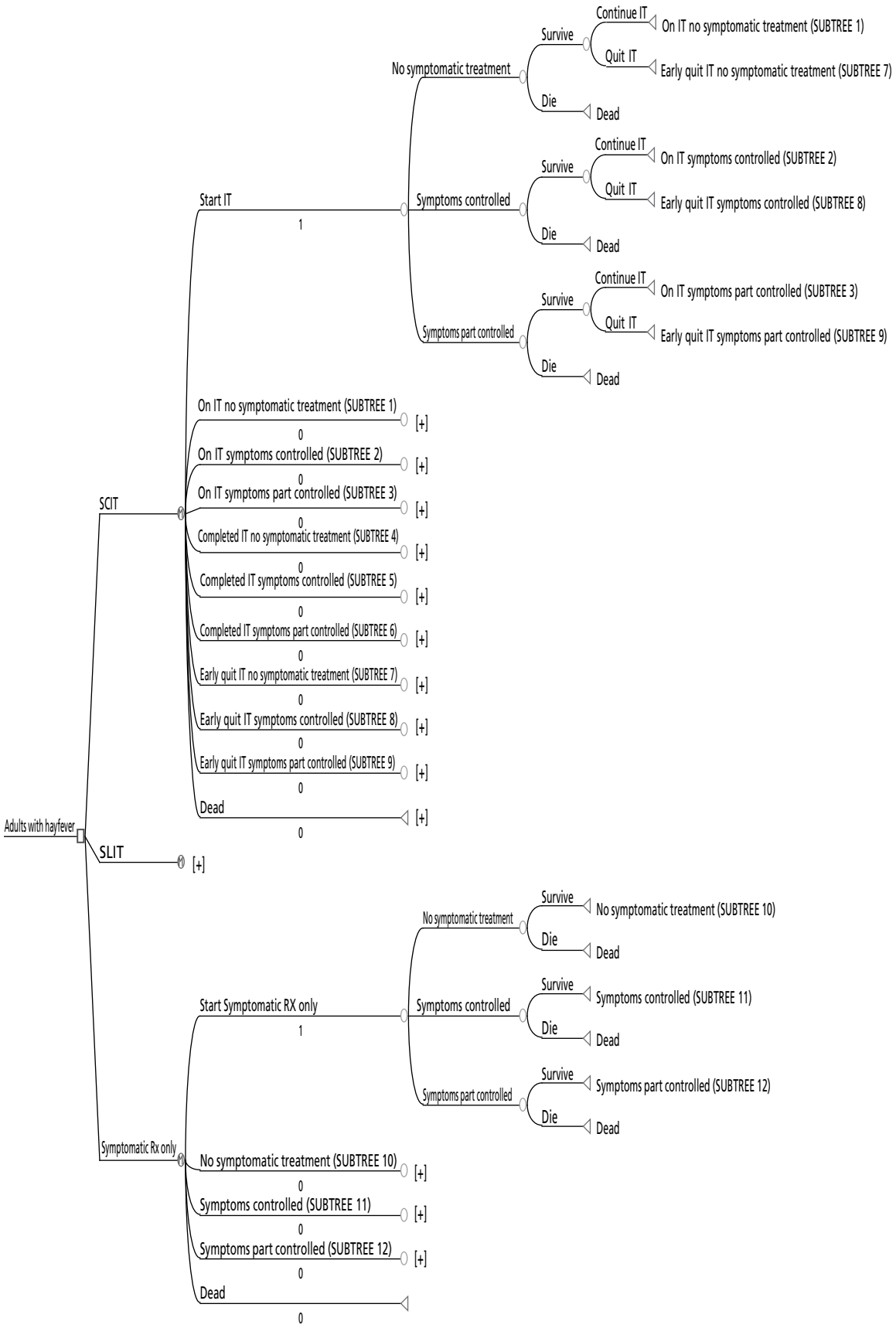

FIGURE 14 Adult Markov model structure: SLIT arm. Note that the health states for the SLIT arm are identical to those in the SCIT arm.

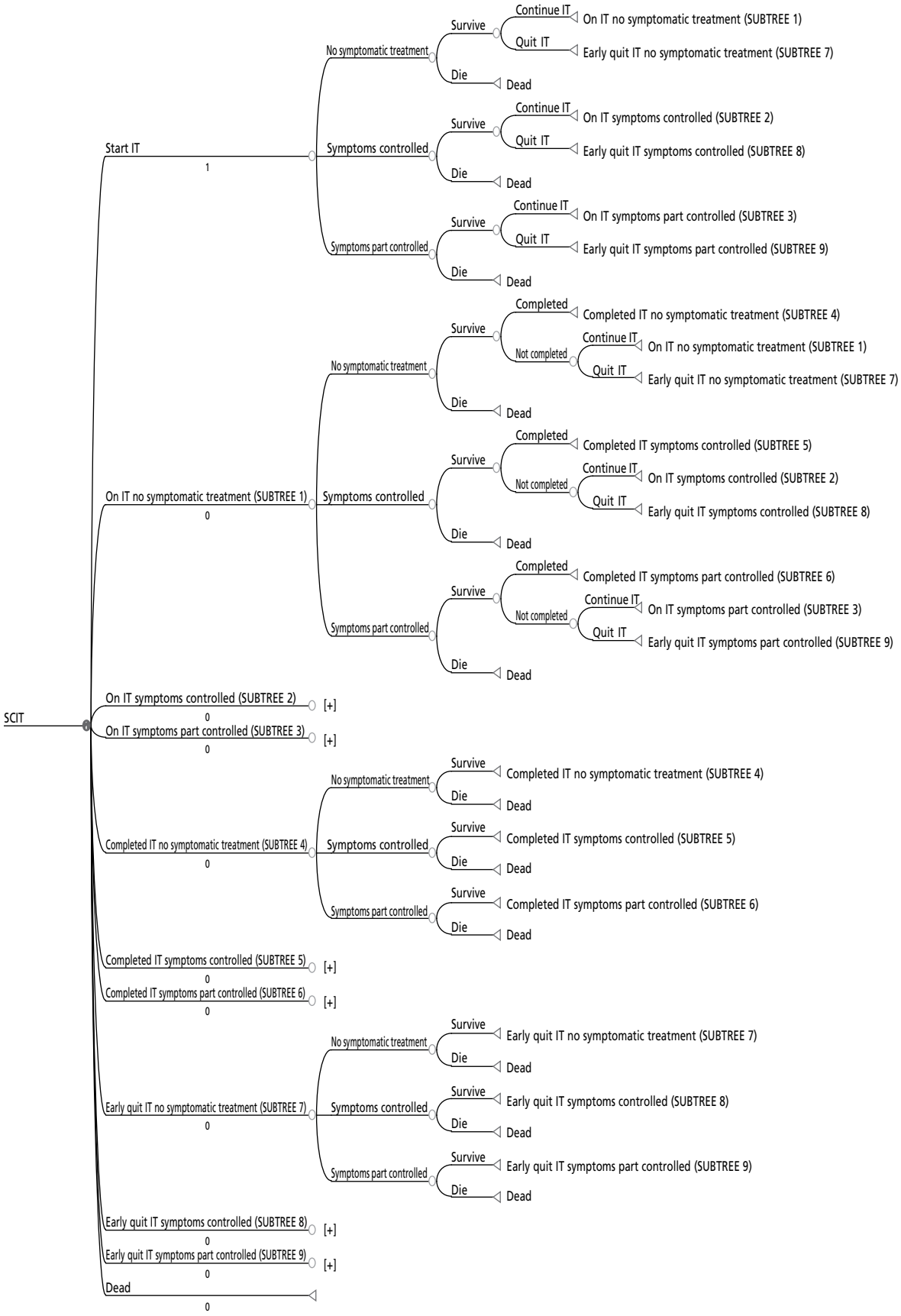

FIGURE 15 Adult Markov model structure: SCIT arm. [+], same structure as the first expanded structure directly above but with appropriate changes in probabilities.

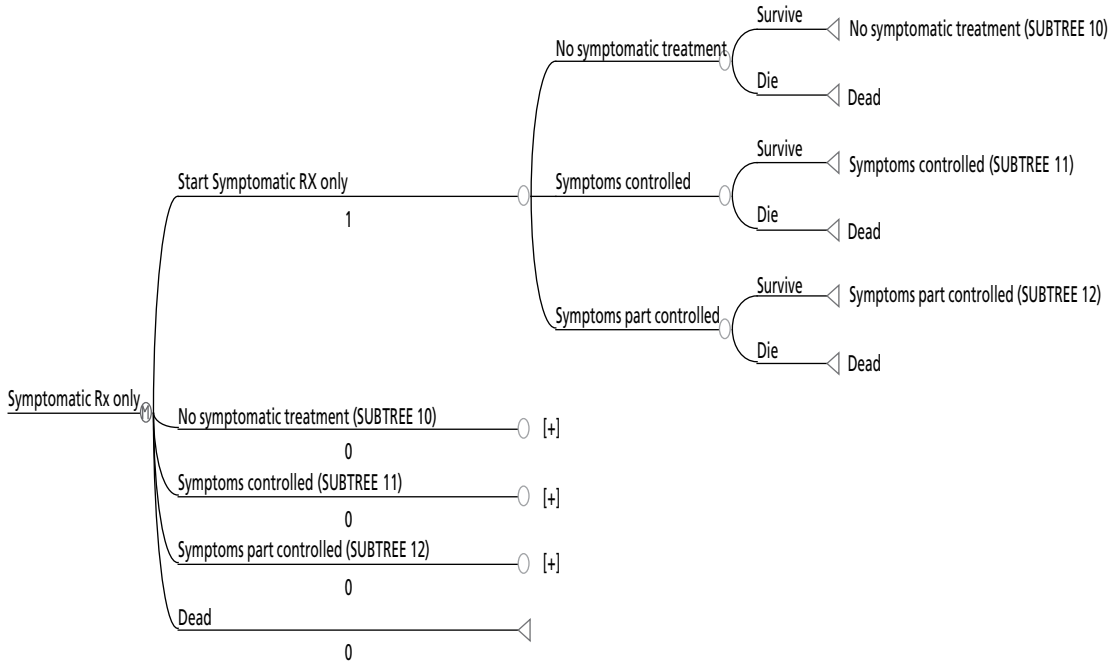

FIGURE 16 Adult Markov model structure: ST arm. [+], same structure as the first expanded structure directly above but with appropriate changes in probabilities.

Subcutaneous immunotherapy arm

The Markov process for the SCIT arm begins with the initial health state called 'Start IT' representing individuals with SAR eligible for treatment with SCIT. Following the 'Start IT' health state, the model then distinguishes between patients who, in addition to SCIT, would receive treatment to control all, or some, of their symptoms (symptoms controlled and symptoms part controlled), as well as patients who would not receive any ST at all as they are assumed to be symptom free (no ST).

In the second or third year, patients who complete the previous year of SCIT (with or without ST) may then continue with, or quit, SCIT. In total, patients can move to one of 10 possible health states. The first three represent variations of patients continuing with SCIT with or without ST ('on IT no ST', 'on IT symptoms controlled' or 'on IT symptoms partly controlled'). The next three health states are for patients who have completed SCIT and then continue with or without ST (i.e. 'complete IT no ST', 'complete IT symptoms controlled' or 'complete IT symptoms partly controlled'). Patients who remained on SCIT for 3 years move to one of these states at the end of the third year. Another three health states depict options for patients who continue with or without ST having quit SCIT in the first or second year (i.e. 'Early quit IT no ST', 'Early quit IT symptoms controlled' or 'Early quit IT symptoms partly controlled'). The last health state is 'Dead'. Moving on from nine of these 10 health states (excluding 'Dead'), the model also allowed for a change in ST. For instance, given that an adult with AR completed treatment with SCIT in the first or second year and was not on any other treatment, what was the probability that they would add treatments to control all, or some, of their symptoms at some point within the following year?

The symptomatic treatment-only arm

The starting point for the Markov process in the ST-only arm is the health state called 'Start Symptomatic Rx only' representing individuals with SAR eligible for treatment with SCIT or SLIT, but only receiving treatment to relieve their AR symptoms. Following the 'Start Symptomatic Rx only' health state, the model then distinguishes between patients who continue with treatment to control all or some of their symptoms (symptoms controlled and symptoms part controlled) as well as patients who stop receiving any ST completely (no ST). In the second or third year, patients who survive the previous year with or without ST can then move to one of four possible health states: have no ST (No ST), have treatment to control all

of their symptoms (Symptoms controlled), have treatment to control some of their symptoms (Symptoms partly controlled) or die (Dead).

Child Markov model

Methods of delivering SIT were similar to those in the adult model, but with appropriate adjustments in dosages. The resultant clinical pathways were also designed to mirror the natural progression of AR in the children with health resources use for all three groups also modelled. The goal for this model was also to enable model-based predictions of costs and outcomes to be compared for the SCIT, SLIT and ST groups in a CUA from the UK NHS and patient perspectives.

Child model structure and model inputs

The structure of the child Markov model is similar to that for adults except it incorporates asthma in all outcomes in order to account for the probability of developing the condition among children with AR (*Figures 17–20*). Only health states for the SCIT and 'Symptomatic treatment' arms are presented. The health states for the 'SLIT' arm are identical to those in the 'SCIT' arm.

Subcutaneous immunotherapy arm

The Markov process for the SCIT arm begins with the initial health state called 'Start IT', representing children with SAR who are eligible for treatment with SCIT. Following the 'Start IT' health state, the model then distinguishes between children who, in addition to SCIT, would receive treatment to control all, or some of their symptoms (symptoms controlled and symptoms part controlled), as well as children who would not receive any ST at all (no ST). In the second or third year, asthmatic and non-asthmatic children who complete the previous year following SCIT (with or without ST) may then continue with, or quit, SCIT. Therefore, patients can move to 1 of 19 possible health states. The first six represent variations of asthmatic and non-asthmatic children continuing with SCIT with or without ST ('on IT no ST with asthma', 'on IT no ST without asthma', 'on IT symptoms controlled with asthma', 'on IT symptoms controlled without asthma', 'on IT symptoms partly controlled with asthma' or 'on IT symptoms partly controlled without asthma'). The next six present states for asthmatic and non-asthmatic children who complete SCIT and then continue with or without ST (i.e. 'complete IT no ST with asthma', 'complete IT no ST without asthma', 'complete IT symptoms controlled with asthma', 'complete IT symptoms controlled without asthma', 'complete IT symptoms partly controlled with asthma' or 'complete IT symptoms partly controlled without asthma'). Patients who remained on SCIT for 3 years move to one of these states at the end of the third year. Another six health states depict options for asthmatic and non-asthmatic children who continue with or without ST having quit SCIT in the first or second year (i.e. 'Early quit IT no ST with asthma', 'Early quit IT no ST without asthma', 'Early quit IT symptoms controlled with asthma', 'Early quit IT symptoms controlled without asthma', 'Early quit IT symptoms partly controlled with asthma' or 'Early quit IT symptoms partly controlled without asthma'). The last health state is 'Dead'. Moving from 18 of these 19 health states (excluding 'Dead'), the model also allowed for a change in ST. For instance, given that an asthmatic child with AR completed treatment with SCIT in the first or second year and was not on any other treatment, what was the probability that they would add treatments to control all or some of their symptoms at some point within the following year?

The symptomatic treatment-only arm

The starting point for the Markov process in the ST-only arm is the health state called 'Start Symptomatic Rx only', representing children with SAR who are eligible for treatment with SIT but who are receiving treatment to relieve only their AR symptoms. Following the 'Start Symptomatic Rx only' health state, the model then distinguishes between children who continue with treatment to control all or some of their symptoms (symptoms controlled and symptoms part controlled), as well as children who would not receive any ST at all (no ST). In the second or third year, both asthmatic and non-asthmatic patients who complete the previous year with or without ST can then move to one of seven possible health states. These include states for asthmatic children who have no ST ('No ST with asthma'), non-asthmatic children who have no ST ('No ST without asthma'), asthmatic children who have treatment to control all of their symptoms ('Symptoms controlled with asthma') and non-asthmatic children who have treatment to

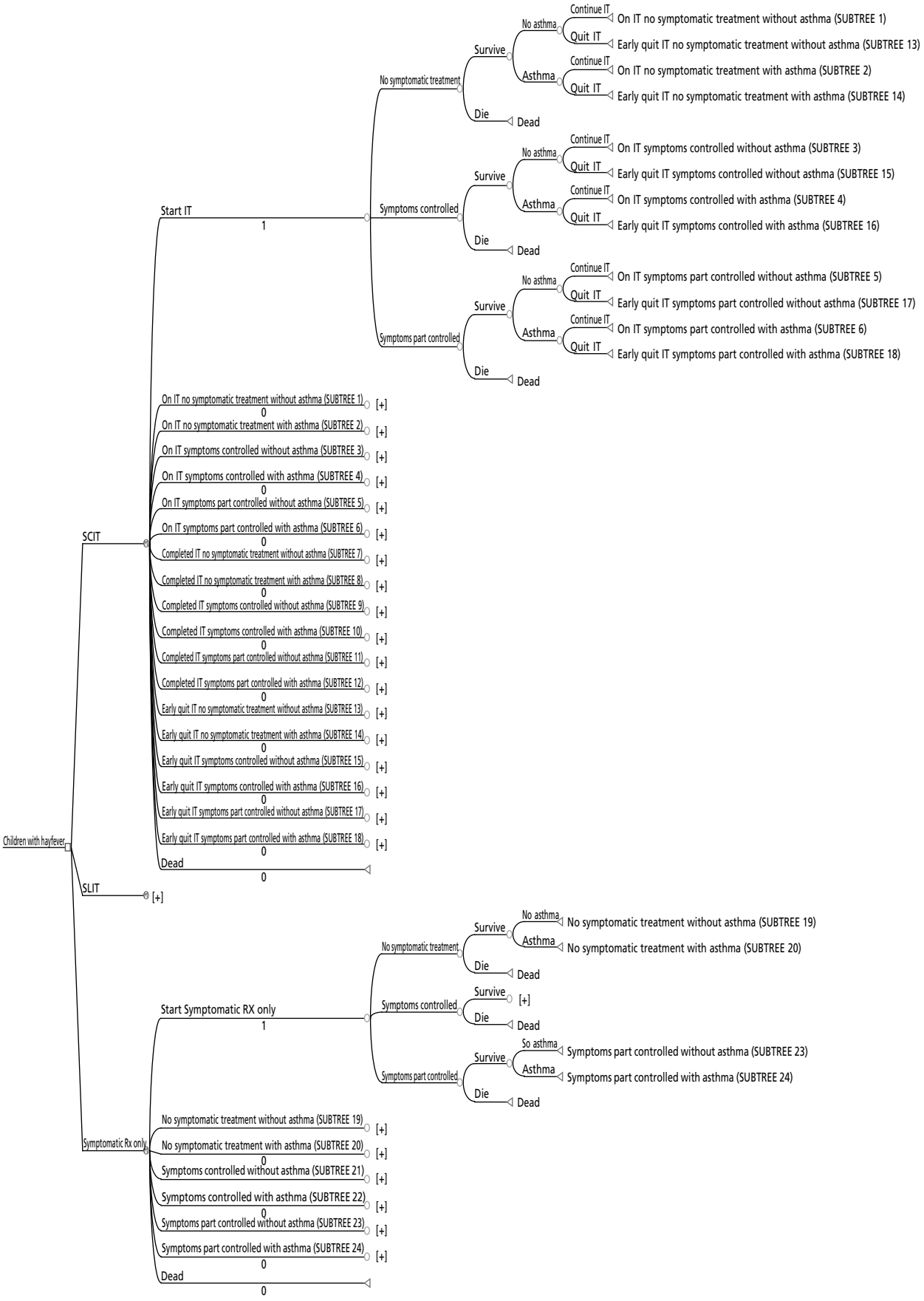

FIGURE 17 Child Markov model structure. Note that the health states for the SLIT arm are identical to those in the SCIT arm.

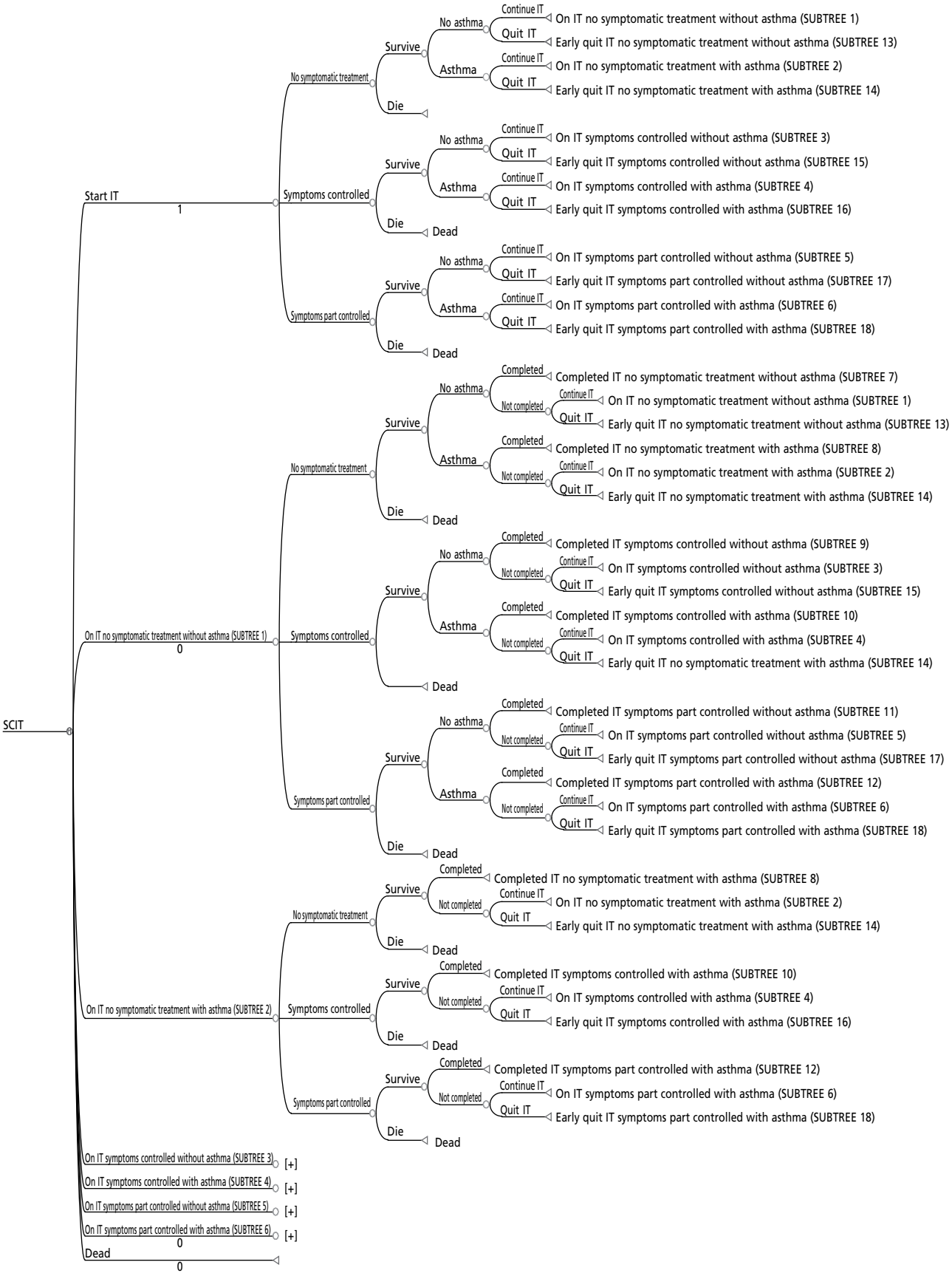

FIGURE 18 Child Markov model structure: SCIT arm (subtrees 1–6). [+], same structure as the first expanded structure directly above but with appropriate changes in probabilities.

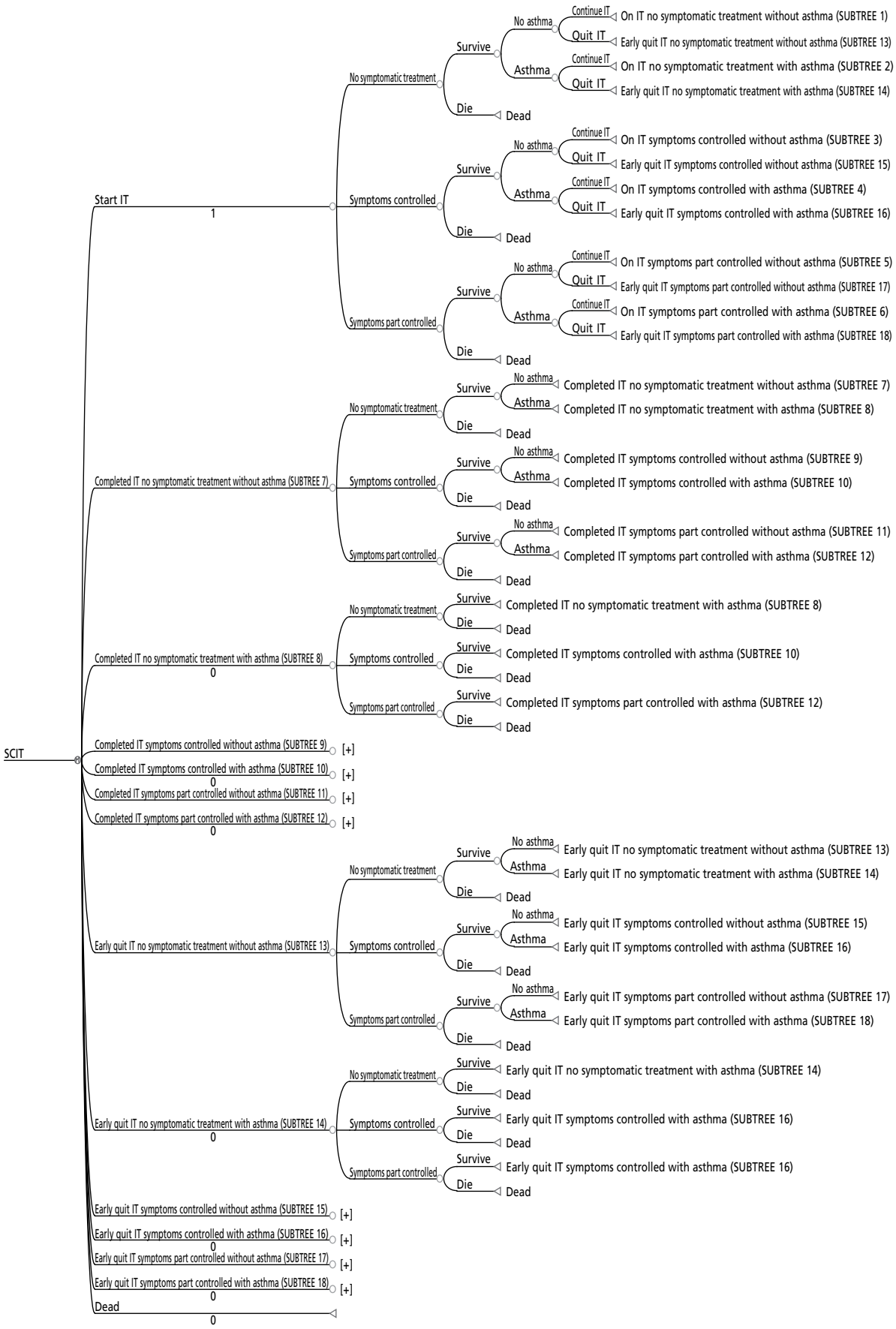

FIGURE 19 Child Markov model structure: SCIT arm (subtrees 7–18). [+], same structure as the first expanded structure directly above but with appropriate changes in probabilities.

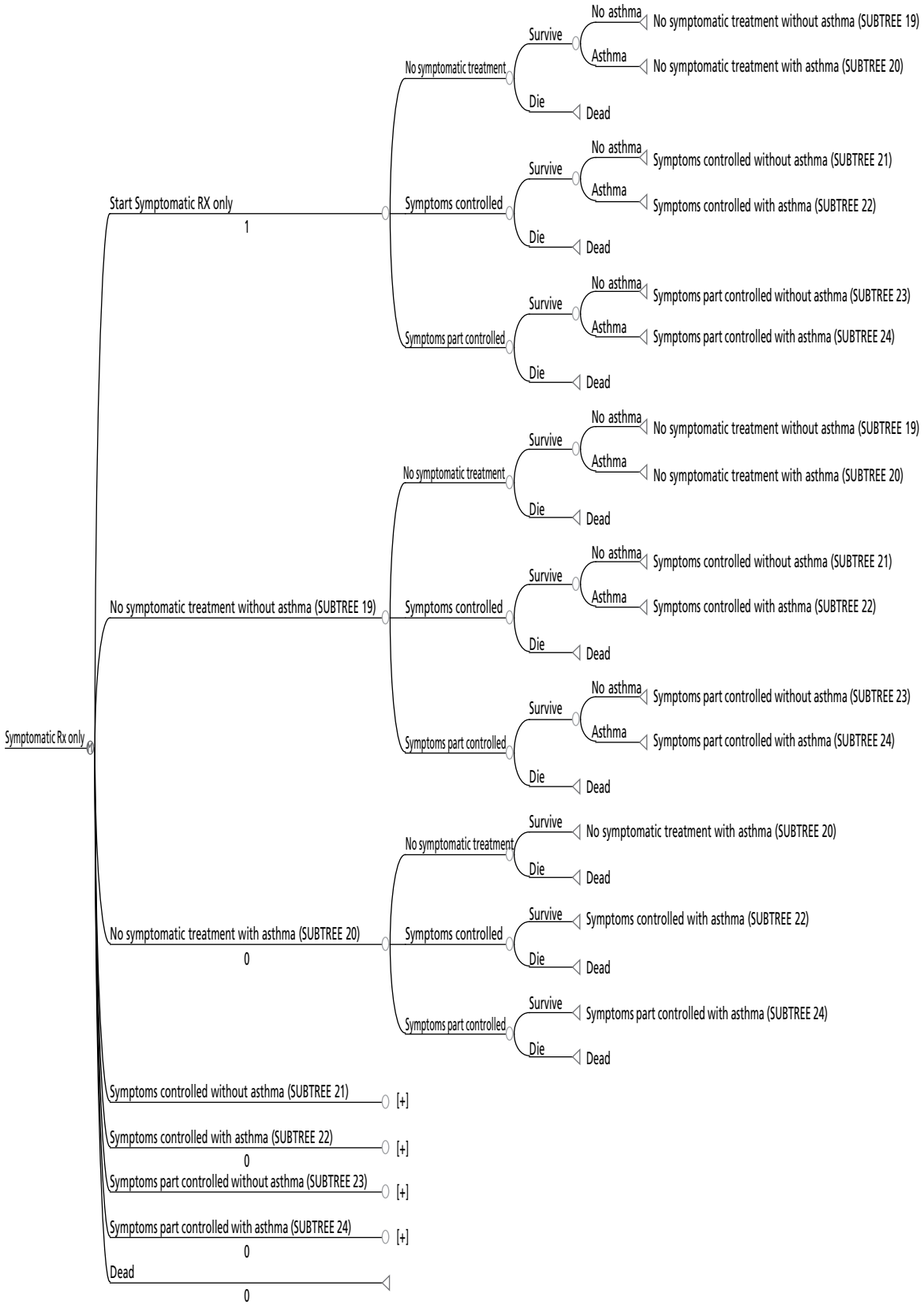

FIGURE 20 Child Markov model structure: ST arm. [+], same structure as the first expanded structure directly above but with appropriate changes in probabilities.

control all of their symptoms ('Symptoms controlled without asthma'). The rest of health states are for asthmatic children who have treatment to control some of their symptoms ('Symptoms partly controlled with asthma'), non-asthmatic children who have treatment to control some of their symptoms ('Symptoms partly controlled without asthma') and 'Dead'.

Inputs for both the adult and child Markov models

To conduct long-term comparative cost-effectiveness analyses of SCIT and SLIT when used to treat AR, a number of parameters (costs, outcomes and probabilities) were to be identified from the systematic review of EEs, systematic review of clinical effectiveness and other relevant studies.

Resource use and costs

All costs were to be reported in UK pounds at 2011–12 unit prices and, where appropriate, discounted at 3.5% as recommended by the UK NICE.[249] Resource use data were to be obtained from studies reviewed, as well as from expert opinion. Unit cost data were to be derived from nationally representative sources, such as the BNF (2012),[250] the National Schedule for Reference Costs and the Unit Costs of Health and Social Care (PSSRU).[251]

Utility values

As the primary outcome was to be expressed in terms of costs per QALYs gained, studies were of interest if they reported utility scores to reflect the health-related QoL associated with each health state in the model.

Transition probabilities

To complete the process of populating the model, it is necessary to obtain transition probabilities governing movement between the different health states in both adult and child models from studies in this review. A full list of transition probabilities required for the two models is provided in *Appendix 11*.

Challenges met when identifying model inputs for the preferred Markov models

One purpose of conducting the systematic review was to identify data associated with IT interventions or that on health states within AR pathways that could be used to populate the preferred Markov models described above. Both model- and non-model-based studies were considered in this respect. In particular, four types of model inputs and information were sought:

1. UK costs associated with IT strategies. Where UK cost data were not available, other data from countries with similar or transferable characteristics were sought.
2. Utility-based outcome data associated with health states within AR pathways.
3. Markov model structures that could be populated with UK specific data to enable the modelling of long-term cost-effectiveness of different types of IT treatments. Where possible, data on health states (from both Markov and decision tree models) that could be adapted and used in the preferred Markov models.
4. Information on transition probabilities governing movements between health states in Markov and decision tree models.

It was not possible to identify much suitable data from the 16 included EEs and reviews. The reasons are discussed below by type of model input/information.

Cost data

Two studies[228,231] were conducted using samples that included subjects from the UK, both of which compared SLIT with standard care. They presented detailed UK costs associated with AR, based on

resource use data such as visits to the GP, allergy specialist, and A&E department. In addition, costs of symptomatic and asthma medication, as well as indirect costs associated with production loss, were also presented. The cost estimates reported in these studies lend themselves to replication in our model and we would therefore consider these estimates to be credible inputs to our model. Despite these cost estimates all being based on the GT–08 GRAZAX trial,[93] it is likely that these results would be transferable to the UK generally. Other potentially useful cost estimates were identified in four other European studies.[225,226,230,234]

Outcome measures

Over 15 different types of outcome measures have been reported in the studies evaluated.

As described above (see *Quality of economic evaluations*), the vast number of these outcomes were not expressed as utilities but rather as 'natural' outcomes, and, as such, cannot be used in the Markov model. These include the number of asthma and rhinitis exacerbations, number of hospital visits and absence from nursery or school, SSs and MSs or the RQLQ.

Some studies did report utility-based outcome measures that could be converted into QALYs. As outlined above (see *Main characteristics of economic evaluations*), these utility-based outcomes were based on EQ-5D for four of the studies[228,230–232] and on an unspecified instrument for one study.[229] Studies whose QALYs were based on EQ-5D did not present EQ-5D data in sufficient detail to allow for their replication in our model. In particular, no baseline or follow-up values were reported in three of these studies,[228,230,231] with only the final results being reported in terms of cost per QALY gained. In the Beriot-Mathiot *et al*. study,[232] EQ-5D could be read off a diagram, but these were not disaggregated according to SLIT or ST. Brüggenjürgen *et al.*[229] reported utility scores for the following health states: mild AR (0.7579); moderate to severe AR (0.7378); severe AR and mild allergic asthma (0.7317); severe AR and moderate to severe allergic asthma (0.6985); no symptoms (0.7841); and death (0.0). Much higher utility scores were reported by Tamayama *et al*.[242] for similar AR health states: 0.96 (mild), 0.94 (moderate), 0.89 (severe) and 0.83 (severest). Provided that information on transition probabilities could have been obtained, these values could potentially have been used. In order to explore the possibility of using utility data based on a UK population, study authors from the GT–08 trial[93] were contacted, but it was not possible to obtain the necessary data.

Model structure and transition probabilities

Only five studies[224,226,227,229,235] were model-based studies (EEs or effectiveness studies): three[226,227,235] were based on decision tree models, whereas the other two[224,229] used Markov models.

Berto *et al.*[226] compared SLIT (with standard care) to standard care only, in a decision tree framework based on a sample of 2230 patients. A model structure was presented but the health states analysed are not the same or adaptable to those in our model. More importantly, information of transition probabilities depicting movements between health states is not presented in the study,[226] making it impossible for the model to be replicated using UK cost data.

The second decision tree model-based evaluation[235] was based on a cohort of 2000 patients and compared SCIT with ST. This study[235] presented some potentially useful data on probabilities in terms of asthma symptoms: the proportion of patients with AR and asthma compared with those with AR only; patients with asthma symptoms compared with those without asthma symptoms following either symptomatic or specific IT treatment; proportion of patients who develop asthma compared with proportion who do not among patients previously without asthma; and the proportion of patients who stop having asthma symptoms compared with proportion who continue with the symptoms among patients previously with asthma. The target outcome was the number of additional patients free from asthma symptoms after 10 years. However, it was difficult to ascertain how robust these probabilities were as the sources were not described in detail. Changes in symptoms or severity of AR were not incorporated into this analysis.

The third evaluation based on a decision tree model[226] compared SCIT, SLIT and ST for adults and children with AR and asthma. Some potentially important transition probabilities were also presented in this study.[226] However, most of these were based on expert opinion from a Delphi panel, whereas some information was obtained from an unpublished report. All epidemiological data ('hypotheses') for children were determined by the Delphi panel. For both children and adults, for example, the study[227] gives proportions that help determine the following probabilities: having rhinitis only as opposed to having rhinitis and asthma; having moderate compared with having severe rhinitis; and having mild compared with moderate asthma, as well as the percentage decrease in ST associated with IT by type of allergy and by SCIT or SLIT. However, attempts to replicate the model using UK cost data are not possible, as not all of the probabilities required to populate the model are presented, for example the proportion of patients who were either asymptomatic, who had an improvement in symptoms or those for whom the response to IT was inadequate.

Brüggenjürgen *et al*.[229] presented an analysis based on a Markov model. This study[229] was based on a hypothetical cohort of 2000 patients and compared SCIT in addition to ST to ST alone. An overview of the Markov model was given in the paper but the actual structure or the parameter estimates are not presented. This makes it difficult to assess the suitability of the model inputs for use in our model or for replicating the model using UK cost data.

The second Markov model-based study[224] was a cost analysis comparing SCIT, SLIT and variations of SCIT with standard care. The structure of the model was presented in the paper showing various pathways taken by patients following different treatment options. The health states presented in this model are not the same as those in our preferred model, and, more importantly, there was a lack of detail on the transition probabilities governing movement between health states, which precluded attempts to replicate the model using UK cost data.

Suitable data on transition probabilities, i.e. proportion of patients moving between different health states or levels of disease severity depending on treatment, were also not identified in any of the clinical effectiveness studies reviewed for this report.

Summary

Detailed information was available on cost data. A number of studies (both UK and non-UK) reported direct and indirect costs in sufficient detail to allow for their replication in our model. In particular, data from Bachert *et al*.[228] and Nasser *et al.*[231] were useful, supplemented with those obtained from expert opinion. Furthermore, data on utility scores associated with some severity levels of AR were also available based on German[229] and Japanese[230] populations. It may therefore have been possible to adapt these data for use in our models.

The biggest challenge faced, however, was the lack of information on transition probabilities. Although some model structures were presented in sufficient detail in some studies,[224,227] and utility data were provided in others,[229] not enough information on transition probabilities was given in all of the studies to allow for model replication using UK cost data.

Economic evaluation of immunotherapy

Because of the challenges faced with obtaining model inputs for the preferred Markov models, it was decided that an alternative approach to estimating the cost-effectiveness of SCIT, SLIT and ST would be taken. A novel EE was conducted, with results expressed in terms of ICERs calculated as costs per unit improvement in RQLQ and costs per QALY gain.

Methods

Costs estimation

Total costs were estimated by combining resource use data on staff, medication, supplies and productivity loss with unit costs. Resource use data are reported in *Table 42*, and unit costs are shown in *Table 43*.

Resource use for the sublingual immunotherapy group

The number of clinic visits for patients receiving SLIT was assumed to be 13 over a 3-year period, with an initial visit before commencing SLIT, followed by four outpatient visits per year (A Huissoon, Birmingham Heartlands Hospital, 9 March 2012, personal communication). Each visit for SLIT was assumed to last 20 minutes (0.33 hours) and patients would be seen by a consultant and a grade 8 nurse. Estimates of SLIT medication were based on Grazax, with one tablet taken daily throughout the year.[46] Over a 3-year period, the total number of tablets taken was 1095. Information on doses for two STs [desloratadine (Neoclarityn®, Schering-Plough) and budesonide (Budelin Novolizer®, Meda)] was obtained from the BNF (2012);[46] the dose of desloratadine was 5 mg daily, whereas 0.1–0.8 mg of budesonide was given twice daily. In line with the BSACI guidelines[2] (2008), ST was assumed to be administered for 3.5 months per year (2 weeks before, and then during the EPS). Estimates of productivity loss due to hours missed from work and hours at work with reduced productivity were obtained from a trial[231] that assessed the cost-effectiveness of Grazax in the UK.

Resource use for the subcutaneous immunotherapy group

Subcutaneous immunotherapy medication costs were based on Alutard. Although Pollinex is the only licensed product in the UK, treatment using Alutard is more representative of clinical practice in the UK (A Huissoon, personal communication). Pollinex is a preseasonal treatment consisting of six injections each year for 3 years, whereas Alutard is given throughout the year. After an updosing period (weekly injection for 12 weeks, followed by one injection after 2 weeks), maintenance injections are given once every 4 weeks. Thus, the total number of injections with Alutard over a 3-year period was assumed to be 46, i.e. 20 in year 1, and 13 in both years 2 and 3. Treatment with Alutard using 6-weekly, rather than 4-weekly, maintenance injections was also explored in an additional analysis. A clinic visit to receive an injection was assumed to last 0.27 hours, on the basis that a typical clinic, staffed by a consultant and a grade 8 nurse, would last about 4 hours, during which time 15 patients would be seen (A Huissoon, personal communication). Supplies used during each clinic visit were assumed to be one swab, one syringe, two hypodermic needles and a pair of gloves for each patient. Proportional differences in doses of symptomatic medication between SCIT and SLIT were taken from the study by Pokladnikova *et al*.,[225] which assessed the comparative cost-effectiveness of SCIT and SLIT; these proportions were 204/241 (SCIT/SLIT). Estimates of productivity loss for SCIT and SLIT were calculated based on data in the Pokladnikova *et al*. study[225] and the Nasser *et al*. study[231] Hours missed from work and hours at work with reduced productivity for the SCIT group were 14.03/5.75 and 16.25/7.77 those for SLIT, respectively.

Resource use for the symptomatic treatment group

The only resources considered in this group were symptomatic medication and estimates of productivity loss. Proportional differences in symptomatic medication doses between SLIT and ST observed in Nasser *et al*.[231] were used in estimating incremental doses for SLIT and ST. Desloratadine and budesonide doses for ST were therefore assumed to be 15.88/13.22 and 22.43/15.68 those of SLIT, respectively. The estimates of productivity loss due to hours missed from work and hours at work with reduced productivity were obtained from Nasser *et al*.[231]

Unit costs for the sublingual immunotherapy, subcutaneous immunotherapy and symptomatic treatment groups

These are shown in *Table 43*. Hourly wages for consultants (£137) and averaged hourly wages for band 8 nurses (£40.69) were obtained from Curtis.[251] The costs of supplies (swabs, syringes, needles and gloves) were estimated from a commercial website.[252] Drug costs for SLIT and symptomatic medications were based on the BNF (2012)[46] or were obtained from the manufacturer of Alutard (A Young, ALK-Abelló,

TABLE 42 Resource use (SLIT, SCIT and ST)

Staff costs, consumables and productivity loss	Units	Source
Staff (hours per visit)		
SLIT clinic visits		
Consultant	0.33[a]	Expert opinion
Band 8 nurse	0.33[a]	Expert opinion
SCIT clinic visits		
Consultant	0.27[b]	Expert opinion
Band 8 nurse	0.27[b]	Expert opinion
Supplies (no. of items per SCIT injection/visit)		
Swabs	1	Expert opinion
Syringes	1	Expert opinion
Needles	2	Expert opinion
Gloves	1	Expert opinion
Medication		
SLIT medication		
Grazax[c]	One tablet daily	BNF (2012)[46]
SCIT medication		
Alutard[d]	10–100,000 units/ml	Personal communication
Symptomatic medicine[e]		
Desloratadine	5 mg/daily	BNF (2012)[46]
Budesonide	0.1–0.8 mg twice daily[f]	BNF (2012)[46]
Productivity loss (SLIT)		
Hours missed from work	2.12	Nasser *et al.* (2007)[231]
Hours at work with reduced productivity	4.73	Nasser *et al.* (2007)[231]
Productivity loss (SCIT)[g]		
Hours missed from work	5.17	Pokladnikova *et al*. (2008),[225] Nasser *et al.* (2007)[231]
Hours at work with reduced productivity	9.89	

continued

TABLE 42 Resource use (SLIT, SCIT and ST) (*continued*)

Staff costs, consumables and productivity loss	Units	Source
Productivity loss (ST)		
Hours missed from work	6.27	Nasser *et al.* (2007)[231]
Hours at work with reduced productivity	14.04	Nasser *et al.* (2007)[231]

a It was assumed that patients would make five visits in year 1 and four visits in each of years 2 and 3, with every visit taking 20 minutes (0.33 hours).

b This was estimated as 4 hours in a typical SCIT clinic for 15 patients.

c Grazax tablets were assumed to be taken daily over the course of 3 years, i.e. 365 tablets per year.

d It was assumed that patients undergoing SCIT would have 46 injections over 3 years: 20 in year 1 and 13 in each of years 2 and 3.

e Proportional differences in symptomatic medication dosages between SCIT and SLIT observed in Pokladnikova *et al.*[225] were applied. As a result, total symptomatic treatment dosage for SCIT was assumed to be 204/241 that of SLIT. Similarly, proportional differences in symptomatic medication dosages between SLIT and ST observed in Nasser *et al.*[231] were used in estimating incremental dosages for SLIT and ST. Desloratadine and budesonide dosages for ST were assumed to be 15.88/13.22 and 22.43/15.68 those of SLIT, respectively.

f The average of this dosage range was used in the base-case analysis, i.e. 0.45 mg twice daily.

g Based on the proportional differences in estimates of productivity loss between SCIT and SLIT observed in Pokladnikova *et al.*,[225] estimates used for SCIT were inflated from those applied to the SLIT group, i.e. hours missed from work and hours at work with reduced productivity were 14.03/5.75 and 16.25/7.77 those of SLIT, respectively.

TABLE 43 Unit costs (SLIT, SCIT and ST)

Staff costs, consumables and productivity loss	Units	Source
Staff (wage per hour)		
Consultant	£137.00	Curtis (2011)[251]
Band 8 nurse	£40.69[a]	Curtis (2011)[251]
Supplies (cost per item)		
Swabs	£0.01	Medisave (2011)[252]
Syringes	£0.10	Medisave (2011)[252]
Needles	£0.03	Medisave (2011)[252]
Gloves	£0.03	Medisave (2011)[252]
Medication		
SLIT medication		
Grazax	£2.23 per tablet	BNF (2012)[46]
SCIT medication		
Alutard	£61.97–93.82/ml[b]	Manufacturer communication
Symptomatic medicine		
Desloratadine	£0.02/mg	BNF (2012)[46]
Budesonide	£0.44/mg	BNF (2012)[46]
Productivity loss		
Average wage/hour	£9.62[c]	Office for National Statistics (2011)[253]

a An average wage for the four grades within band 8 was used.

b This unit cost varies according to the amount of Alutard vaccine units in each 1-ml injection, i.e. from 10 to 100,000 units per millilitre.

c This was estimated as the gross hourly rate for the UK in 2011 (£14.82) minus tax, pension and national insurance contributions, valued at 35% of the average gross rate.

29 March 2012, personal communication). The opportunity costs associated with productivity loss were estimated as the gross hourly rate for the UK in 2011 minus tax, pension and national insurance contributions valued at 35% of the average gross rate.[254] As this hourly rate was £14.82 (Office for National Statistics[253]), the opportunity cost associated with productivity loss was assumed to be £9.62.

Outcome estimation

Two outcomes were assessed in this EE: the RQLQ and QALYs.

Rhinoconjunctivitis Quality of Life Questionnaire

Two sets of mean RQLQ changes (and associated CIs) were used in this model. The first set was based on meta-analyses of SLIT compared with ST, and SCIT compared with ST (direct comparisons; see *Chapter 3*, *Results*). The second set was based on results from the ICMR (SLIT compared with ST, SCIT compared with ST and SCIT compared with SLIT (see *Chapter 3*, *Indirect comparison subcutaneous immunotherapy versus sublingual immunotherapy*).

Quality-adjusted life-years

These were based on changes in the EQ-5D, with an assumption that the EQ-5D changes applied to a 3-month period during the pollen season. To calculate EQ-5D, a mapping algorithm was used to convert mean RQLQ changes associated with either SCIT or SLIT to mean EQ-5D changes. The most appropriate method of developing a mapping equation between two measures is to apply both measures to a common group of patients. As no data set based on such a comparison was available, nor the result of any mapping exercise based on such a comparison, it was necessary to make a number of assumptions in calculating the EQ-5D values. The RQLQ scale is from 0 (best) to 6 (worst). It is assumed that the top end of the scale maps to the EQ-5D state representing no problems in any of the five dimensions. By definition, this state has a QoL score of '1'. The bottom end of the RQLQ scale was mapped to the EQ-5D state representing maximum problems with usual activities, pain/discomfort and anxiety/depression, but no problems with mobility or self-care, which are assumed to be unaffected by SAR. This state has a QoL score of –0.07 on the standard UK tariff. Therefore, it was assumed that going from worst to best was a six-point reduction in RQLQ and a 1.07-point increase in the EQ-5D score. As a result, each unit decrease (improvement) in RQLQ was assumed to map to a 0.178-point increase in QoL score (assuming that a unit decrease has the same value at all points on the scale).

Incremental cost-effectiveness ratio calculation

The generic formula for an ICER[255] was used to calculate cost-effectiveness estimates. For an outcome based on costs per QALY in a comparison between SCIT and ST, for example, the formula would be given by:

$$ICER = \frac{\text{Cost of SCIT} - \text{Cost of ST}}{\text{QALYs for SCIT} - \text{QALYs for ST}} \quad (1)$$

Discounting

All costs are reported in UK pounds at 2010–11 unit prices. All future costs and outcomes, where appropriate, were discounted at 3.5% as recommended by NICE.[249]

Duration of analysis

Based on expert clinical opinion and observations from clinical trials (the GT–08 trial[93]), it was assumed that 3 years of IT would result in a sustained effect of a further 3 years. Therefore, a 6-year time horizon was used in the base-case analysis of this study.[93] For illustration purposes, however, a time horizon of up to 10 years (7 years post IT) was also considered. Costs included from years 4 to 10 were only those associated with ST and productivity loss. As SLIT and SCIT medication was assumed to be given for only 3 years, only 3-year cumulative costs were incorporated in the analysis of costs beyond 3 years.

Results

Costs

The annual and cumulative costs associated with SLIT, SCIT and ST are shown in *Tables 44–46*. The annual costs of SCIT were higher than those for either SLIT or ST. Over a 3-year period, the cumulative costs for SCIT were £2869 and £5537 higher than those for SLIT and ST, respectively. The major cost drivers for the SCIT group were staff and SCIT medication costs; this was the same in the SLIT group, although not to the same extent as for SCIT. Costs associated with productivity loss were highest in the ST group (about 35% and 30% higher than for the SCIT and SLIT groups, respectively).

A similar hierarchy of costs could be observed when costs were extrapolated from 3 years to a time horizon of between 4 and 10 years (*Tables 47–49*). However, the differences between SCIT and ST and between SLIT and ST reduced gradually with time, whereas those between SCIT and SLIT increased.

Cost-effectiveness results

Results based on both direct comparisons and indirect comparisons of the difference in RQLQ between the three groups are presented below.

Direct comparisons

As shown in *Table 50,* the mean change in RQLQ for the comparison between SLIT and ST was 0.340 (95% CI 0.18 to 0.49) in favour of SLIT. Based on a cost difference between the two groups of £2668, an ICER of £7848 per unit improvement in RQLQ was obtained. *Table 50* also shows that between 3 and 10 years after the start of IT, the cost difference between SLIT and ST reduces from £2668 to £1820. Over the same period, QALY gains favouring SLIT increase from 0.0440 to 0.1305. The ICERs based on QALYs gained over this period therefore reduce from £60,704 to £13,951. An ICER of £27,269 was obtained 6 years after the start of IT. This reduction in costs per QALY gained is shown graphically in *Figure 21*.

TABLE 44 Costs: SLIT

Staff costs, consumables and productivity loss	Costs		
	Year 1	Year 2[a]	Year 3[a]
Staff during clinic visits			
Consultant	£226.05	£174.72	£168.82
Band 8 nurse	£67.14	£51.89	£50.14
SLIT medication			
Grazax	£813.95	£786.42	£759.83
Symptomatic medicine			
Desloratadine	£20.44	£19.75	£19.08
Budesonide	£35.43	£34.24	£33.08
Productivity loss			
Hours missed from work	£20.39	£19.70	£19.04
Hours at work with reduced productivity	£45.50	£43.96	£42.48
Total annual costs	**£1228.91**	**£1130.70**	**£1092.46**
Total cumulative costs	**£1228.91**	**£2359.61**	**£3452.07**

a Costs discounted at 3.5%.

TABLE 45 Costs: SCIT

Staff costs, consumables and productivity loss	Costs		
	Year 1	Year 2[a]	Year 3[a]
Staff during clinic visits			
Consultant	£739.80	£464.61	£448.90
Band 8 nurse	£219.73	£137.99	£133.33
Supplies/consumables[b]	£4.00	£2.51	£2.43
SCIT medication			
Allergy medicine			
Alutard	£1239.46	£1178.42	£1138.57
Symptomatic medicine			
Desloratadine	£24.15	£23.33	£22.54
Budesonide	£41.86	£40.45	£39.08
Productivity loss			
Hours missed from work	£49.74	£48.05	£46.43
Hours at work with reduced productivity	£95.14	£91.92	£88.82
Total annual costs	**£2413.88**	**£1987.29**	**£1920.08**
Total cumulative costs	**£2413.88**	**£4401.16**	**£6321.25**

a Costs discounted at 3.5%.
b Supplies are made up of swabs, syringes, hypodermic needles and gloves.

TABLE 46 Costs: ST

Consumables and productivity loss	Costs		
	Year 1	Year 2[a]	Year 3[a]
Medication			
Symptomatic medicine			
Desloratadine	£24.55	£23.72	£22.92
Budesonide	£50.68	£48.97	£47.31
Productivity loss			
Hours missed from work	£60.32	£58.28	£56.31
Hours at work with reduced productivity	£134.78	£130.22	£125.82
Total annual costs	**£270.33**	**£261.19**	**£252.35**
Total cumulative costs	**£270.33**	**£531.52**	**£783.87**

a Costs discounted at 3.5%.

TABLE 47 Sublingual immunotherapy costs from years 4 to 10

Staff costs, consumables and productivity loss[a,b]	Costs						
	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Staff during clinic visits							
Consultant	–	–	–	–	–	–	–
Band 8 nurse	–	–	–	–	–	–	–
SLIT medication							
Grazax	–	–	–	–	–	–	–
Symptomatic medicine							
Desloratadine	£18.44	£17.81	£17.21	£16.63	£16.07	£15.52	£15.00
Budesonide	£31.96	£30.88	£29.83	£28.83	£27.85	£26.91	£26.00
Productivity loss							
Hours missed from work	£18.39	£17.77	£17.17	£16.59	£16.03	£15.49	£14.96
Hours at work with reduced productivity	£41.04	£39.65	£38.31	£37.02	£35.76	£34.56	£33.39
Total annual costs	**£109.83**	**£106.12**	**£102.53**	**£99.06**	**£95.71**	**£92.48**	**£89.35**
Total cumulative costs[b]	**£3561.91**	**£3668.02**	**£3770.55**	**£3869.61**	**£3965.33**	**£4057.80**	**£4147.15**

a Costs discounted at 3.5%.

b Includes cumulative cost of SLIT incurred in years 1–3.

TABLE 48 Subcutaneous immunotherapy costs for years 4–10

Staff costs, consumables and productivity loss	Costs						
	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Staff during clinic visits							
Consultant	–	–	–	–	–	–	–
Band 8 nurse	–	–	–	–	–	–	–
SCIT medication							
Alutard	–	–	–	–	–	–	–
Symptomatic medicine							
Desloratadine	£21.78	£21.05	£20.33	£19.65	£18.98	£18.34	£17.72
Budesonide	£37.76	£36.48	£35.25	£34.06	£32.90	£31.79	£30.72

TABLE 48 Subcutaneous immunotherapy costs for years 4–10 (*continued*)

Staff costs, consumables and productivity loss	Costs						
	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Productivity loss							
Hours missed from work	£44.86	£43.34	£41.88	£40.46	£39.09	£37.77	£36.49
Hours at work with reduced productivity	£85.81	£82.91	£80.11	£77.40	£74.78	£72.25	£69.81
Total annual costs	**£190.21**	**£183.78**	**£177.56**	**£171.56**	**£165.76**	**£160.15**	**£154.74**
Total cumulative costs[a,b]	**£6511.46**	**£6695.24**	**£6872.80**	**£7044.36**	**£7210.12**	**£7370.27**	**£7525.01**

a Costs discounted at 3.5%.

b Includes cumulative cost of SCIT incurred in years 1–3.

TABLE 49 Symptomatic treatment costs for years 4–10

Consumables and productivity loss	Costs						
	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Medication							
Symptomatic medicine							
Desloratadine	£22.15	£21.40	£20.67	£19.97	£19.30	£18.65	£18.02
Budesonide	£45.71	£44.17	£42.67	£41.23	£39.84	£38.49	£37.19
Productivity loss							
Hours missed from work	£54.40	£52.56	£50.79	£49.07	£47.41	£45.81	£44.26
Hours at work with reduced productivity	£121.56	£117.45	£113.48	£109.64	£105.93	£102.35	£98.89
Total annual costs	**£243.82**	**£235.58**	**£227.61**	**£219.91**	**£212.48**	**£205.29**	**£198.35**
Total cumulative costs[a,b]	**£1027.69**	**£1263.27**	**£1490.88**	**£1710.79**	**£1923.26**	**£2128.55**	**£2326.90**

a Costs discounted at 3.5%.

b Includes cumulative cost of SCIT incurred in years 1–3.

TABLE 50 Economic evaluation results: SLIT vs ST (based on direct comparisons)

Cost difference (£) at	
3 years	2668
4 years	2534
5 years	2405
6 years	2280
7 years	2159
8 years	2042
9 years	1929
10 years	1820
RQLQ difference	0.340 (95% CI 0.180 to 0.490)
ICER (£): costs/unit improvement in RQLQ	7848 (95% CI 5445 to 14,823)
Total QALY gain in 3 years	0.0440 (95% CI 0.0233 to 0.0633)
ICER (£): costs per QALY	60,704 (95% CI 42,121 to 114,663)
Total QALY gain in 4 years	0.0576 (95% CI 0.0305 to 0.0830)
ICER (£): costs per QALY	43,977 (95% CI 30,514 to 83,067)
Total QALY gain in 5 years	0.0708 (95% CI 0.0305 to 0.0830)
ICER (£): costs per QALY	33,948 (95% CI 23,556 to 64,124)
Total QALY gain in 6 years	0.0836 (95% CI 0.0443 to 0.1205)
ICER (£): costs per QALY	27,269 (95% CI 18,921 to 51,508)
Total QALY gain in 7 years	0.0959 (95% CI 0.0508 to 0.1383)
ICER (£): costs per QALY	22,504 (95% CI 15,615 to 42,508)
Total QALY gain in 8 years	0.1078 (95% CI 0.0571 to 0.1554)
ICER (£): costs per QALY	18,935 (95% CI 13,139 to 35,767)
Total QALY gain in 9 years	0.1194 (95% CI 0.0632 to 0.1720)
ICER (£): costs per QALY	16,164 (95% CI 11,216 to 30,532)
Total QALY gain in 10 years	0.1305 (95% CI 0.0691 to 0.1880)
ICER (£): costs per QALY	13,951 (95% CI 9680 to 26,351)

Table 51 shows the results comparing SCIT with ST. The mean change in RQLQ in favour of SCIT was 0.740 (95% CI 0.56 to 0.92) and this resulted in an ICER of £7483 per unit improvement in RQLQ (based on a cost difference of £5537). Between 3 and 10 years after starting IT, the cost difference between SCIT and ST reduced from £5537 to £5198, whereas the QALY gains in favour of SCIT increased from 0.0957 to 0.2840. Consequently, the cost per QALY gained between the same time period reduced from £57,883 to £18,304 as shown in *Figure 22*. The value of this ICER was £29,579 6 years after the start of IT.

Indirect comparisons

Table 52 presents the results of the comparison between SLIT and ST. The mean change in RQLQ favouring SLIT was 0.247 (95% CrI –0.156 to 0.729) and this resulted in an ICER of £10,802 per unit improvement in RQLQ (based on a cost difference of £2668). The cost differences between the two groups reduced from £2668 to £1820 over a period of 3–10 years post commencement of IT. As in the direct comparison, the QALY gains favouring SLIT increased from 0.0319 to 0.0948 over the same period. This resulted in a

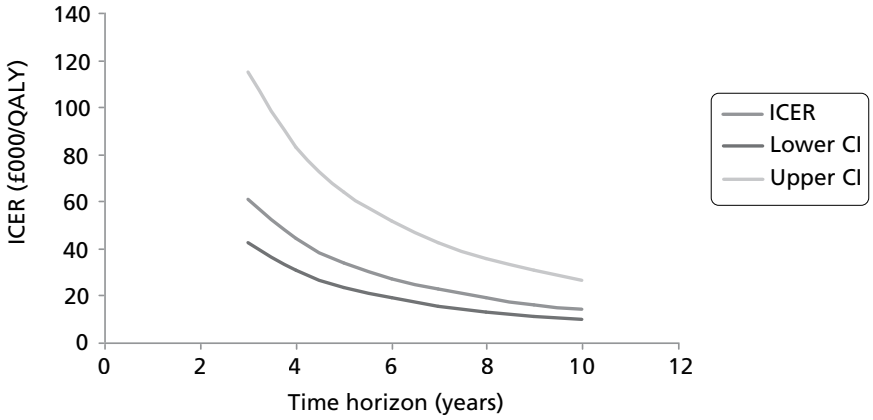

FIGURE 21 Cost-effectiveness of SLIT vs ST (direct comparisons).

TABLE 51 Economic evaluation results: SCIT vs ST (based on direct comparisons)

Cost difference (£) at	
3 years	5537
4 years	5484
5 years	5432
6 years	5382
7 years	5334
8 years	5287
9 years	5242
10 years	5198
RQLQ difference	0.740 (95% CI 0.560 to 0.920)
ICER (£): costs/unit improvement in RQLQ	7483 (95% CI 6019 to 9889)
Total QALY gain in 3 years	0.0957 (95% CI 0.0724 to 0.1189)
ICER (£): costs per QALY	57,883 (95% CI 46,558 to 76,488)
Total QALY gain in 4 years	0.1254 (95% CI 0.0949 to 0.1559)
ICER (£): costs per QALY	43,722 (95% CI 35,168 to 57,776)
Total QALY gain in 5 years	0.1542 (95% CI 0.1167 to 0.1917)
ICER (£): costs per QALY	35,233 (95% CI 28,340 to 46,558)
Total QALY gain in 6 years	0.1820 (95% CI 0.1377 to 0.2262)
ICER (£): costs per QALY	29,579 (95% CI 23,792 to 39,087)
Total QALY gain in 7 years	0.2088 (95% CI 0.1580 to 0.2596)
ICER (£): costs per QALY	25,545 (95% CI 20,547 to 33,756)
Total QALY gain in 8 years	0.2347 (95% CI 0.1776 to 0.2918)
ICER (£): costs per QALY	22,524 (95% CI 18,117 to 29,764)
Total QALY gain in 9 years	0.2598 (95% CI 0.1966 to 0.3230)
ICER (£): costs per QALY	20,178 (95% CI 16,230 to 26,664)
Total QALY gain in 10 years	0.2840 (95% CI 0.2149 to 0.3531)
ICER (£): costs per QALY	18,304 (95% CI 14,723 to 24,188)

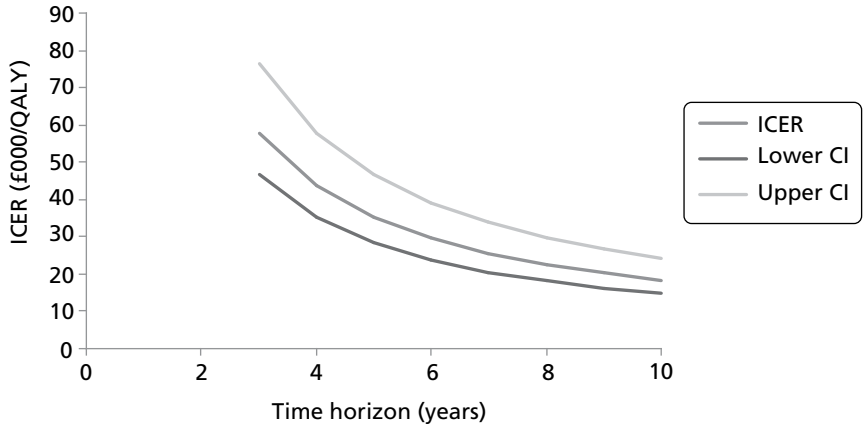

FIGURE 22 Cost-effectiveness of SCIT vs ST (direct comparisons).

reduction in the costs per QALY gained from £83,560 to £19,203 over the same period of time as depicted in *Figure 23*. The value of the ICER 6 years after the start of IT was £37,537.

In the comparison between SCIT and ST (*Table 53*), the mean change in RQLQ favouring SCIT was 0.764 (95% CrI 0.425 to 1.116). Based on a cost difference of £5537, an ICER of £7248 per unit improvement in RQLQ was found. As in the direct comparisons, the cost difference between the two groups reduced over a period of 8 years (3–10 years after the start of IT) from £5537 to £5198. The QALY gains in favour of SCIT increased from 0.0988 to 0.2932 over the same period. As depicted in *Figure 24*, the resultant ICERs therefore decreased from £56,064 to £17,729 over this period. The ICER, 6 years after the start of IT, was £28,650 per QALY gained.

The last comparison was between SCIT and SLIT (*Table 54*). The mean change in RQLQ (favouring SCIT) was 0.517 (95% CrI –0.0710 to 1.045) resulting in an ICER of £5550 per unit improvement in RQLQ, based on a cost difference of £2869. The cost differences between the two groups reduced from £2869 to £3378 over a period of 3–10 years following commencement of IT. QALY gains favouring SCIT increased from 0.0668 to 0.1984 over the same period. This resulted in a reduction in the costs per QALY gained from £42,928 to £17,025 over the same period of time as depicted in *Figure 25*. The value of the ICER, 6 years after the start of IT, was £24,404.

Six-weekly treatment schedule

Using a 6-weekly maintenance schedule instead of a 4-weekly one resulted in lower costs (fewer clinic visits and fewer injections) (*Table 55*). The effectiveness was assumed to be the same, therefore the cost-effectiveness was increased. The differences in ICERs (at 6 years) between the two maintenance schedules are shown below (full details are shown in *Appendix 12*).

NHS perspective only

Costs were considered from the NHS and patient perspectives because of the burden that AR places on both the NHS and patients. For purposes of reimbursement, however, only NHS costs are important. We therefore also conducted a CEA (results not shown) based on NHS costs only, and the results were not altered significantly. IT (when compared with ST) was found to be cost-effective around 7 years after the start of treatment (1 year later than when productivity costs are included). The only exception was the comparison between SLIT and ST based on indirect comparison results where this threshold increased to more than 10 years after the start of IT. In the comparison between SCIT and SLIT, SCIT was shown to be more cost-effective as early as 4 years after the start of treatment (1 year earlier than when productivity costs are included).

TABLE 52 Economic evaluation results: SLIT vs ST (based on indirect comparisons)

Cost difference (£) at	
3 years	2668
4 years	2534
5 years	2405
6 years	2280
7 years	2159
8 years	2042
9 years	1929
10 years	1820
RQLQ difference	0.247 (95% CI –0.1560 to 0.729)
ICER (£): costs/unit improvement in RQLQ	10,802 (3660 to ST dominates)
Total QALY gain in 3 years	0.0319 (95% CI –0.0202 to 0.0942)
ICER (£): costs per QALY	83,560 (28,312 to ST dominates)
Total QALY gain in 4 years	0.0419 (95% CI –0.0264 to 0.1236)
ICER (£): costs per QALY	60,535 (20,510 to ST dominates)
Total QALY gain in 5 years	0.0515 (95% CI –0.0325 to 0.1519)
ICER (£): costs per QALY	46,730 (15,833 to ST dominates)
Total QALY gain in 6 years	0.0607 (95% CI –0.0384 to 0.1792)
ICER (£): costs per QALY	37,537 (12,718 to ST dominates)
Total QALY gain in 7 years	0.0697 (95% CI –0.0440 to 0.2057)
ICER (£): costs per QALY	30,977 (10,496 to ST dominates)
Total QALY gain in 8 years	0.0783 (95% CI –0.0495 to 0.2312)
ICER (£): costs per QALY	26,065 (8831 to ST dominates)
Total QALY gain in 9 years	0.0867 (95% CI –0.0548 to 0.2559)
ICER (£): costs per QALY	22,250 (7539 to ST dominates)
Total QALY gain in 10 years	0.0948 (95% CI –0.0599 to 0.2798)
ICER (£): costs per QALY	19,203 (6506 to ST dominates)

'ST dominates' means that ST is more effective and also cheaper.

Interpretation of the cost-effectiveness results

Staff costs for SCIT were higher compared with those for SLIT owing to the greater number of clinic visits made by patients in this group over a 3-year period, i.e. 46 compared with 13. The costs of SCIT medication per unit were also higher than those for SLIT thereby driving the costs for SCIT further up. As would be expected, SCIT was associated with higher productivity losses owing to the nature of treatment that warranted absence from work. Individuals in the ST group had highest overall productivity losses. This finding is consistent with those found in other studies.[228,230,231] Costs associated with asthma and AE medication were not included in the analysis because the cost differences in medications between SCIT, SLIT and ST were assumed to be negligible. This was based on expert clinical opinion and a review of the literature.

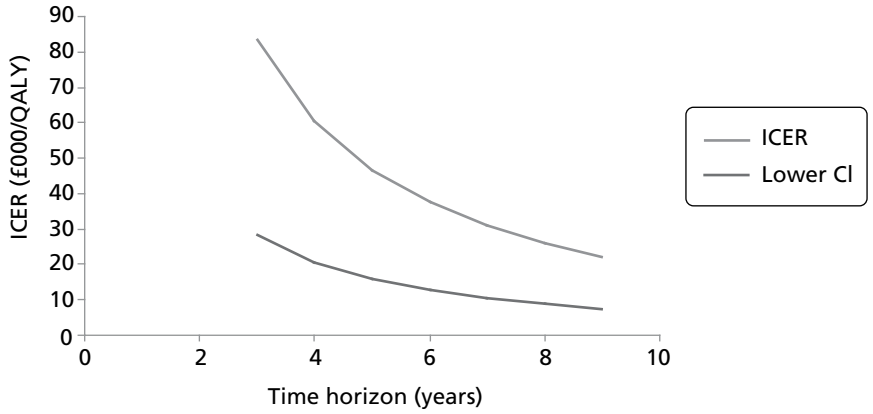

FIGURE 23 Cost-effectiveness of SLIT vs ST (indirect comparisons).

TABLE 53 Economic evaluation results: SCIT vs ST (based on indirect comparisons)

Cost difference (£) at	
3 years	5537
4 years	5484
5 years	5432
6 years	5382
7 years	5334
8 years	5287
9 years	5242
10 years	5198
RQLQ difference	0.764 (95% CI 0.425 to 1.116)
ICER (£): costs/unit improvement in RQLQ	7248 (95% CI 4962 to 13,029)
Total QALY gain in 3 years	0.0988 (95% CI 0.0549 to 0.1443)
ICER (£): costs per QALY	56,064 (95% CI 38,381 to 100,784)
Total QALY gain in 4 years	0.1295 (95% CI 0.0720 to 0.1892)
ICER (£): costs per QALY	42,349 (95% CI 28,992 to 76,128)
Total QALY gain in 5 years	0.1592 (95% CI 0.0885 to 0.2325)
ICER (£): costs per QALY	34,126 (95% CI 23,362 to 61,347)
Total QALY gain in 6 years	0.1879 (95% CI 0.1045 to 0.2744)
ICER (£): costs per QALY	28,650 (95% CI 19,613 to 51,502)
Total QALY gain in 7 years	0.2156 (95% CI 0.1199 to 0.3149)
ICER (£): costs per QALY	24,743 (95% CI 16,939 to 44,479)
Total QALY gain in 8 years	0.2423 (95% CI 0.1348 to 0.3540)
ICER (£): costs per QALY	21,816 (95% CI 14,935 to 39,218)
Total QALY gain in 9 years	0.2682 (95% CI 0.1492 to 0.3918)
ICER (£): costs per QALY	19,544 (95% CI 13,380 to 35,133)
Total QALY gain in 10 years	0.2932 (95% CI 0.1631 to 0.4283)
ICER (£): costs per QALY	17,729 (95% CI 12,137 to 31,871)

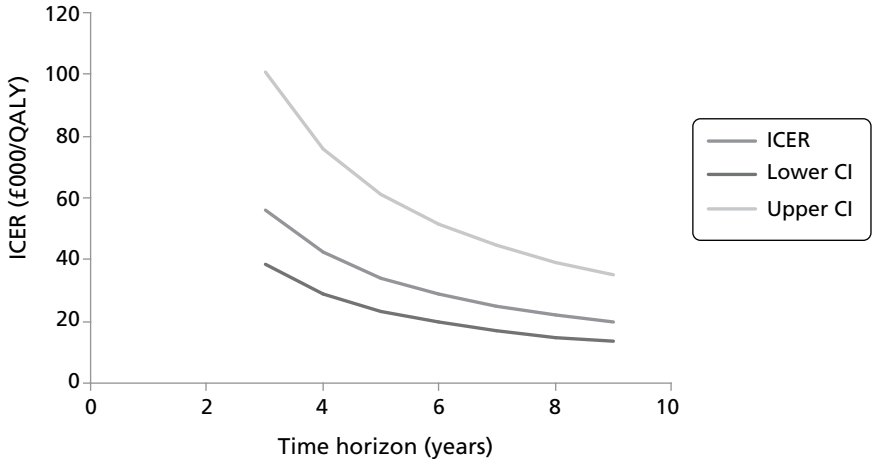

FIGURE 24 Cost-effectiveness of SCIT vs ST (indirect comparisons).

In the results based on direct and indirect comparisons, SCIT and SLIT were both found to be more effective than ST as shown by the difference in RQLQ. The results from the indirect comparison also suggest that SCIT may be more effective than SLIT; however, this is associated with uncertainty (a non-significant result) and must be interpreted cautiously (see *Chapter 3, Indirect comparison of subcutaneous immunotherapy versus sublingual immunotherapy*). As the QALYs used in this analysis were based on an algorithm that mapped the RQLQ to EQ-5D, the same direction of effect observed in the RQLQ was also seen in the QALY gains.

In terms of cost per unit improvement in RQLQ, ICERs of £7848 and £10,802 were obtained in the comparison between SLIT and ST, whereas ICERS of £7483 and £7248 were estimated for the comparison between SCIT and ST. As IT in the two sets of comparisons was both more costly and effective, it would be considered to be cost-effective only if decision-makers were willing to pay at least £11,000 for each unit improvement in RQLQ. For the comparison between SCIT and SLIT, SCIT would be considered a more cost-effective alternative if decision-makers were willing to pay at least £5600 for a similar improvement in RQLQ. A unit change of 0.5 may be considered clinically significant.

Cost-effectiveness results based on costs per QALY gained can be assessed against a threshold of £20,000–30,000, the conventional threshold adopted by decision-makers in the UK NHS, such as NICE.[249] The results of the analysis show that IT, when compared with ST, becomes cost-effective around 6 years after the start of treatment (7 years for NHS perspective only). The only exception is the comparison between SLIT and ST based on indirect comparisons, where this threshold increased to 7 years (10 years for NHS perspective only). In the comparison between SCIT and SLIT, SCIT was shown to be more cost-effective as early as 5 years after the start of treatment (4 years for NHS perspective only). These results are consistent with those for studies that reported outcomes in terms of ICERs (shown in *Table 39*), although the ICERs in our study were much higher.

In view of the many simplifications required in performing the CEA, these results must be regarded as indicative. The results using direct comparisons suggest that either SLIT or SCIT may be cost-effective compared with symptomatic treatment (ST), applying usual UK standards of cost-effectiveness. However, this tentative conclusion depends on there being a good reason to believe that clinical effectiveness will be sustained for somewhat longer than the 3 years' period following cessation of treatment.

When the results from the indirect comparisons were used, the cost-effectiveness results for SCIT compared with ST were largely unchanged. For SLIT compared with ST, however, the results for a difference in RQLQ were no longer statistically significant at the 95% confidence level. It is clear that SLIT is more costly than ST. Accordingly, there is no finite upper confidence limit for the ICER: the CI stretches into

TABLE 54 Economic evaluation results: SCIT vs SLIT (based on indirect comparisons)

Cost difference (£) at	
3 years	2869
4 years	2950
5 years	3027
6 years	3102
7 years	3175
8 years	3245
9 years	3312
10 years	3378
RQLQ difference	0.517 (95% CI –0.0710 to 1.045)
ICER (£): costs/unit improvement in RQLQ	5550 (2746 to SLIT dominates)
Total QALY gain in 3 years	0.0668 (95% CI –0.0092 to 0.1351)
ICER (£): costs per QALY	42,928 (21,238 to SLIT dominates)
Total QALY gain in 4 years	0.0876 (95% CI –0.0120 to 0.1771)
ICER (£): costs per QALY	33,661 (16,653 to SLIT dominates)
Total QALY gain in 5 years	0.1077 (95% CI –0.0148 to 0.2177)
ICER (£): costs per QALY	28,105 (13,904 to SLIT dominates)
Total QALY gain in 6 years	0.1271 (95% CI –0.0175 to 0.2569)
ICER (£): costs per QALY	24,404 (12,074 to SLIT dominates)
Total QALY gain in 7 years	0.1459 (95% CI –0.0200 to 0.2948)
ICER (£): costs per QALY	21,764 (10,768 to SLIT dominates)
Total QALY gain in 8 years	0.1640 (95% CI –0.0225 to 0.3315)
ICER (£): costs per QALY	19,787 (9789 to SLIT dominates)
Total QALY gain in 9 years	0.1815 (95% CI –0.0249 to 0.3668)
ICER (£): costs per QALY	18,251 (9030 to SLIT dominates)
Total QALY gain in 10 years	0.1984 (95% CI –0.0272 to 0.4010)
ICER (£): costs per QALY	17,025 (8423 to SLIT dominates)

'ST dominates' means that ST is more effective and also cheaper.

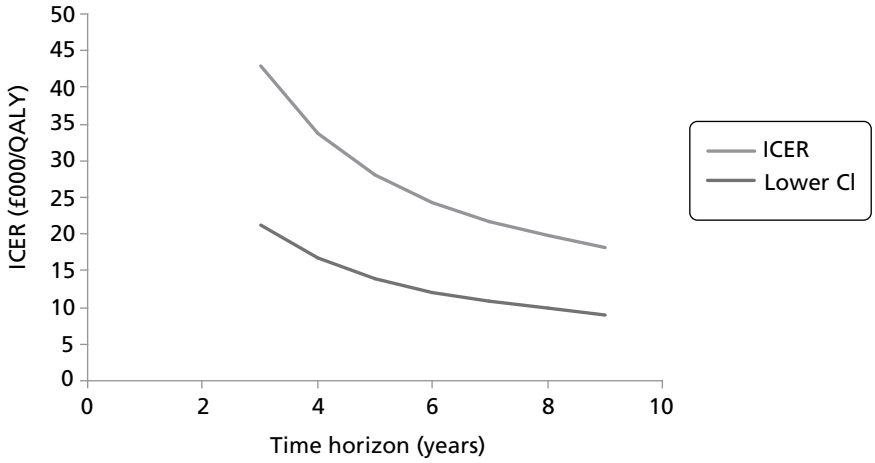

FIGURE 25 Cost-effectiveness of SCIT vs SLIT.

TABLE 55 Incremental cost-effectiveness ratios for 4- and 6-week maintenance schedules (at 6 years)

	Alutard maintenance	
Comparison	4-weekly	6-weekly
SCIT vs ST (direct comparisons)	£29,579	£21,599
SCIT vs ST (indirect comparisons)	£28,650	£20,920
SCIT vs SLIT	£24,404	£12,982

the region where ST dominates (is less costly and more effective than) SLIT. *Figure 26* illustrates this point. It is shown in terms of mean improvement in RQLQ, but exactly the same principles apply to the results when effectiveness is estimated in QALYs.

Using the point estimate of difference in effectiveness based on RQLQ, SCIT appears to be cost-effective compared with SLIT. However, as for SLIT compared with ST, the CI for difference in effectiveness crosses zero, so again there is no finite upper limit for the CI in the ICER.

It is acknowledged that there is considerable relative uncertainty in the inputs concerning costs relating to symptomatic medication and productivity loss. However, these form a sufficiently small part of the overall cost difference between treatments that making plausible changes to those values would not make any appreciable difference to the results quoted. Formal sensitivity analysis on these inputs has not been carried out, as such analysis would add nothing of value to the illustrative results already quoted, and risks being quoted out of context as giving some spurious indication of the robustness of the results. In particular, it is not possible, on the evidence available to the research team, to produce a meaningful estimate of the probability that each treatment is cost-effective at any given threshold ICER, or the value of perfect information at any such threshold.

Repeating the CEA using a 6-weekly (rather than 4-weekly) maintenance schedule for Alutard resulted in slightly lower ICERs. This was based on an assumption that clinical effectiveness remained the same and was undertaken only to illustrate the potential impact of a reduction in costs. The use of shorter treatment courses, such as preseasonal treatment using Pollinex, is likely to reduce costs even further, but there is uncertainty around the long-term effectiveness.

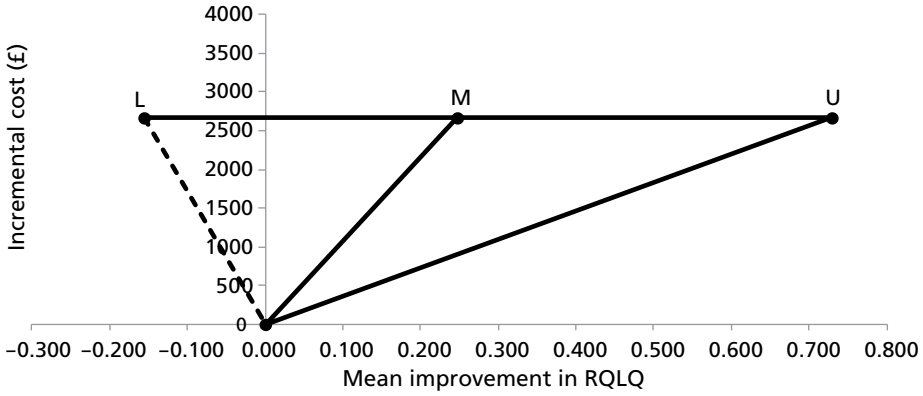

FIGURE 26 Incremental cost-effectiveness plane for SLIT vs ST using the results of the indirect comparison. The incremental cost is fixed at approximately £2700 per patient. The points L, M and U show this incremental cost combined with the lower, mean and upper limits of the CI for improvement in RQLQ, respectively. The gradient of the line from the origin to M is the point estimate of the ICER. The gradient of the line from the origin to U is the *lower* confidence limit of the ICER. The dashed line from the origin to L has a negative gradient indicating that, if L were the true representation of the cost and effect difference, ST would dominate (be less costly and more effective than) SLIT. In such a case, the magnitude of the slope of the dashed line is of no importance: ST would be preferred in any case. It should also be noted that the negative ICER represented by point L should be considered as higher than all positive ICERs, not lower. For the reasons given in the preceding sentences, it is not appropriate to quote a numerical upper confidence limit for the ICER, and the statement 'ST dominates' has been placed instead of such a limit in the results tables.

No analysis based on RQLQ was possible for children. One study that reported a paediatric version of the RQLQ was identified;[152] however, differences compared with the adult RQLQ meant that equivalent mapping to the EQ-5D could not be undertaken.

One of the limitations of the CEA is that it does not take into account any health benefits or potential cost savings from future cases of asthma prevented. This would be particularly relevant when considering the treatment of children with SAR, as they are more likely to develop asthma than children without SAR. A simple calculation based on costs for SCIT and SLIT as outlined above, and number of asthma cases avoided based on the PAT study[54–56] (for SCIT) and Novembre *et al*.[57] (for SLIT) is presented below [see also *Chapter 1*, *The role of specific (allergen) immunotherapy in asthma prevention*]. Both studies are in children with SAR, with no asthma at the start of treatment. The numbers needed to treat (NNT) to prevent one case of asthma were derived from the number of patients with and without asthma in the respective treatment arms, and CIs were calculated around these (method given in Armitage *et al*.[256]). The NNT was multiplied by the cost difference (at 3 years) between SCIT (or SLIT) and symptomatic treatment only (*Table 56*).

The results suggests that if each case of asthma costs over £10,627 (SLIT) or over £22,000–27,500 (SCIT) in treatment costs over a lifetime (appropriately discounted) then SLIT or SCIT could be potentially cost saving compared with symptomatic treatment. These results should be seen as indicative only, as they are based on effectiveness data from relatively small open-label studies. Health benefits and costs associated with a reduction in SAR symptoms are not considered in these calculations.

What is required as a top priority is to establish the extent to which the data already collected in past primary research can be used to populate a useful cost-effectiveness model, which captures all relevant benefits and costs. This means making the data available to independent researchers who will be able to analyse it using a common, and economically useful, framework. Only when this has been done will it be possible to carry out a more meaningful analysis, possibly using a value of information framework, to determine whether or not further primary research is worthwhile and to set the priorities for such research.

TABLE 56 Cost per asthma case avoided

Study	NNT	Cost difference IT and ST (£)	Cost (£) per asthma case avoided (95% CI)
SCIT: PAT study,[55] 3-year data ($n = 205$)	5	5537	27,500 (15,598 to 104,660)
SCIT: PAT study,[56] 5-year data ($n = 183$)	4	5537	22,000 (14,374 to 68,807)
SCIT: PAT study,[54] 10-year data ($n = 147$)	5	5537	27,500 (14,745 to 183,571)
SLIT: Novembre *et al*. 2004,[57] 3-year data ($n = 113$)	4	2668	10,627 (6348 to 63,004)

Chapter 5 Discussion

Clinical effectiveness

Main findings

A total of 28 new DBPC RCTs of SCIT ($n = 17$) or SLIT ($n = 11$) compared with placebo for SAR were identified, bringing the total number of relevant RCTs in this area to around 128. Assessment of the risk of bias was hampered by a lack of reporting of all relevant criteria, but, while risk of bias was often unclear, there were very few instances of high risk of bias. Overall, results were unlikely to be affected by the studies reporting instances of high risk of bias.

The updated findings are consistent with the Cochrane reviews and find statistically significant benefits for both SCIT compared with placebo and SLIT compared with placebo across all outcome measures and for the majority of subgroup analyses.

In trials of SCIT for SAR, the total number of studies and participants included in the present review was only slightly higher than those for the earlier Cochrane review, and results of meta-analyses remained very similar, with moderate effect sizes in favour of SCIT for all outcomes. Greater improvements in both SSs and MSs, compared with placebo,were found with increasing vaccine allergen content, consistent with the recognised dose–response relationship in SCIT. Note that this was based on non-randomised comparisons from subgroup analyses and should therefore be interpreted cautiously. It was beyond the scope of this report to look at randomised comparisons of allergen content, although such comparisons exist. There was only one small trial[152] of SCIT in children and this found significantly lower SSs and MSs, and improved QoL, in the actively treated group (after 3 years of treatment).

Consistent with previous literature, randomised, double-blind trials of SLIT show efficacy in all major outcomes compared with placebo. Few differences were found compared with the earlier Cochrane review, despite restriction to SAR and increased sample sizes in many cases. However, a number of previously non-significant results reached statistical significance in the present review – namely, SSs in studies with $<5\mu$g of MAC, MSs in studies with $>20\mu$g of MAC, and MSs in ragweed allergy. Only one previously significant result became non-significant: of the five studies in *Parietaria* allergy included in the Cochrane review, removal of the study by Pajno *et al.*[35] (which was restricted to SAA) resulted in loss of significance; however, all of these studies had very small sample sizes (total number in remaining studies was 124).

Perhaps more importantly, despite a small increase in total sample size, and limitation to SAR, MSs in children still failed to show a significant improvement with active treatment compared with placebo. The clinical significance of this finding is unclear. The MS in isolation may not be able to reflect the effectiveness of SLIT, which is why the combined SMS is a preferred measure. It is also possible that medication use differs in children compared with adults, as it may be influenced by parental preferences. Another possibility is that SLIT is less effective in children than in adults.

Consistent with this hypothesis, the pooled SMD in SSs in children decreased by over 50% compared with the Cochrane review of SLIT. However, the result did remain statistically significant in favour of SLIT. The Cochrane review included studies of both SAR and PAR, and subgroup analysis of SAR studies only (while maintaining very similar participant numbers of >1300 children) appears to have been associated with a reduction in treatment effect. It may be possible that SLIT treatment is more appropriate for perennial allergens in paediatric populations than for seasonal allergens. Consistent with this, exploratory subgroup analysis of SSs from paediatric studies in PAR only indicates a much larger effect size than for SAR (combined SMD –0.89 vs –0.24, respectively). Although the findings in the PAR studies were more variable

than those in SAR, and the pooled result failed to reach statistical significance, this was based on a much smaller sample size overall (total $n = 328$, compared with $n = 1343$ for SAR).

None of the trials in children included in this review take into consideration future benefits from SLIT, such as avoidance of asthma or new sensitisations, although there are trials currently under way to evaluate this (see *Chapter 3*, *Ongoing trials*). Ten-year data from the PAT study[54] (open-label RCT) suggests that the incidence of asthma in the treatment arm was lower than that of the control arm. Further follow-up of this study is ongoing.

In contrast with SCIT, no relationship between increased MAC and effect size was apparent from subgroup analyses, but this finding may be related to different sample sizes or due to other sources of heterogeneity in the allergen content subgroups. The estimate for the low-allergen group had wider CIs and is associated with more uncertainty. Again, these findings are not based on randomised groups and should thus be interpreted cautiously.

Overall, both SLIT and SCIT resulted in statistically significant improvements in QoL scores. Although SCIT improved RQLQ scores by 0.74 points compared with placebo, SLIT resulted in only a 0.31-point improvement compared with placebo, despite both of these meta-analyses including a similar number of participants (955 compared with 924, respectively).

All of these studies were conducted in adults (alternative versions of the RQLQ have been validated for use in paediatric and adolescent populations) and the findings are consistent with those for SSs and MSs, suggesting a greater clinical benefit from SCIT, at least in adults.

Quality-of-life data in children are scarce; eight studies of SCIT[25,102,112,189,191,192,200,202] and 11 of SLIT[142–144,148,152,156,161,164–166,173] reported QoL outcomes (not all included in the meta-analyses), but only one study in each intervention was restricted to paediatric or adolescent[152,189] participants. SLIT is more commonly prescribed than SCIT in this population, largely due to a perceived reduced risk of potentially severe AEs. Given the possibility that efficacy of SLIT in children is poorer in terms of SSs and MSs than in adults, the presence or absence of benefit in terms of QoL in children should be further explored. In addition, more studies using the paediatric or adolescent version of the RQLQ are needed in order that clinical as well as statistical significance may be assessed. Nevertheless, both studies (one for SCIT and SLIT, respectively) found statistically significant benefits in terms of QoL in children with active treatment.

The overall incidence of AEs following treatment with SCIT was slightly higher than for SLIT (79% vs 65%, respectively, experienced at least one AE); however, as SCIT is administered under clinical supervision, reporting of AEs could be expected to be more stringent. With both routes of administration, the majority of AEs were local reactions at the site of injection (SCIT) or in the oral cavity or gastrointestinal system (SLIT), and resolved spontaneously without treatment. Where severity of systemic AEs was reported, most were graded as mild or moderate, and, again, many did not require special treatment; however, 19% of systemic AEs occurring following SCIT treatment were graded as severe, compared with only 2% following SLIT treatment.

Based on six trials[155,166,179,181,185,257] that reported rates of events per injection, 129 systemic reactions occurred following 2909 administrations of active SCIT (4.4%). This number is much higher than the 0.2% suggested by a recent review of the literature.[258] However, that review included studies of both seasonal, perennial and venom IT, IT for other atopic conditions besides AR, and reports from trials, retrospective studies, surveys, and clinical observations. It seems likely that the strict reporting requirements of RCTs may provide a more realistic representation of the true rate of systemic reactions. Similar incidence-per-dose data were not available from the studies of SLIT included in the present review. No fatalities as a result of treatment were reported for either SCIT or SLIT.

Funnel plot evaluations of SSs for both SCIT and SLIT trials showed slight evidence of plot asymmetry (see *Appendix 13*), with larger effect sizes tending to be associated with smaller trial size. Possible sources of asymmetry include publication bias or poorer methodological quality in smaller studies, sampling variation or chance,[259] and these findings should be interpreted with caution. Further, not all studies reported large effect size estimates in favour of the active treatment, and comparison of combined SMD using both fixed-effect and random-effect meta-analyses identified little difference between the two methods. Thus, any small-study effects are unlikely to impact significantly on the overall effect estimates for the interventions.[259]

In contrast to the large number of placebo-controlled trials, only one small double-blinded head-to-head RCT of SCIT compared with SLIT was identified; this study did not find a significant difference between the two types of treatment, although both were better than placebo. Given the paucity of this type of data, an indirect comparison was conducted.

As there was some evidence of heterogeneity both within and between sets of placebo-controlled trials, ICMR with various covariates was performed in order to explore and potentially reduce heterogeneity. However, adjusting for type of allergen, allergen content and duration of treatment did not substantially reduce heterogeneity. Statistically significant findings favouring SCIT over SLIT (for SSs and MSs, not adjusted for covariates) were associated with substantial heterogeneity. In the analysis using combined SMS, arguably a preferred outcome measure, none of the differences in adjusted and non-adjusted analyses were statistically significant, but were associated with reduced heterogeneity. The difference in RQLQ score (0.517; 95% CrI –0.071 to 1.045) was also found to be not statistically significant. Many of the best estimate probabilities found that SCIT was most likely to be the best treatment, but this needs to be interpreted in the context of the standardised score difference results.

Year of publication appeared to account for a degree of heterogeneity (for SSs). Analyses were suggestive of earlier studies showing greater benefit for SCIT compared with studies published at a later date finding less benefit. It seems unlikely that SCIT has become less effective over time, and alternative explanations for the apparent reduction in effectiveness of SCIT include improved trial protocols and reduced dosages of SCIT being administered for safety reasons. Another possibility is that with increasingly stringent requirements for registration of clinical trials, the potential for publication bias may have reduced over time. However, these results are based on use of a post hoc defined variable and must be considered exploratory in nature.

The use of standardised units makes interpretation difficult, and where significant differences were found favouring SCIT, it is difficult to gauge how much of a clinical difference this would make.

A strength of this review is that a robust review methodology was used, including a comprehensive search strategy. It is unlikely that many relevant studies were missed in this update.

One limitation of both the Cochrane reviews and this review is that many studies do not contribute to the direct and indirect comparison meta-analyses. In this review only 5 out of 17 SCIT and 5 out of 11 SLIT RCTs contributed to at least one meta-analysis. This was partly because different outcome measures were used or that data were not presented in a way that was suitable for meta-analysis. Findings from any studies not represented in a meta-analysis were presented and were found to be consistent with the meta-analyses in their findings (benefit from IT over placebo). By far the largest of the new trials identified for SCIT compared with placebo (DuBuske *et al.*,[145] $n = 1028$) did not contribute to meta-analyses, as outcomes were expressed as number of 'well-days' and 'bad-days'. This study[145] evaluated the effect of an ultrashort course of SCIT and found significant benefits for SCIT over a 4-week period; longer-term outcomes were not reported.

A major limitation is the inconsistent use of outcome measures across studies [see *Chapter 1*, *Outcome measures in randomised controlled trials of specific (allergen) immunotherapy*, for further details]. Although almost all studies use the same four-point scale to assess symptom severity, the number and type of symptoms measured in different studies is so diverse as to preclude any useful comparison of results (see *Appendix 7*). The inconsistency in choice of outcome measure is also reflected in MSs and combined SMSs. A consequence of the highly variable outcome reporting across studies is that the pooled summary measures from meta-analyses can only be reported as SMDs, which are difficult to interpret clinically. Although effect sizes can be classified as small, moderate or large, these do not necessarily correspond to clinically meaningful changes. So, although it can be stated with some certainty that allergen IT shows consistent benefit, and that pooled results are statistically significant, there is no good estimate of the proportion of patients who, for example, have more 'well-days' or fewer 'worst-days'.

The COMET (Core Outcome Measures in Effectiveness Trials) Initiative[260] is attempting to develop standardised sets of outcomes ('core outcomes') that represent the minimum that should be measured and reported in all clinical trials of a specific condition, although this does not mean that outcomes have to be restricted to only core ones. Ultimately, this would make it easier for the results of trials to be compared and combined. Similarly, guidelines on AE reporting[23,134,261] should be followed more consistently.

A further limitation was the inclusion of studies of variable methodological study design or risk of bias. This is in addition to the clinical heterogeneity observed. We did not use a quality threshold for including studies, as quality criteria were often poorly reported and inclusion would therefore have been on the basis of reporting rather than actual quality. Contacting all study authors would have been beyond the scope of this report.

The impact of IT in patients with severe, uncontrolled SAR was of particular interest when conducting this review; however, this information was not always included in the published reports of trials, and it is conceivable that there was a degree of variation in severity across trials. The concept of 'severe chronic upper airway disease' has recently been proposed;[262] this defines patients with uncontrolled AR despite adequate pharmacological treatment based on guidelines, and could potentially be used as an inclusion criterion for future trials.

It was beyond the scope of this review to address the issue of optimum dosing and treatment regimen (see *Chapter 1*, *Treatment schedule*, for further details). Similarly, the review did not address issues around the efficacy of different SIT products [e.g. differences in depot formulations, modification of the allergen extract with adjuvants, use of allergen fragments; see *Chapter 1*, *Specific (allergen) immunotherapy formulations* and *Non-standard therapies*]. Routes of administration other than sublingual or subcutaneous were also not explored (e.g. epicutaneous, intralymphatic).

Cost-effectiveness

A systematic review of EEs identified 13 relevant studies of varying quality, most funded by a manufacturer of SIT products. All studies had some limitations regarding the reporting and/or robustness of data feeding into their analyses or models.

Overall, results from some of the better-quality studies suggested that SLIT was likely to be cost-effective in terms of cost per QALY compared with symptomatic treatment at thresholds of £20,000. Two studies[229,233] of SCIT compared with symptomatic treatment reporting cost per QALY also found that SCIT was likely to be cost-effective at this threshold, but these studies were less transparent in their reporting. Limited evidence of SCIT compared with SLIT was suggestive of SCIT being more beneficial and less costly. None of the models included in the evaluations were described with sufficient information to be suitable for adaptation to a UK setting.

A preferred model was therefore constructed, which included health states describing patients with and without symptoms, or with partly controlled symptoms for the different treatment arms (SCIT, SLIT or symptomatic treatment). Although cost data were readily available from the literature and standard UK sources, and it may have been possible to make plausible utility estimates, it was not possible to identify suitable data on transition probabilities with which to populate the model.

Obtaining data on transition probabilities was problematic as effectiveness outcomes are almost exclusively reported as changes in a mean score (e.g. symptom and/or medication), and it is not possible to translate this into proportions (probabilities) of patients moving from one health state to another. Where this sort of data has been used in previous EEs, it has either not been adequately reported, or has been based on assumptions or expert opinion. It was also not possible to obtain EQ-5D data for different health states directly from the study authors.

An alternative cost-effectiveness model was therefore constructed based on pooled MDs in RQLQ from meta-analyses, and indirect comparison meta-analyses.

Incremental cost-effectiveness ratios (cost per QALY) varied depending on the effectiveness data used (from direct or indirect comparisons) and consistently decreased with increasing years of treatment. Up to year 6, they ranged from £28,650 (year 6) to £57,883 (year 3) for SCIT compared with symptomatic treatment, and from £27,269 to £83,560 for SLIT compared with symptomatic treatment. Thus, with increasing time, both SCIT and SLIT were found to be approaching cost-effectiveness thresholds of £20,000–30,000. Estimates of effectiveness post year 6 are associated with uncertainty as good-quality data supporting sustained effectiveness after this time are not (yet) available. These ICERs are higher than those reported in the literature.

The indirect comparison found an ICER of between £24,404 (year 6) and £42,928 (year 3) for SCIT compared with SLIT, with SCIT being both more costly and more effective. It should be noted that this is based on a difference in effectiveness obtained from an indirect comparison analysis that was non-significant, and associated with a substantial degree of heterogeneity. This finding of SCIT being more costly is in contrast with the two EEs identified, which found SCIT to be both better and less costly; however, one of these was associated with substantial uncertainty around model inputs and neither reported a combined cost-effectiveness measure.

The ICERs should be seen as indicative mainly because they are based on a very simple analysis. There are a number of other factors that limit their robustness. They are based on results from a relatively small pool of studies (eight[143,144,156,161,164–166,173] for SCIT and four[25,102,200,202] for SLIT vs symptomatic treatment). A large proportion of available effectiveness evidence is thus not contributing to this analysis. Furthermore, sustained effectiveness (up to 6–10 years) has been assumed and, although this has been shown in randomised trials and/or cohort studies for other effectiveness measures, the RQLQ data used here are based on more variable treatment and follow-up periods. Furthermore, the RQLQ used in isolation may not be the most appropriate outcome measure to demonstrate effectiveness of SIT; increasingly, the combined SMS or improvement during 'worst-days' are being recommended as outcome measures.

A number of assumptions were made when using RQLQ data in the absence of a validated mapping from RQLQ to EQ-5D based on the same patients answering both questionnaires. One was that the 0–6 point scale of the RQLQ scale could be mapped to the whole range of three of the five dimensions of the EQ-5D scale (usual activities, pain/discomfort and anxiety/depression). The effect of this was that a score of 6 (representing severe impairment in the domains of activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function) would be equivalent to a score of –0.07 on the EQ-5D (representing a state worse than death). It could be argued that these are not comparable states, and that even the most severe impairment of QoL due to AR would not be equivalent to the lowest possible EQ-5D score. If this were the case, then QALY gains would be lower than those reported, and ICERs correspondingly higher. An alternative would be to use only a proportion of the EQ-5D

scale; however, no source could be found for any validated cut-off points and any point chosen would have been completely arbitrary.

Sensitivity analyses were restricted to varying the time horizon of the analysis and using the upper and lower confidence limits of the RQLQ improvement. More detailed sensitivity analysis was not performed, as the effect of plausible changes to cost inputs would have been much smaller than the effect of uncertainty in the clinical outcome and therefore would be unlikely to substantially affect the overall results. The estimates have been based on costs for a 3-year treatment schedule, which has been found to be associated with sustained benefits. Increasingly, shorter, more intensive courses of SCIT are being evaluated (rush or cluster IT), which are associated with less clinic time and are therefore less costly. However, there is as yet no evidence of long-term effectiveness and, therefore, such an analysis was not included. Should long-term effectiveness be demonstrated, this would likely result in greater cost-effectiveness.

It was not possible to model cost-effectiveness in children owing to limitations in the available data. Given the resource use associated with treating asthma, and the potential of SIT to prevent the development of asthma in this population, there is a potential for substantial cost savings. Including this in a model would likely decrease the ICER further over time. Although associated with some uncertainty, our calculations suggest that if each case of asthma costs > £10,627 (SLIT) or > £22,000–27,500 (SCIT) in treatment costs over a lifetime (appropriately discounted), then SLIT or SCIT could be potentially cost saving compared with symptomatic treatment.

Overall, the disparate nature of the existing research and the lack of reporting of key parameters have made it difficult to generate robust findings that are of use to inform reimbursement decisions. However, the results are indicative of IT being cost-effective in the longer term (6–7 years) at conventional thresholds used by decision-makers in the UK NHS.

Current guidelines suggest severity criteria for selecting patients, i.e. those uncontrolled on conventional treatment, but if the aim of treatment is asthma prevention then the initial severity is less of an issue. The presence of AR identifies a population at risk of asthma, with no evidence to suggest that the level of risk is affected by the level of severity.

Future research recommendations

Given the difficulties in comparing and combining results across studies using different outcome measures, there is a clear need for greater consistency in the use of validated outcome measures. Further research is also needed into outcomes that (1) take into consideration that the relative effectiveness of IT compared with symptomatic medication varies depending on prevailing allergen levels and (2) could best inform more meaningful EEs.

In view of the limitations of the indirect comparison analysis in this report, consideration should be given to a head-to-head trial of SCIT compared with SLIT. For both SCIT and SLIT, at present the most appropriate treatment regimens to be compared would be those with 3-year protocols, as this is where the best evidence exists in terms of long-lasting efficacy.

Ultra-short IT treatment schedules have shown promise in terms of clinical efficacy, and these protocols place considerably less burden on patients in terms of time and inconvenience. Ultra-short IT is also likely to have major cost benefits compared with conventional schedules. However, little evidence exists as to the duration of clinical benefits beyond treatment cessation and this is likely to be an important area of future research.

In terms of EEs, the main priority for future research will be to assess the extent to which results of all previous primary research can be made available to independent researchers. Only when this has been done can meaningful model-based value of information analysis be carried out to direct future primary research.

Chapter 6 Conclusions

Based on a large number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than symptomatic treatment only and this remains the case for the vast majority of subgroups analyses based on differences in population and treatment protocols. It is uncertain to what extent this statistical significance translates to clinically significant differences across the different types of outcome measures used. An indirect comparison is suggestive of SCIT being more beneficial than SLIT based on SSs and MSs, but no such difference could be shown for combined SMSs or QoL and firm conclusions cannot be drawn. Cost-effectiveness analyses suggest that both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per QALY at around 6 years (NHS and patient perspective). This is based on limited data and the use of a number of assumptions. Potential future cost savings resulting from cases of asthma avoided were not included in this analysis. There is a need for consistent reporting of validated outcome measures, ideally in head-to-head trials, which would allow for a more meaningful data synthesis and use of results to inform model-based economic analyses.

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Contribution of authors

Angela Meadows contributed to study selection, data extraction and quality assessment, data analysis and writing of the report.

Billingsley Kaambwa undertook the systematic review of economic evaluations, and contributed to the development of new economic models and the writing of the report.

Nicola Novielli ran the indirect comparisons and contributed to the writing of the report.

Aarnoud Huissoon advised on the clinical context of the project and contributed to the clinical effectiveness analysis and economic evaluation.

Catherine Meads contributed to protocol development, study selection, project management and writing of the report.

Anne Fry-Smith devised the search strategy and carried out the searches.

Pelham Barton contributed to the development of new economic models and the writing of the report.

Janine Dretzke, principal investigator, contributed to protocol development, study selection, data extraction and quality assessment, project management and report writing.

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Appendix 1 Original protocol

Project title

Allergen immunotherapy in adults and children with severe hay fever: systematic review of effectiveness and economic modelling

Planned investigation

Background

'Hay fever' is the common name classically given to seasonal allergic rhinitis or rhinoconjunctivitis. This is a disorder of the nose and eyes characterised by nasal obstruction, rhinorrhoea, itching of the nose and sneezing, with itching, redness, soreness and watering of the eyes. The relative severity of these symptoms varies between patients. Symptoms are caused by an IgE-mediated inflammation of the membranes lining the nasal cavity and conjunctiva occurring in response to an allergen. Common allergens include tree or grass pollen, moulds, animal dander and house dust mite. In Britain, the main cause of allergic rhinitis is grass pollen, particularly perennial rye (*Lolium perenne*) and timothy grass (*Phleum pratense*), with symptoms peaking in June and July.[1]

The term 'hay fever' emerges from the traditional classification of allergic rhinitis into 'seasonal', 'perennial' and 'occupational' according to the time of exposure to the underlying allergen. Seasonal allergic rhinitis, or hay fever, is typically caused by a response to pollens and outdoor moulds while perennial allergic rhinitis is caused by house dust mites, animal dander and indoor moulds. In 2001 a new classification was suggested by the World Health Organisation ARIA (Allergic Rhinitis and its Impact on Asthma) Workshop.[2] This new classification relies on the measurement of the frequency and duration of symptoms (see table 1) rather than upon the timing of the presence of the allergen.

Allergic rhinitis is an extremely common disease, with estimates of worldwide prevalence being in the region of 25% of the population. Estimates of the prevalence of allergic rhinitis in the UK vary from 15–30%[3,4] although the true prevalence is difficult to ascertain because many people with symptoms self-diagnose and use over-the-counter remedies. It is believed the prevalence of seasonal allergic rhinitis is higher in children and adolescents than it is in adults, with perennial allergic rhinitis being more common in adults.[2] Allergic rhinitis tends to be more common in 'Western' developed countries.

General practice consultation rates for allergic rhinitis in England show an increase in new patients with this diagnosis year on year between 2001 and 2005. A rate of 5.57 per 1000 person years in 2001 rose

TABLE 1 ARIA classification of allergic rhinitis, 2001[2]

Intermittent Symptoms	Persistent Symptoms
<4 days / week	≥4 days / week
or	and
<4 weeks	≥4 weeks
Severity: Mild	Severity: Moderate – Severe
Normal sleep	Abnormal sleep
Normal daily activities, sport, leisure	Impairment of daily activities, sport, leisure
Normal work and school	Problems caused at work or school
No troublesome symptom	Troublesome symptoms (one or more items)

to 7.41 by 2005, an increase of 33%. At the same time there was a 41% increase in the number of prescriptions issued (antihistamines 45.5%, 'drugs used in nasal allergies' 35.5%).[5]

Allergic rhinitis is not usually a severe or life threatening disease but it can detrimentally affect school[6] and work performance[7], as well as causing social disruption to individuals who suffer from it. The economic burden of allergic rhinitis is high, both in terms of costs to the NHS and due to work days lost.[3,8]

Allergic rhinitis is an independent risk factor for asthma. Around 80% of people with asthma also have symptoms of allergic rhinitis. Studies have shown a temporal relationship – with rhinitis frequently preceding asthma.[2] Those who have allergic rhinitis are around three times more likely to get asthma than those who do not.[9]

Inflammation of the nasal membranes in allergic rhinitis can cause a worsening of asthma through various different mechanisms and so optimal treatment of rhinitis may, to some extent, improve coexisting asthma.[2]

Diagnosis of allergic rhinitis is usually clinical with a typical history being given, in the case of hay fever, of seasonal symptoms over several years. The more common symptoms of sneezing, rhinorrhoea, stuffy nose and conjunctivitis may be accompanied by others such as anosmia (loss of smell), snoring or other sleep problems, facial pain, wheezing and tightness of the chest. Diagnosis is confirmed by a skin prick test, which demonstrates an IgE mediated allergic reaction of the skin to a specific allergen. There is no widely accepted measure of the severity of nasal obstruction. In the new ARIA classification severity of allergic rhinitis is assessed through the effect the condition has on everyday functioning of the individual.

In clinical trials, the primary outcome measures generally used are symptom score and use of (rescue) medication. Symptom scoring systems vary widely across trials, and can include physician or patient self-rated questionnaires. One more common scoring system is a score from 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe symptoms) for symptoms such as runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes.[10] QoL is more likely to be a secondary outcome measure. A well validated scale is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[11], a disease specific quality of life measure. Generic QoL measures have also been used in some trials, such as the EQ–5D or SF–36. Objective outcome measures include blood IgE levels.

Treatment

The British Society for Allergy and Clinical Immunology (BSACI) have produced guidelines[4] for the management of allergic rhinitis. Management may include allergen avoidance, medication (pharmacological treatment), education and immunotherapy.

BSACI guidelines can be summarised as follows. Following diagnosis, first-line treatment of allergic rhinitis is allergen avoidance (where possible and practicable). The nature and severity of symptoms determines the type of medication offered. If symptoms are mild a non-sedating oral or topical H1-antihistamine is given. Where symptoms are moderate to severe, first-line therapy is with a topical intranasal steroid. If these treatments fail further agents may be added according to the troublesome symptom – ipratropium for watery rhinorrhoea, a non-sedating H1-antihistamine for itch or sneeze, a leukotriene-receptor antagonist for catarrh if asthmatic. Blockage of the nose may require a decongestant, oral corticosteroids or a long-acting non-sedating H1 antihistamine. If there is further treatment failure, and if the symptoms are predominantly due to one allergen, then immunotherapy may be considered. The guidelines lack specific or broadly authorised recommendations for immunotherapy, which may be a reflection of the lack of an international consensus to date on the role of this therapy.[12] There are currently no NICE guidelines on treatment of allergic rhinitis.

A survey[13] of UK general practices found that 54% of patients with seasonal allergic rhinitis reported partial or poor control of their symptoms. Of these, 69.4% were not taking their medication as per current

guidelines, the remaining 30.6% were already using their drugs as per guidelines and were still sub-optimally controlled. For these patients immunotherapy may be beneficial.

Immunotherapy

Allergen immunotherapy is a method of reducing sensitivity to a specific allergen by repeated administration of a dose of that allergen. The benefit is dependent on the dose and the route of administration. Various mechanisms have been proposed to explain the efficacy of immunotherapy, including the induction of allergen-specific IgG4, deviation of allergen-induced cytokine production, and allergen-specific T regulatory cells that reduce the late-phase response to the allergen. For any form of specific immunotherapy, the patient's symptoms must be attributable to one or a few dominant allergens.[12]

There are different routes of administration for specific allergen immunotherapy: subcutaneous (injection), sublingual, nasal and oral. For subcutaneous (injection) immunotherapy, weekly injections of incremental doses of allergen are given until a maintenance dose is reached. This maintenance dose is given monthly for 2–3 years. Injections can cause minor adverse events and, whilst systemic reactions are rare, occasional fatalities due to anaphylaxis have been reported.[14] Nasal administration is thought to be effective, but may be limited by local side effects, whilst studies assessing the oral route have indicated a lack of efficacy. Trials comparing sublingual immunotherapy to placebo have found significant reductions in symptoms and medication requirements.[14]

Immunotherapy can be effective in the treatment of symptoms of allergic rhinitis and is the only treatment that can have an effect upon the natural history of the condition i.e. offer long term remission.[4] In one randomised controlled trial a three- year course of immunotherapy to grass pollen remained effective three years after treatment ceased.[15] Where patients have allergic rhinitis only, immunotherapy may prevent the onset of asthma, as shown by the results of a10-year multicentre prospective study of immunotherapy in children with seasonal allergic rhinitis.[16]

There are two licensed products available in the UK for the treatment of seasonal allergic hay fever due to grass or tree pollen in patients who have failed to respond to anti-allergy drugs. Pollinex® (grasses and rye or tree pollen extract) is given by subcutaneous injection, but this was licensed in the 1970s and uses a shortened dosing regime. Grazax® (grass pollen Phleum pratense extract) was recently licensed and is given sublingually.[17] Furthermore, there is considerable specialist use of unlicensed subcutaneous immunotherapy products (mainly Alutard® and Allergopharma®), under CTA (clinical trial authorisation). These include various allergens such as grass and tree pollens, house dust mite, cat and dog danders (personal communication AH). Most recent data regarding the efficacy of subcutaneous immunotherapy is derived from dosage regimes using such products.

Existing research

Clinical effectiveness reviews

The Cochrane review by Calderon *et al.* (2007)[18] identified 51 RCTs comparing subcutaneous (injection) allergen-specific immunotherapy to placebo in patients with seasonal allergic rhinitis. Eight RCTs included participants younger than 18 years and one had an age range of 6–56 years. There were no studies exclusively in children. It is unclear to what extent conventional treatment was inadequate in the included populations. The review found significant reductions in symptom scores and medication use and a relatively low risk of severe adverse events. Searches for this review were completed in February 2006.

The Cochrane review by Wilson *et al.* (2003)[19] included 22 RCTs comparing sublingual immunotherapy (SLIT) to placebo in patients with seasonal allergic rhinitis. The authors found that SLIT significantly reduces symptoms and medication requirements in adults. The treatment effect in children, based on five studies ($n = 218$), was not significant. The treatment appeared to be very safe with no systemic side effects identified in any of the studies. Searches for this review were completed in February 2003. The

review was updated in 2006 and results presented in 2007 at EAACI (European Academy of Allergy & Clinical Immunology) and in 2008 at AAAAI[20] (American Academy of Allergy, Asthma & Immunology) and a further update is due shortly with searches up to September 2009 (personal communication DW). The results of the updated review were broadly consistent with the previous review and showed that sublingual immunotherapy was effective in reducing symptoms and use of medication, with mostly mild side effects.

There is a Cochrane protocol only (McDonald *et al*., 2009)[21] for local nasal immunotherapy for allergic rhinitis.

The systematic review by Penagos (2006)[22] included ten studies of sublingual immunotherapy for allergic rhinitis in children and found evidence of effectiveness of immunotherapy compared to placebo. This was confirmed by the review by Larenas-Linnemann (2009), which included later studies. The review by Röder (2008)[23] included 28 studies on the effectiveness of immunotherapy compared to placebo or another route of administration. In contrast to the reviews by Penagos (2006) and Larenas-Linnemann (2009), the authors found no evidence of benefit for sublingual immunotherapy. Moderate evidence of effect was found for nasal immunotherapy. (It should be noted that these reviews included some trials where the children had house mite allergies).

Head-to-head comparisons of different routes of administration of immunotherapy

Compared to the evidence base of immunotherapy compared to placebo, there appear to be few studies directly comparing different routes of administration. Two RCTs[24,25] were identified comparing subcutaneous with sublingual immunotherapy. No significant differences were found between the treatments in these two small studies.

Cost-effectiveness reviews

There are several studies, which have conducted cost comparisons only. Ariano (2006)[26] found overall lower costs for subcutaneous immunotherapy compared to symptomatic drug treatment (based on a study with 30 patients with pollen-induced rhinitis and asthma). Pokladnikova (2008)[27] compared the mean costs of subcutaneous with sublingual grass pollen immunotherapy and found that sublingual therapy was cheaper overall. Berto (2005)[28] found that in a study of children with pollen and dust mite induced asthma and rhinitis, sublingual immunotherapy was comparable in cost to conventional treatment. None of these studies incorporate quality of life measurements.

Our scoping search identified four studies that conducted cost-effectiveness analyses and calculated cost per QALY gained. Two of these were based on a large multi-centre RCT[10,11] comparing Grazax® with standard care. Quality of life was measured by the EQ–5D. Canonica (2007) looked at a group of southern European countries (France, Italy, Austria and Spain) and found a cost per QALY of between 13,870 and 21,659 Euros for Grazax® compared to standard care. Bachert (2007)[29] conducted the analysis for a group of northern European countries including the UK and calculated a cost per QALY of Grazax® versus standard care of between 12,930 and 18,263 Euros. These values are all below a threshold of £20,000. Both these studies assumed that, after three years of treatment, tolerance to grass pollen would continue for another six years. A further study (Nasser 2008)[8], also based on the same trial, found a cost per QALY of between £4319 and £11,769 in UK patients with allergic rhinitis co-existing with asthma. The cost was found to be sensitive to duration of effect and productivity at work.

One German study was identified (Brüggenjürgen 2008),[30] which found a cost per QALY of 8308 Euros for subcutaneous immunotherapy compared to symptomatic treatment in patients with allergic rhinitis and allergic asthma. This study was not conducted as part of an effectiveness study, but comprised a model with inputs estimated from various literature sources or informed by an expert panel. The cost per QALY was found to be sensitive to costs of subcutaneous therapy and the target population (e.g. age).

We did not identify any cost-effectiveness studies solely in children.

Rationale for project

Allergic rhinitis is an increasing problem with high associated costs, both monetary and social. Conventional therapies cannot control symptoms well for all patients and do not represent a cure. There is a wealth of evidence in the form of randomised controlled trials, particularly for adults, which overall shows benefit of immunotherapy over placebo. Despite this, there is a lack of clear guidelines in the UK on whether immunotherapy should be recommended as standard where conventional treatments have failed. There are two well conducted Cochrane reviews, with the one on sublingual immunotherapy due to be updated shortly (searches up to September 2009, personal communication DW). The searches for the one on subcutaneous immunotherapy were completed in 2006, and we would expect to identify additional data for the time period 2006–2010 as this is a topic of ongoing interest. Further data from the final years of the GT08 Grazax® trial are also expected by the time this project would commence (personal communication AH).

For children there is a smaller evidence base, with some reports finding conflicting evidence of effectiveness for immunotherapy. A definitive and up-to-date conclusion on the evidence of effectiveness for children for both sublingual and subcutaneous immunotherapy is clearly needed.

None of the above reviews include an economic evaluation. A scoping search identified four studies that generated cost-effectiveness estimates in terms of cost per QALY gained, for sublingual (three studies) and subcutaneous immunotherapy (one study). However, none of the cost-effectiveness analyses were based on a systematic review of clinical effectiveness. The two main cost-effectiveness analyses (Canonica 2007 and Bachert 2007) made an assumption of ongoing tolerance to grass pollen for six years after treatment. The availability of further data from the GT08 Grazax® trial would provide further evidence on long-term effectiveness and make an economic model less reliant on assumptions. We did not identify a cost-effectiveness analysis/model solely for children, or for a comparison of different routes of administration of immunotherapy.

For these reasons we believe that a cost-effectiveness analysis/economic model for both adults and children based on an up-to date systematic review of clinical effectiveness is necessary and could contribute to establishing more specific UK guidelines on whether immunotherapy should be recommended, and for whom.

Research methods

Key research questions

Based on the scoping search and clinical advice, we have found little evidence that oral or nasal immunotherapy is of benefit or likely to be used in practice, and we will therefore not include these types of immunotherapy. The key questions are thus as follows:

Clinical effectiveness

1. To identify the evidence for the clinical effectiveness of sublingual specific allergen immunotherapy compared to standard care in adults and children.
2. To identify the evidence for the clinical effectiveness of subcutaneous specific allergen immunotherapy compared to standard care in adults and children.
3. To identify the evidence for the relative clinical effectiveness of sublingual versus subcutaneous allergen immunotherapy in adults and children.

Further questions of interest are:

- duration of effect/recurrence of symptoms
- adverse events
- evidence for the prevention of asthma or other allergies
- most effective dose and dosing regimen

- impact of findings on policy.

Cost-effectiveness

Cost-effectiveness modelling will be performed based on the systematic review evidence of clinical effectiveness. Preliminary research questions are:

1. To determine the cost-effectiveness of sublingual immunotherapy compared to standard care in adults and children.
2. To determine the cost-effectiveness of subcutaneous immunotherapy compared to standard care in adults and children.
3. To compare the cost-effectiveness of subcutaneous versus sublingual immunotherapy compared to standard care in adults and children.

Future research

Any gaps in the current evidence base will be highlighted and will inform recommendations for future primary research. This will include recommendations on study design, populations, intervention, comparators and relevant outcomes based on the EPICOT guidelines.[31]

Search strategy

A scoping search has already been undertaken, which involved interrogation of bibliographic databases such as MEDLINE and EMBASE, health economic databases, the Cochrane Library and HTA websites. The purpose of this was to identify existing reviews and cost-effectiveness studies, to inform this project description, and to gauge the number of relevant studies likely to be included.

Given that there are two relevant well-conducted Cochrane reviews on sublingual and subcutaneous immunotherapy (reviewing 73 RCTs), we plan to build on these and update the searches rather than repeat them. New searches will thus run from 2006 to 2010. Separate searches will be performed to identify relevant studies on cost-effectiveness and for relevant economic model parameters. Search strategies will be developed by an experienced information specialist. Search filters for study design will be included where possible. A combination of text words and index terms relating to the condition and the treatment will be used. There will be no language restrictions.

The following sources will be searched:

- bibliographic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index)
- MEDLINE, EMBASE, NHS EED for studies relating to cost and cost-effectiveness
- Current Controlled Trials *meta*Register, ISRCTN database and ClinicalTrials.gov for ongoing studies
- consultation with experts in the field
- checking of reference lists of relevant reviews
- selected websites
- hand-searching of a selection of relevant journals guided by clinical expertise in the project team.

Study selection strategy

Titles and abstracts of retrieved studies will be screened independently for inclusion by two reviewers. Where it is unclear whether studies meet the inclusion criteria on the basis of title and abstract, full copies will be obtained for assessment. Any discrepancy between reviewers will be resolved through discussion or referral to a third reviewer. The following inclusion and exclusion criteria will apply to clinical effectiveness studies:

Study design

Randomised controlled trials (RCTs). RCTs constitute the most robust form of evidence and given the availability of in excess of 73 RCTs, we are unlikely to extend the inclusion criteria to other study designs.

However, if we find that there is insufficient long-term follow-up data for use in the economic model, we may look at large well-designed cohort studies. Scoping searches indicate that follow-up times of RCTs vary between less than six months to more than a year.

Population

Adults or children with a confirmed diagnosis of seasonal allergic rhinitis (hay fever). Confirmation is likely to be through a skin prick test and/or blood test. If we identify any trials where patients have been included on the basis of symptoms only, we will include these and consider them separately. Patients with co-morbidities such as asthma will be included.

The brief specifies adults and children (examined separately) with severe hay fever, which does not respond to conventional treatment. We anticipate that not all trials will provide this information, or use different classifications for 'severe' or 'not responding to conventional treatment'. Where the information is provided, populations may still be heterogeneous. Where possible we will consider trials (or subgroups of trials) separately where patients meet specified severity criteria.

Where we are using existing Cochrane reviews, we will check whether the included trials meet our inclusion criteria.

Intervention

Allergen-specific subcutaneous (injection) or sublingual immunotherapy in any setting. There will be no restrictions regarding a particular dose or dosing regimen.

Comparator

This is likely to be placebo in most cases, with conventional (rescue) medication given alongside in both treatment arms. We will also include as a comparator a different route of administration of immunotherapy.

Outcomes

As specified in the brief, at least one of the following will need to be reported for the trial to be included: symptom severity, reduction in medication, cost-effectiveness, frequency of exacerbations, quality of life, adverse events, dose-effect relationships. We are also interested in any studies reporting the prevention of new asthma cases.

Data extraction

Data extraction will be performed by one reviewer and independently checked by a second reviewer. A piloted data-extraction form will be used. Data will be extracted on trial design, patient characteristics, intervention (route of administration, dose, frequency), comparator and outcomes.

Quality assessment

Quality assessment of all included studies will be performed using the Cochrane guidelines[32] on assessment of risk of bias (selection bias, performance bias, attrition bias, detection bias, reporting bias). Of particular importance to these trials is blinding of patients, investigators and outcome assessors, due to the subjective nature of some of the outcomes (e.g. reduction in symptom severity).

Data synthesis

As there is a large number of trials, meta-analysis has been undertaken in the two relevant Cochrane reviews. We would expect to update these analyses using Stata 10 where new data is available. If data is available, we will also consider conducting meta-analysis for immunotherapy in children.

There is likely to be a large amount of heterogeneity between trials, for example in terms of how patients were recruited, severity of hay fever, type of allergen, dosage as well as route of administration. We will examine clinical and statistical heterogeneity before attempting to pool data. There are also likely to be a

variety of outcome measures used to measure reduction in symptom severity, therefore the standardised mean difference will be used when pooling data. Studies on sublingual and subcutaneous immunotherapy will be pooled separately. Where we are unable to incorporate study results into meta-analyses, these will be tabulated and described separately, and the consistency of the results with those of the meta-analyses discussed.

The likelihood of publication bias will be investigated through the construction and evaluation of Funnel plots.

We are likely to identify only few head-to-head trials of different routes of administration. We will investigate the possibility of conducting an indirect comparison, however this is likely to be hampered by heterogeneity between the studies.

Economic evaluation

Literature review

A formal search will be undertaken as outlined in section 3.2 in order to identify additional studies reporting cost or resource use, quality of life and cost-effectiveness. Relevant cost-effectiveness studies will be summarised formally appraised using the Drummond checklist[33] and may be used to inform the model. Information on the following key items will be extracted: type of economic analysis, population, intervention, comparator, perspective, time horizon, structure and assumptions of model, effectiveness data, resource and cost data, discounting and results of base case and sensitivity analyses.

We will conduct a systematic search of the QoL literature in order to identify studies that directly measure utility values for example through the use of the EQ–5D.

Economic model

Depending on the suitability of existing models we may adapt these, or develop our own model. The model structure will be informed by the patient pathway and will be developed with the help of our clinical experts. As this is a long-term disease we are likely to use a state transition model such as a Markov model.

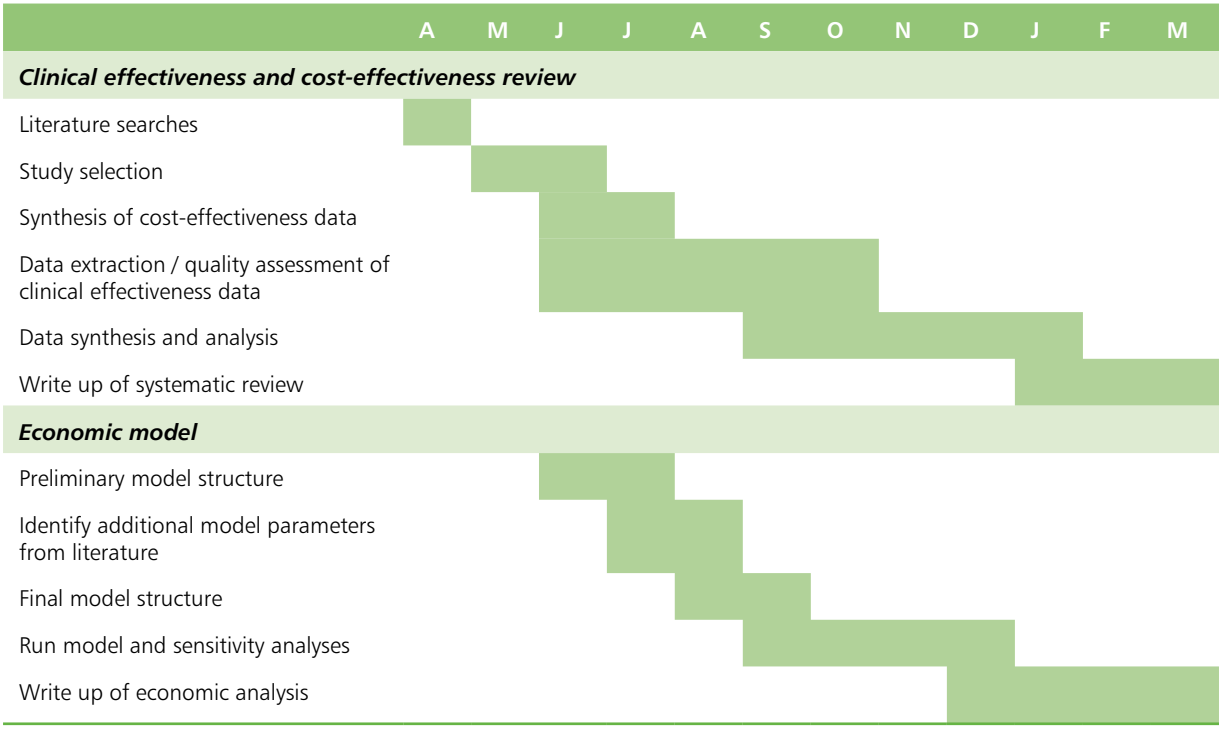
The systematic review of effectiveness will generate the most evidence based parameters to be used in the economic model. Depending on the extent of the evidence base, these may not be summary estimates but represent qualified, best estimates representing current practice. Trials that have measured QoL using the EQ–5D such as the large multi-centre trial[10,11] of Grazax® will be particularly useful. We will approach the trial investigators in order to obtain, if available, effectiveness and QoL data beyond three years (on which the previous economic evaluations were based). Where studies have measured QoL using outcome measures other than the EQ–5D, we will investigate whether QoL results can be converted into a form that will allow them to be combined with the EQ–5D values. Drug and resource costs will be obtained from the literature review, standard sources, and consultation with clinical experts. These will include costs of medication, GP visits, hospitalisation and hours lost from work. We will also include the costs resulting from adverse events wherever possible.

The results of the economic modelling will be expressed as incremental cost per QALY gained. We will run the model using a 'base case' scenario, which will be varied for a number of sensitivity analyses. Parameters which are expected to influence the cost per QALY are drug costs, duration of benefit and population characteristics. If the available data allows, we will conduct separate analyses for adults and children and for subcutaneous and sublingual immunotherapy. Deterministic and probabilistic sensitivity analyses will be undertaken. Decision uncertainty will be displayed through the use of cost-effectiveness acceptability curves and value of information analysis as appropriate. If the evidence is available we will also look at different types of allergen (e.g. grass, tree). We will attempt to incorporate costs savings of prevented cases of asthma.

Our scoping searches indicate that the most evidence is likely to exist for sublingual immunotherapy with grass pollen versus conventional treatment and this is likely to be the primary focus of the economic model. We will however endeavour to also model subcutaneous immunotherapy versus conventional treatment, as well as a comparison between sublingual and subcutaneous administration.

Project timetable

The project is expected to run over a 12-month period. Key stages are outlined below:



Milestones

At 3 months: all relevant studies for inclusion into systematic review identified; preliminary model structure.

At 6 months: submission of HTA progress report; final model structure.

At 7 months: all data extracted and quality appraised.

At 10 months: all data synthesis/analysis completed, all model sensitivity analyses completed.

Expertise

The applicants have extensive experience of conducting systematic reviews and health technology assessments, meta-analysis, economic modelling, information science and clinical immunology. The West Midlands Health Technology Assessment Collaboration (WMHTAC) members have worked together successfully on numerous previous projects and have no commercial interests in their projects.

Janine Dretzke (JD) has been a systematic reviewer with WMHTAC since 2001 and was the main reviewer on four large HTA reports (for NICE/NETSCC HTA), working closely with health economists, clinical experts and information specialists. JD has considerable experience in the subject of this proposal as she has recently completed a systematic review of clinical and cost-effectiveness on provocation/neutralisation testing in food allergy and also contributed to a review on acupuncture for allergic rhinitis. JD will contribute mainly to the systematic review of effectiveness, data analysis and report writing.

Dr Catherine Meads (CM) is a senior systematic reviewer and the Director of WMHTAC. This collaboration has conducted numerous HTAs, systematic reviews and other evidence synthesis reports for a variety of customers including the NIHR HTA programme over the last ten years. She has experience of managing large research grants, particularly for National Institute for Health and Care Excellence (NICE) Technology Appraisals and for the Centre for Public Health Excellence. CM has worked in the Unit of Public Health, Epidemiology and Biostatistics for over 12 years and has extensive systematic review experience, having worked on numerous systematic reviews for NICE, NIHR and other customers. CM will contribute to the systematic review of effectiveness, management of the project and report writing.

Professor Jayne Parry (JP) is the Head of the Unit of Public Health in the University of Birmingham and has an active research programme focusing on the evaluation of health impacts of public policy. She is a senior researcher with excellent project management skills and substantial experience of leading multi-disciplinary research teams. JP will provide input into project management and any other duties as required.

Dr Pelham Barton (PB) is a highly experienced mathematical modeller whose main research area is the application of appropriate simulation modelling techniques to choose between a range of possible strategies for treating a given patient group. He has many published models, dealing with both hospital-based health care interventions, where the focus is on individual patient pathways, and health care interventions where it is essential to consider the effects on the whole population. PB joined the Health Economics Unit in the School of Health and Population Sciences in 1998 and has been closely involved in the WMHTAC technology appraisals for NICE. PB will supervise a health economist, who will carry out most of the work on the economic component, and will contribute to the economic modelling and report writing.

Dr Kristina Routh (KR) is a medical doctor in her final year of Higher Specialist Training in Public Health. Previously trained in Pathology, she has over five years experience of working within a variety of health organisations at both local and regional level. Her public health training will allow her to bring a population-based perspective to this review and, having worked both within the Regional Specialised Commissioning Team and with commissioners in two Primary Care Trusts, she will contribute valuable insights into the requirements of commissioners. KR will contribute to data analysis and report writing, particularly with regard to policy impact.

Anne Fry-Smith (AFS) is a senior information specialist, who leads the information team supporting WMHTAC and ARIF. She has extensive knowledge of research information searching and retrieval strategies. She is the co-author on several NICE reports. AFS will develop and run the search strategies.

The following clinical experts (AH, TK, DW) will support the team with clinical input and access to contacts. Further, we anticipate forming a steering committee consisting of the clinical experts as well as PB, CM and JD in order to ensure that the economic component of the review links up with the clinical effectiveness component, and to enable clinical input to inform the structure of the model from the outset.

Dr Aarn Huissoon (AH) is a consultant immunologist at Birmingham Heartlands Hospital (Heart of England NHS Foundation Trust) and honorary senior lecturer at the Department of Immunity and Infection, University of Birmingham. He has been providing an allergy service including desensitisation immunotherapy for allergic rhinitis for the last 8 years. AH is the local investigator for a number of multicentre placebo-controlled trials of both subcutaneous and sublingual immunotherapy for allergic rhinitis and can therefore bring first-hand in-depth experience of both clinical use and investigation of immunotherapy to the team. In addition he has undertaken a course in systematic reviews, and has published a review of acupuncture in allergic rhinitis.

Dr M Thirumala Krishna (TK) is a consultant immunologist and allergist and honorary senior lecturer at Birmingham Heartlands Hospital. His main interests include allergen immunotherapy and novel treatments in allergic disease, and air pollution and health.

Dr Duncan Wilson (DW) is a consultant respiratory physician at Selly Oak Hospital (University Hospitals Birmingham). His main clinical interest is in airway allergy: allergic rhinitis, asthma and the link between those two conditions. His MD thesis covered clinical and immunological aspects of specific allergen immunotherapy. As well as his clinical duties, he is an honorary senior lecturer at the University of Birmingham and is Clinical Service Lead for Respiratory Medicine. He is the main author of one of the relevant Cochrane reviews on sublingual immunotherapy for allergic rhinitis, and is also involved in the upcoming update of this review. DW can thus act both as a clinical advisor and give advice on systematic review methodological issues.

Service users

Patients who suffer from severe hay fever will have views on the usefulness and appropriateness of immunotherapy treatment. AH has extensive patient contact and is well placed to approach a patient or patients who would act as a patient representative(s) on the project. A patient perspective will help us to put the findings of our review into a patient-relevant context. We also propose to disseminate our findings to service users through leading charities such as Allergy UK (www.allergyuk.org), for example by contributing to one of their Allergy Fact Sheets.

Justification for the support requested

We have, as a group of applicants, very carefully analysed the degree and complexity of the work required to produce high quality clinical effectiveness reviews and economic model. We are in an excellent position to gauge the level of resources required to deliver this type of project as we have several years experience in the delivery of such projects in a variety of topic areas.

We think that one year will be a sufficient time scale for all the work proposed in this application. We have recently conducted similar projects involving systematic reviews and economic modelling for a several customers and the nature of this project is similar in complexity and workload to previous projects. We have found that a senior reviewer with a medical background is invaluable because of the complex nature of the clinical terminology and lack of reporting standards in clinical and methodological terms. The burden of work related to effectiveness review will require two reviewers to enable double study selection, data extraction etc. but neither need to be full-time. For the modelling work, one modeller will need to focus on this work full time for six months, with supervision from the experienced senior modeller. Funding is therefore requested for:

- One systematic reviewer 0.2 WTE and one systematic reviewer 0.5 WTE for 1 year who will carry out mainly the effectiveness review.
- One WTE health economist for 6 months for the economic evaluation.
- Suitable supervision for the clinical effectiveness, economic modelling and the project as a whole.
- A small amount of time from an information specialist, appropriate for one project.

As this work will be performed by staff embedded within a larger HTA organisation, we are able to draw on additional in-house expertise as necessary. In addition, some WMHTAC team members are core-funded so not being paid to work on this project.

The non-staff costs comprise the following:

- Travel and subsistence for one conference to disseminate findings of the research.
- The consumables budget of £1,000 is based on our experience of the number of inter-library loans required for a systematic review, and sundry other administration costs. The small amount for consultancy will be used to nominally reimburse our clinical experts for their time, particularly Dr Aarn Huissoon who will be closely involved with the project

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Appendix 2 Search strategies

Clinical effectiveness

Source: The Cochrane Library (Cochrane Central Register of Controlled Trials) 2011 Issue 1

#1 MeSH descriptor Rhinitis, Allergic, Seasonal, this term only
#2 (rhinoconjunctivitis or rhino next conjunctivitis)
#3 hay next fever
#4 pollen next allergen*
#5 season* next allergic
#6 hayfever or pollinosis or pollenosis or sar
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 MeSH descriptor Rhinitis, this term only
#9 rhinitis
#10 (#8 OR #9)
#11 intermittent* or season* or spring or summer
#12 pollen* or grass* or birch or ragweed or tree*
#13 weed* or mugwort or willow or alder
#14 MeSH descriptor Trees, this term only
#15 (#11 OR #12 OR #13 OR #14)
#16 (#10 AND #15)
#17 MeSH descriptor Desensitization, Immunologic, this term only
#18 MeSH descriptor Allergens, this term only
#19 desensiti* or hyposensiti*
#20 MeSH descriptor Immunotherapy, this term only
#21 immunotherap* or immunomodulatory or allergen* or antigen*
#22 immune next therapy
#23 immunologic next response*
#24 grazax or pollinex or alutard
#25 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#26 (#7 OR #16)
#27 (#25 AND #26)

Source: Ovid MEDLINE(R) 1948 to week 2 April 2011

1. Rhinitis, Allergic, Seasonal/ (11,107)
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (1334)
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (13,935)
4. or/1–3 (22,044)
5. Rhinitis/ (7156)
6. rhinitis.ti,ab. (15,813)
7. or/5–6 (19,981)
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (223,342)
9. Trees/ or Poaceae/ (23,581)
10. 8 or 9 (234,891)
11. 7 and 10 (3812)
12. Desensitization, Immunologic/ (7170)
13. allergens/ (28,104)

14. (desensiti* or hyposensiti*).ti,ab. (22,895)
15. immunotherapy/ (25,148)
16. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (509,932)
17. (grazax or pollinex or alutard).ti,ab. (101)
18. or/12–17 (552,055)
19. 4 or 11 (23,106)
20. 18 and 19 (7716)
21. exp animals/ not humans/ (3,565,261)
22. 20 not 21 (7358)
23. limit 22 to "therapy (optimized)" (1051)

Source: EMBASE (Ovid) 1980 to 2011 week 15

1. exp allergic rhinitis/ (22,724)
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (2038)
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (16,538)
4. or/1–3 (35,766)
5. rhinitis/ (11,928)
6. rhinitis.ti,ab. (20,790)
7. or/5–6 (27,861)
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (278,114)
9. tree/ or grass pollen/ (16,418)
10. or/8–9 (284,179)
11. 7 and 10 (5386)
12. desensitization immunologic/ (13,113)
13. allergen/ (31,586)
14. (desensiti* or hyposensiti*).ti,ab. (25,828)
15. immunotherapy/ (38,113)
16. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (552,975)
17. (grazax or pollinex or alutard).ti,ab. (191)
18. or/12–17 (604,305)
19. 4 or 11 (36,735)
20. 18 and 19 (12,139)
21. exp animal/ not human/ (1,254,356)
22. 20 not 21 (12,046)
23. limit 22 to "treatment (2 or more terms min difference)" (1982)

Source: Cumulative Index to Nursing and Allied Health Literature (EBSCOhost) 1982–2011

S1
(MH "Rhinitis, Allergic, Seasonal")

S2
TX rhinoconjunctivitis or TX "rhino conjunctivitis"

S3
TX "hay fever" or TX hayfever or TX pollinosis or TX pollenosis or TX sar or TX par or TX "pollen allergen*" or TX "season*allergic"

S4
S1 or S2 or S3

S5

(MH "Rhinitis")

S6
TX Rhinitis

S7
S5 or S6

S8
TX intermittent* or TX season* or TX spring or TX summer or TX pollen* or TX grass* or TX birch or TX ragweed or TX tree* or TX weed* or TX mugwort or TX willow

S9
TX alder or TX poaceae

S10
S8 or S9

S11
S7 and S10

S12
(MH "Desensitization, Immunologic")

S13
(MH "Allergens")

S14
TX desensiti* or hyposensiti*

S15
(MH "Immunotherapy")

S16
TX immunotherap* or TX immunomodulatory or TX "immune therapy" or TX "immunologic response*" or TX allergen* or TX antigen*

S17
TX grazax or TX pollinex or TX alutard

S18
s12 or s13 or s14 or s15 or s16 or s17

S19
s4 or s11

S20
s18 and s19View Results (455)

S21
s18 and s19

Limiters - Clinical Queries: Therapy - Best Balance; Human

View Results (93)

Source: Science Citation Index (Web of Knowledge) 1900–2011

#1
12,037
TS=”seasonal allergic rhinitis

#2
1757
TS=rhinoconjunctivitis

#3
95
TS=”rhino conjunctivitis”

#4
21,338
TS=(hayfever or pollinosis or pollenosis or sar)

#5
7479
TS=(“hay fever” or “pollen allergen*” or “season* allergic”)

#6
29,405
#5 OR #4 OR #3 OR #2 OR #1

#7
17,492
TS=rhinitis

#8
>100,000
TS=(intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder or poaceae)

#9
4902
#8 AND #7

#10
>100,000
TS=(allergen* or desensiti* or hyposensiti* or immunotherap* or immunomodulatory or antigen* or grazax or pollinex or alutard)

#11
774
TS="immune therapy"

#12
1640
TS="immunologic response*"

#13
>100,000
#12 OR #11 OR #10

#14
31,306
#9 OR #6

#15
6212
#14 AND #13

#16
>100,000
TS=(trial OR random* OR control* OR placebo)

#17
2068
#15 AND #16

Economic evaluations

Source: The Cochrane Library (NHS Economic Evaluation Database)

Refer to The Cochrane Library effectiveness search strategy above.

Source: Ovid MEDLINE(R) 1948 to week 2 April 2011

1. Rhinitis, Allergic, Seasonal/ (11,107)
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (1334)
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (13,935)
4. or/1–3 (22,044)
5. Rhinitis/ (7156)
6. rhinitis.ti,ab. (15,813)
7. or/5–6 (19,981)
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (223,342)
9. Trees/ or Poaceae/ (23,581)
10. 8 or 9 (234,891)
11. 7 and 10 (3812)
12. Desensitization, Immunologic/ (7170)
13. allergens/ (28,104)
14. (desensiti* or hyposensiti*).ti,ab. (22,895)
15. immunotherapy/ (25,148)

16. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (509,932)
17. (grazax or pollinex or alutard).ti,ab. (101)
18. or/12–17 (552,055)
19. 4 or 11 (23,106)
20. 18 and 19 (7716)
21. exp animals/ not humans/ (3,565,261)
22. 20 not 21 (7358)
23. economics/ (25,995)
24. exp "costs and cost analysis"/ (155,450)
25. cost of illness/ (13,777)
26. exp health care costs/ (37,323)
27. economic value of life/ (5134)
28. exp economics medical/ (13,145)
29. exp economics hospital/ (17,088)
30. economics pharmaceutical/ (2221)
31. exp "fees and charges"/ (25,111)
32. (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (338,786)
33. (expenditure$ not energy).tw. (14,033)
34. (value adj1 money).tw. (18)
35. budget$.tw. (14,277)
36. or/23–35 (462,608)
37. 22 and 36 (164)

Source: EMBASE (Ovid) 1980–2011 week 15

1. exp allergic rhinitis/ (22,724)
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (2038)
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (16,538)
4. or/1–3 (35,766)
5. rhinitis/ (11,928)
6. rhinitis.ti,ab. (20,790)
7. or/5–6 (27,861)
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (278,114)
9. tree/ or grass pollen/ (16,418)
10. or/8–9 (284,179)
11. 7 and 10 (5386)
12. desensitization immunologic/ (13,113)
13. allergen/ (31,586)
14. (desensiti* or hyposensiti*).ti,ab. (25,828)
15. immunotherapy/ (38,113)
16. (immunotherap* or immunomodulatory or immune therapy or immunologic response* or allergen* or antigen*).ti,ab. (552,975)
17. (grazax or pollinex or alutard).ti,ab. (191)
18. or/12–17 (604,305)
19. 4 or 11 (36,735)
20. 18 and 19 (12,139)
21. exp animal/ not human/ (1,254,356)
22. 20 not 21 (12,046)
23. cost benefit analysis/ (55,170)
24. cost effectiveness analysis/ (71,637)

25. cost minimization analysis/ (1826)
26. cost utility analysis/ (3413)
27. economic evaluation/ (6090)
28. (cost or costs or costed or costly or costing).tw. (300,972)
29. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (157,655)
30. (technology adj assessment$).tw. (3043)
31. or/23–30 (466,067)
32. 22 and 31 (375)

Quality of life

Source: Ovid MEDLINE(R) 1948 to week 5 June 2011

1. Rhinitis, Allergic, Seasonal/ (11,285)
2. (rhinoconjunctivitis or rhino conjunctivitis).ti,ab. (1375)
3. (hay fever or hayfever or pollinosis or pollenosis or SAR or pollen allergen* or season* allergic).ti,ab. (14,414)
4. or/1–3 (22,665)
5. Rhinitis/ (7326)
6. rhinitis.ti,ab. (16,122)
7. or/5–6 (20,398)
8. (intermittent* or season* or spring or summer or pollen* or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti,ab. (228,206)
9. Trees/ or Poaceae/ (24,071)
10. 8 or 9 (239,962)
11. 7 and 10 (3885)
12. 4 or 11 (23,747)
13. quality of life/ (92,016)
14. life style/ (35,811)
15. health status/ (48,471)
16. health status indicators/ (16,723)
17. value of life/ (5167)
18. quality adjusted life.mp. (6813)
19. or/13–18 (183,446)
20. 12 and 19 (472)

Appendix 3 Indirect comparison methodology and results

Methods

Indirect comparison meta-analysis

Four continuous outcomes were included in the review (SSs, MSs, SMSs and QoL scores). Each score y_{jk} can be assumed to have a normal likelihood with standard deviation sd_{jk}, sample size N_{jk} and, therefore, standard error $se_{jk} = \frac{sd_{jk}}{N_{jk}}$ for study j and arm k (*Equation 2*). Scores have been measured on different scales across studies. Therefore, these needed to be standardised before the inclusion in the meta-analysis by means of the pooled SD (SD_j)[263,264] (*Equation 3*). Standardised mean scores are represented by μ_{jk} in *Equation 3*, whereas SMDs δ_{jk}s are estimated via a linear regression model (*Equations 4a* and *4b*), where a random-effects parameter σ^2 can be estimated as an alternative to the fixed-effects model, where $\delta_{jk} = d_k - d_{bj}$ would replace *Equation 4b*, where d_k is the pooled SMD score between treatment k (2 = SCIT; 3 = SLIT) and placebo (i.e. $b_j = 1$ for every study j, the reference baseline intervention arm for every study included in the ICMA). Finally, the indirect comparison of SLIT vs SCIT can be estimated by subtracting the pooled SMD slope between SLIT and placebo and the pooled SMD slope between SCIT and placebo as in *Equation 5*. A positive value for d_{32} would indicate that the SLIT pooled score is higher than the SCIT pooled score (i.e. SCIT is a better treatment); similarly, a negative value for d_{32} would indicate that SLIT is a better treatment.

$$y_{jk} \sim dnorm\left(mean\_score_{jk}, se_{jk} = \frac{sd_{jk}}{N_{jk}}\right) \tag{2}$$

$$mean\_score_{jk} = \mu_{jk} * SD_j \tag{3}$$

$$\mu_{jk} = \begin{cases} base_j & Interventionb_j \\ base_j + \delta_{jk} Interventionk \end{cases} \tag{4a}$$

$$\delta_{jk} \sim Normal\left(\left(d_k - d_{b_j}\right), \sigma^2\right) \tag{4b}$$

$$d_{32} = d_3 - d_2 \tag{5}$$

Indirect comparison meta-regression

Random-effects modelling is a first step to account for unexplained between-study variability or heterogeneity.[265] Heterogeneity can be further explored by means of meta-regression when covariates are available from the review. In this review a number of covariates were available. The linear regression model described in *Equations 4a* and *4b* would instead become as in *Equation 6a*, where each comparison d_k is substituted by a regression equation where α_k is the intercept, β_k is the slope and X_j is the covariate for study j (i.e. $d_k = \alpha_k + \beta_k * X_j$). The indirect comparison of SCIT compared with SLIT for a given level of the covariate $X_j = x$ is then described in Equation 6b.

$$\delta_{jk} \sim Normal\left(\left(a_k - b_{b_j}\right) + \left(\beta_k - \beta_{b_j}\right)\mathrm{X}_j, \sigma^2\right) \tag{6a}$$

$$d_{32,x} = \left(a_3 - a_2\right) + \left(\beta_3 - \beta_2\right)\chi \tag{6b}$$

In meta-regressions, α_k corresponds to $d_{k,x=0}$ (i.e. when the covariate value is zero). For example, the dichotomous covariate Age has been coded as 1 = Adult and 0 = Child; therefore, α_2 represents the SMD between treatment 2 and placebo for those studies that only recruited adults. Similarly, variables considered as continuous such as Year of Publication and Number of Symptoms have been centred to AD2005 and six symptoms, respectively. For example, α_2 when Year of publication is included in the model represents the SMD between SCIT and placebo as regressed for AD2005 by the model. Therefore, α_ks have not been explicitly reported in the tables to avoid duplication of reporting of results. For every score, the data sets were composed of a number of studies. The meta-regression models may require the cancellation of the entire record of the study where the covariate value is missing (e.g. it is not reported or it is unclear). In this case, the DIC and pD (the estimate of the effective number of parameters in the model) for the null model with the same number of studies is included in the meta-analysis.

Implementation

Parameter estimates were obtained via Bayesian modelling and Markov chain Monte Carlo (MCMC) modelling. The software for Bayesian modelling WinBUGS 1.4[139] was used to implement the models. There was no preconceived prior opinion on the values of the intervention and baseline parameters and therefore these were given non-informative prior distributions. Heterogeneity parameter was given a priori uniform distribution between 0 and 300 (on the between-study SD) and, for sensitivity analysis, a gamma prior with parameters both equal to 0.001 (on the between-study variance).[266]

Multiple chains were run by initialising every chain in different points of the space of parameters; convergence and the length of the burn-in period[267] were assessed by setting the burn-in period to zero and by looking at history plots (available by default in WinBUGS) for those chains simultaneously. The length of the chain after the burn-in period was determined so that the MC error was lower than 10^{-4}, where the MC error measures the proportion of variability that is consequent to sampling algorithm, i.e. the higher the number of iterations the lower the MC error.[268] Longer chains were also useful to adjust parameter estimates in case of autocorrelation in the MCMC chains.

The choice between random- and fixed-effects models and the significance of regression parameters when heterogeneity was explored by means of covariates was assessed by means of the DIC.[269] The DIC statistic is a compound measure of the model fit (the deviance) and the complexity of the model (pD). The lower the DIC, the better the fit; for choosing between two models, a minimum difference of 5 in the DIC is recommended.[139]

Results

Model checking

Convergence was achieved in the first 50 iterations for every model; model results did not appear to be sensitive to initial values. Autocorrelation in the MCMC chains was found, especially on the between-studies variance parameter (i.e. the maximum lag was >40 iterations). Therefore, long chains were run, with a burn-in period of 10,000 iterations, and a further 100,000 iterations were used to build posterior distributions. Model results were not sensitive to the choice of prior distribution for the heterogeneity parameter.

The following interpretation of SSs is given as an example.

Symptom scores

For every meta-analysis and meta-regression model, *Table 57* presents estimates of parameters and of the model fit statistic DIC for symptoms scores. Probabilistic analysis is given in *Table 58*, where for every model, and eventually for all (where possible) or some significant levels of the covariate, the probability of each treatment being the best treatment is given.

The fixed- and random-effects model for symptoms score included 59 studies. The DIC for the random-effects model (508) is meaningfully lower than the DIC for the fixed-effects model (542), although the difference in pD (+34) indicates that it is far more complex. The indirect comparison of SLIT with SCIT is in favour of SCIT, whereas the difference between scores is significantly positive {i.e. SCIT corresponds to lower SS [d_{32} 0.351 (0.127 to 0.586)]}. The probabilistic analysis also indicates SCIT as the best treatment when symptoms scores are considered, with a probability associated with SCIT being the best treatment nearly equal to 100%. For every meta-analysis and meta-regression model, probabilistic analyses indicate the probability of zero that placebo is the best treatment. The data present a substantial amount of unexplained heterogeneity [σ^2 0.089 (CrI 0.027 to 0.187)]. Meta-regression results are presented below separately for each covariate. For simplicity, as the fixed-effects model corresponds to a much worse fit to the data than the random-effects model, meta-regression will be fit on the random-effects model, and therefore the null model will refer to the random-effects model without covariate effects.

Age of participants (59 records)

Age of participants did not improve model fit significantly, with a difference of –2 points in DIC (506) when compared with the null model. In fact, CrIs for regression coefficients included the no-effect value of zero [β_2 0.455 (CrI –0.434 to 1.358); β_3 0.186 (CrI –0.083 to 0.466)] and the between-study variance remained unchanged compared with the random-effect null model [σ^2 0.091 (CrI 0.028 to 0.192)]. The probabilistic analysis indicates that there is a high probability a posteriori that SCIT is the best treatment for adults (around 96%), reflecting a significantly positive estimates of the indirect comparison of SLIT vs SCIT via the estimated SMD score [$d_{32,\text{adult}}$ 0.328 (CrI 0.088 to 0.579)]. However, for studies that included only children this probability is almost even and the SMD indirectly estimated from the model was not significantly different from zero [$d_{32,\text{child}}$ 0.059 (CrI –0.837 to 0.966)]. This uncertainty can be explained by the fact that there is only one study comparing SCIT with placebo in children and indicates that more studies may be needed.

Year of publication (59 records)

Year of publication (time) can be considered a source of differences between studies that depend on time, for example a proxy for technological advancements that are not explicitly considered. For symptoms scores, year of publication improves the fit of the model to the data compared with the null model (i.e. six-point improvement in DIC: 502 compared with 508). In fact, the between-study variance seems to be slightly lower than for the null model [σ^2 0.067 (CrI 0.017 to 0.147)]. The effect of time affects mainly the comparison SCIT vs placebo [σ_2 0.056 (CrI 0.027 to 0.086], whereas there is a 50% posterior probability that time has a positive effect (or negative effect) for the comparison of SLIT with placebo [β_3 0.001 (CrI –0.024 to 0.025)], the posterior CrI is nearly symmetrical around the posterior mean. The indirect comparison of SLIT vs SCIT favours SCIT until 2005, then from 2006 seems to be more favourable to SLIT.

Tables of results

TABLE 57 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-SSs

Symptom scores						
Model (covariate included in the model)	*n*	Parameter	SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)	SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)	SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)	DIC (pD)
Fixed effects (no covariates)	59	d_k	–0.604 (–0.720 to –0.489)	–0.317 (–0.374 to –0.261)	0.287 (0.160 to 0.416)	542 (61)
Random effects (no covariates) **null model**	59	d_k	–0.713 (–0.921 to –0.521)	–0.362 (–0.484 to –0.248)	0.351 (0.127 to 0.586)	508 (95)
		σ^2	0.089 (0.027 to 0.187)			
Random effects (age of participants)	59	β_k	0.455 (–0.434 to 1.358)	0.186 (–0.083 to 0.466)	–	506 (96)
		$d_{k,child}$	–0.282 (–1.156 to 0.586)	–0.223 (–0.461 to 0.015)	0.059 (–0.837 to 0.966)	
		$d_{k,adult}$	–0.736 (–0.953 to –0.537)	–0.409 (–0.551 to –0.276)	0.328 (0.088 to 0.579)	
		σ^2	0.091 (0.028 to 0.192)			
Random effects (year of publication)	59	β_k	0.056 (0.027 to 0.086)	0.001 (–0.024 to 0.025)	–	502 (92)
		$d_{k,2000}$	–0.763 (–0.956 to –0.583)	–0.359 (–0.529 to –0.196)	0.404 (0.159 to 0.655)	
		$d_{k,2005}$	–0.485 (–0.699 to –0.273)	–0.356 (–0.468 to –0.252)	0.128 (–0.113 to 0.364)	
		$d_{k,2010}$	–0.206 (–0.519 to 0.113)	–0.353 (–0.517 to –0.20)	–0.148 (–0.510 to 0.20)	
		σ^2	0.067 (0.017 to 0.147)			
Random effects (no. of symptoms[b])	48	β_k	–0.090 (–0.209 to 0.024)	0.022 (–0.036 to 0.078)	–	449 (79) [529 (75)][c]
		$d_{k,3sym}$	–0.410 (–0.912 to 0.095)	–0.473 (–0.787 to –0.158)	–0.062 (–0.658 to 0.534)	
		$d_{k,6sym}$	–0.679 (–0.934 to –0.439)	–0.407 (–0.584 to –0.235)	0.273 (–0.024 to 0.578)	
		$d_{k,12sym}$	–1.217 (–1.884 to –0.592)	–0.275 (–0.547 to –0.020)	0.942 (0.268 to 1.653)	
		σ^2	0.096 (0.019 to 0.213)			

Symptom scores						
Model (covariate included in the model)	*n*	Parameter	SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)	SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)	SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)	DIC (pD)
Random effects (duration[b])	57	β_{k1}	0.558 (–0.126 to 1.277)	–0.011 (–0.313 to 0.287)	–	477 (95) [481 (93)][c]
		β_{k2}	0.639 (0.141 to 1.173)	0.004 (–0.304 to 0.316)	–	
		$d_{k,<6months}$	–1.187 (–1.621 to –0.788)	–0.365 (–0.577 to –0.160)	0.822 (0.379 to 1.299)	
		$d_{k,6–12months}$	–0.629 (–1.205 to –0.066)	–0.376 (–0.599 to –0.164)	0.252 (–0.357 to 0.862)	
		$d_{k,>12months}$	–0.548 (–0.863 to –0.237)	–0.361 (–0.592 to –0.132)	0.187 (–0.199 to 0.577)	
		σ^2	0.112 (0.040 to 0.221)			
Random effects (MAC)[b]	42	β_{k1}	–0.095 (–0.595 to 0.408)	0.182 (–0.176 to 0.556)	–	309 (66) [310 (60)]*
		β_{k2}	–0.447 (–1.013 to 0.072)	0.151 (–0.219 to 0.541)	–	
		$d_{k,<5\mu g}$	–0.460 (–0.845 to –0.089)	–0.476 (–0.813 to –0.155)	–0.016 (–0.516 to 0.483)	
		$d_{k,5–6\mu g}$	–0.556 (–0.891 to –0.226)	–0.294 (–0.458 to –0.133)	0.262 (–0.108 to 0.634)	
		$d_{k,>20\mu g}$	–0.907 (–1.338 to –0.536)	–0.325 (–0.511 to –0.135)	0.582 (0.167 to 1.060)	
		σ^2	0.053 (0.005 to 0.13)			

continued

TABLE 57 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-SSs (*continued*)

Symptom scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo:[a] direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (allergen type[b])	60[d]	β_{k1}	–0.326 (–0.868 to 0.204)	0.053 (–0.423 to 0.538)	–	523 (100) [525 (95)][c]
		β_{k2}	0.196 (–0.291 to 0.699)	–0.108 (–0.438 to 0.223)	–	
		β_{k3}	0.437 (–0.468 to 1.371)	–1.092 (–2.119 to –0.067)	–	
		β_{k4}	0.276 (–196.40 to 197.30)	–	–	
		$d_{k,grass}$	–0.721 (–1.013 to –0.451)	–0.326 (–0.473 to –0.185)	0.396 (0.090 to 0.721)	
		$d_{k,Parietaria}$	–1.047 (–1.532 to –0.599)	–0.272 (–0.728 to 0.188)	0.775 (0.140 to 1.446)	
		$d_{k,tree}$	–0.526 (–0.941 to –0.121)	–0.433 (–0.735 to –0.138)	0.092 (–0.408 to 0.597)	
		$d_{k,Alternaria}$	–0.285 (–1.150 to 0.594)	–1.418 (–2.431 to –0.404)	–1.133 (–2.460 to 0.199)	
		$d_{k,ragweed}$	–0.445 (–197.20 to 196.60)	–0.435 (–0.867 to –0.007)	0.011 (–197.0 to 196.70)	
		σ^2	0.096 (0.030 to 0.20)			

sym, symptoms.

a The DIC (pD) of the null model when the same number of studies is included in the meta-analysis is reported within square brackets.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

c Differences d_k relative to the comparison of A vs B need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

d For Drachenberg (2001, SLIT)[91] the data used were combined scores for allergen types (AT) TREE and GRASS. However, when the effect of different AT was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

TABLE 58 Probabilistic analysis for SSs [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (59)	00.0	>99	00.0
Random effect (59)	00.0	99.9	00.1
Age group of participants (59)			
Child[a]	00.9	54.9	44.2
Adult	00.0	99.6	00.4
Year of publication (59)			
2000	00.0	99.9	00.1
2005	00.0	86.1	13.9
2010	00.0	20.3	79.7
No. of symptoms (48)			
3 symptoms	00.0	41.5	58.5
6 symptoms	00.0	96.5	03.5
12 symptoms	00.0	99.7	00.3
Duration			
Low	00.0	>99	00.0
Medium	00.0	80.1	19.9
High	00.0	83.4	16.6
MAC			
<5 µg	00.0	47.4	52.6
5–20 µg	00.0	92.0	08.0
>20 µg	00.0	99.7	00.3
Allergen type			
Grass	00.0	99.4	00.6
Parietaria	00.0	99.1	00.9
Tree	00.0	64.3	35.7
Alternaria	00.1	04.6	95.3
Ragweed	01.2	50.0	48.8

a Few studies on children compared SCIT vs placebo and SLIT vs placebo.

Figure 27 shows a plot of the results (based on SSs) when year of publication is included in the model. Dashed vertical lines highlight the period 2007–8 when, in theory, SLIT is more likely to be beneficial than SCIT.

Figure 28 shows a plot of the results (based on SSs) when number of symptoms is included in the model.

Figure 29 shows a plot of the results (based on MSs) when year of publication is included in the model.

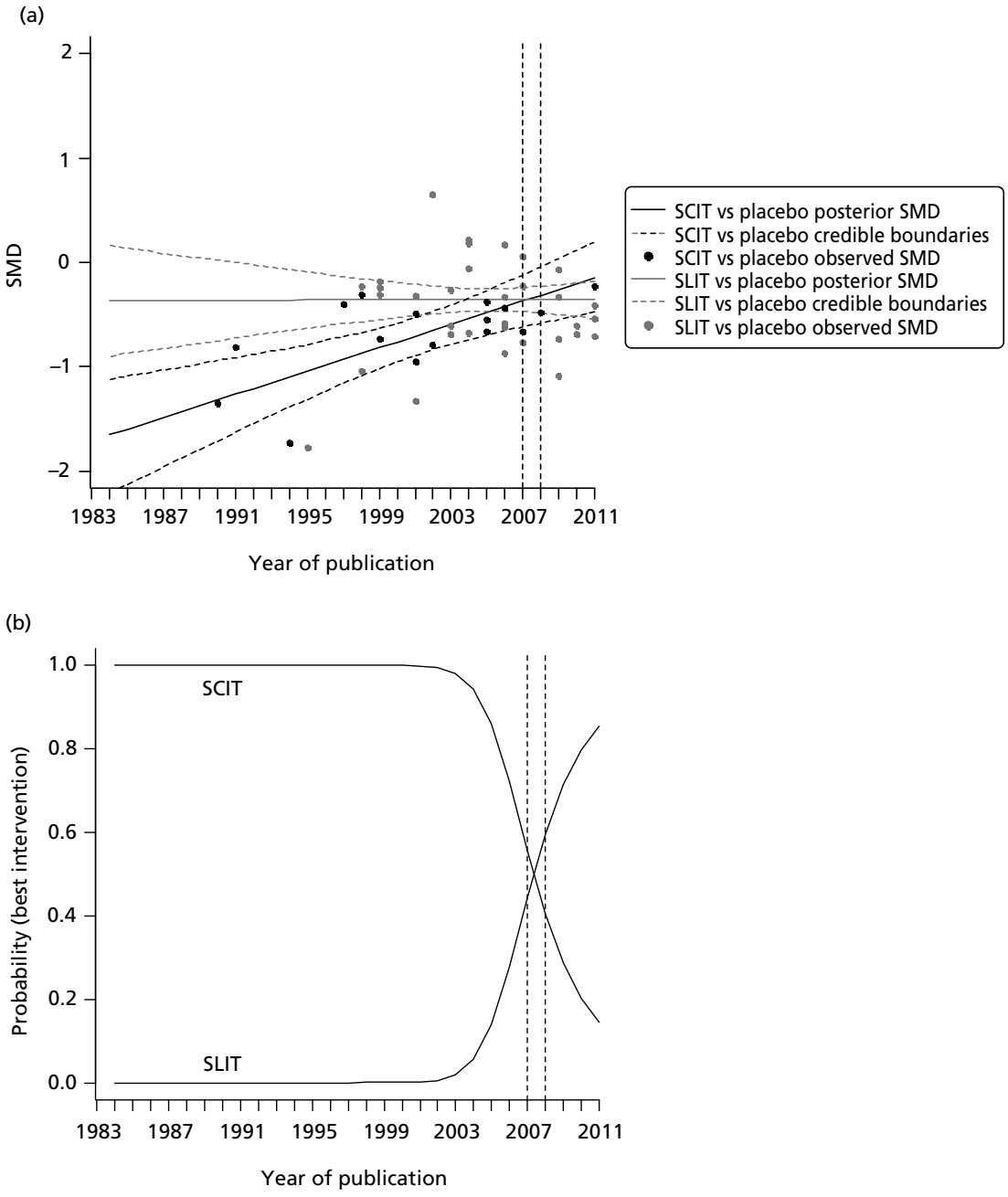

FIGURE 27 (a) Theoretical and observed SMDs (and credible boundaries) vs year of publication for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs year of publication.

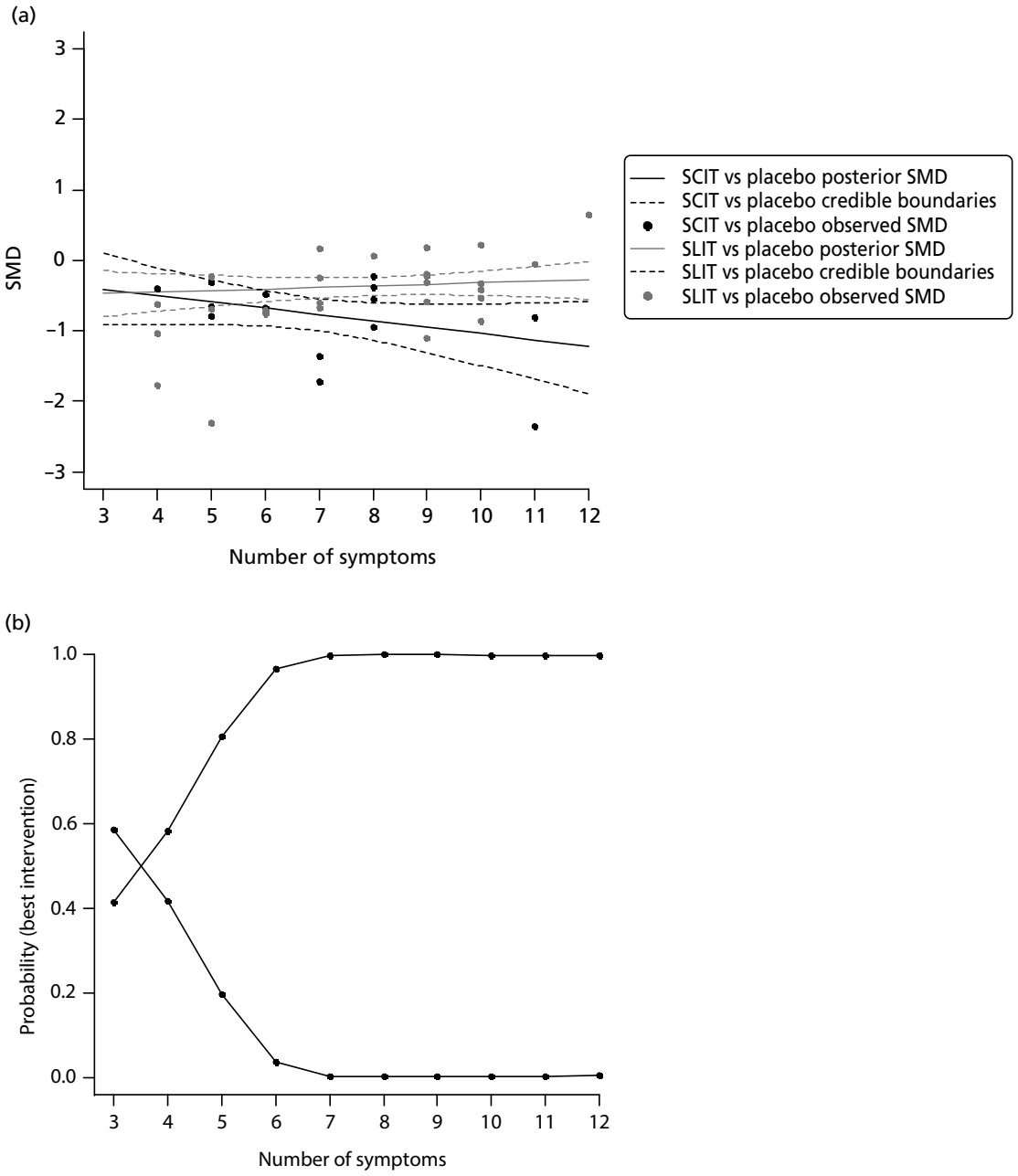

FIGURE 28 (a) Theoretical and observed SMDs (and credible boundaries) vs number of symptoms for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs number of symptoms.

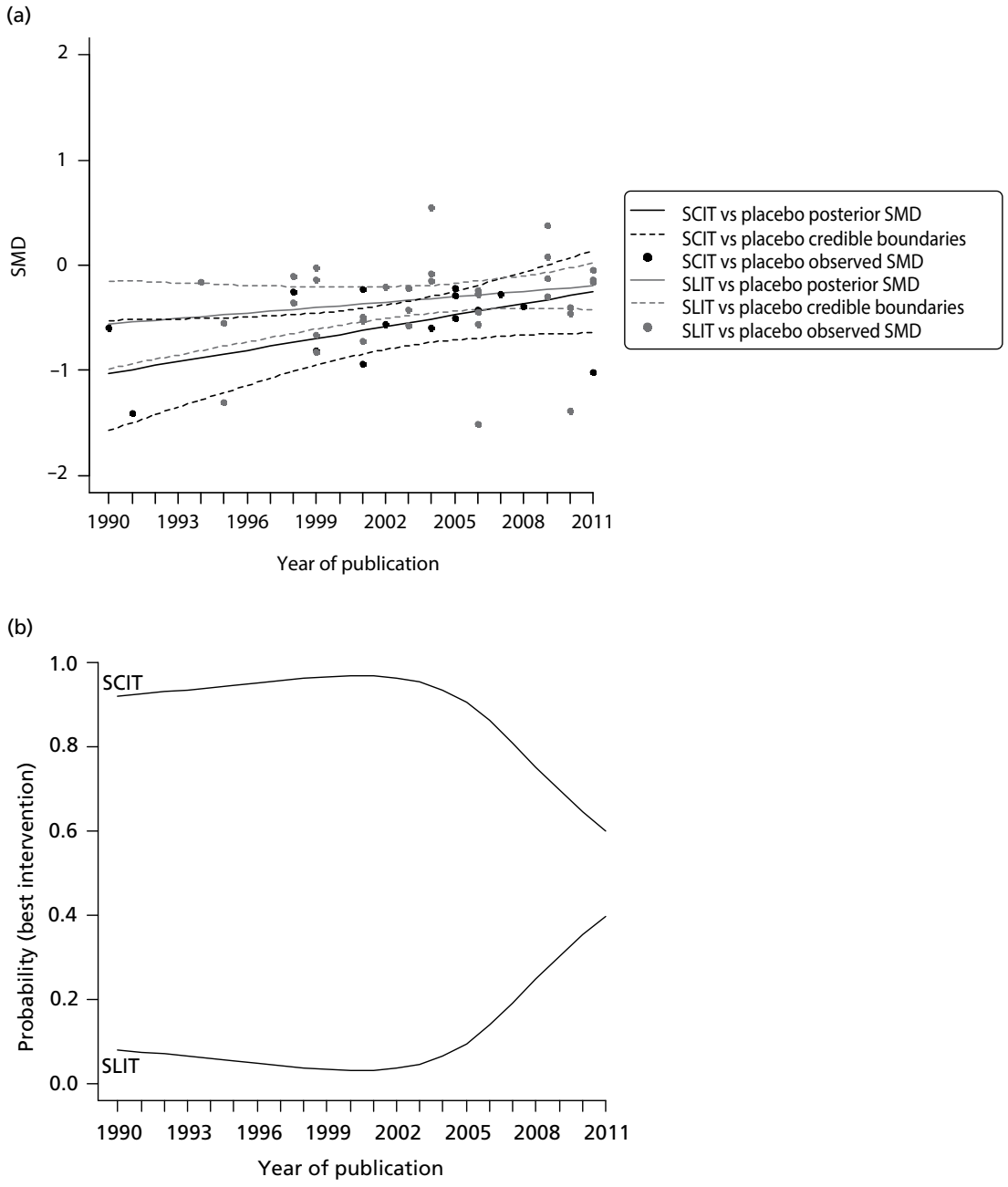

FIGURE 29 (a) Theoretical and observed SMDs (and credible boundaries) vs year of publication for the direct comparisons SCIT vs placebo and SLIT vs placebo, respectively. (b) Given the data included in the meta-regression, probability of SCIT and SLIT, respectively, being the best treatment vs year of publication.

TABLE 59 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-MSs

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	51	d_k	–0.469 (–0.592 to –0.347)	–0.220 (–0.283 to –0.158)	0.249 (0.111 to 0.386)	459 (53)
Random effect (no covariates) **null model**	51	d_k	–0.579 (–0.808 to –0.370)	–0.306 (–0.449 to –0.177)	0.273 (0.027 to 0.529)	423 (83)
		σ^2	0.099 (0.030 to 0.211)			
Random effect (age of participants)	51	β_k	0.017 (–0.085 to 0.125)	–0.002 (–0.064 to 0.063)	–	429 (79)
		$d_{k,child}$	–0.051 (–0.087 to –0.019)	–0.041 (–0.069 to –0.017)	0.009 (–0.031 to 0.050)	
		$d_{k,adult}$	–0.034 (–0.133 to 0.065)	–0.043 (–0.101 to 0.015)	–0.009 (–0.124 to 0.106)	
		σ^2	0.002 (0.001 to 0.005)			
Random effects (year of publication)	51	β_k	0.037 (–0.001 to 0.076)	0.017 (–0.010 to 0.044)	–	422 (82)
		$d_{k,2000}$	–0.661 (–0.899 to –0.437)	–0.388 (–0.576 to –0.208)	0.273 (–0.016 to 0.571)	
		$d_{k,2005}$	–0.476 (–0.715 to –0.247)	–0.302 (–0.439 to –0.176)	0.174 (–0.091 to 0.439)	
		$d_{k,2010}$	–0.291 (–0.650 to 0.067)	–0.217 (–0.416 to –0.029)	0.074 (–0.335 to 0.477)	
		σ^2	0.091 (0.027 to 0.196)			
Random effects (duration[b])	48	β_{k1}	–0.111 (–0.894 to 0.671)	0.075 (–0.261 to 0.405)	–	375 (81) [376 (77)][c]
		β_{k2}	–0.287 (–0.977 to 0.379)	0.219 (–0.142 to 0.589)	–	
		$d_{k,6months}$	–0.395 (–0.994 to 0.202)	–0.389 (–0.620 to –0.170)	0.006 (–0.634 to 0.643)	
		$d_{k,6–12months}$	–0.506 (–1.013 to –0.007)	–0.314 (–0.573 to –0.073)	0.192 (–0.376 to 0.750)	
		$d_{k,>12months}$	–0.682 (–1.010 to –0.375)	–0.170 (–0.461 to 0.114)	0.511 (0.094 to 0.950)	
		σ^2	0.120 (0.039 to 0.255)			

continued

TABLE 59 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*)-MSs (*continued*)

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	37	β_{k1}	–0.135 (–0.670 to 0.397)	0.434 (0.074 to 0.806)	–	243 (57) [243 (53)][c]
		β_{k2}	–0.231 (–0.853 to 0.371)	0.352 (–0.035 to 0.740)	–	
		$d_{k,<5\mu g}$	–0.317 (–0.765 to 0.121)	–0.603 (–0.943 to –0.274)	–0.286 (–0.849 to 0.266)	
		$d_{k,5-6\mu g}$	–0.452 (–0.754 to –0.153)	–0.169 (–0.319 to –0.016)	0.283 (–0.049 to 0.622)	
		$d_{k,>20\mu g}$	–0.549 (–0.981 to –0.139)	–0.251 (–0.461 to –0.054)	0.298 (–0.164 to 0.765)	
		σ^2	0.042 (0.006 to 0.108)			
Random effects (allergen type)	52[d]	β_{k1}	0.276 (–0.317 to 0.915)	–0.297 (–0.776 to 0.184)	–	440 (87) [438 (83)][c]
		β_{k2}	0.351 (–0.142 to 0.879)	–0.199 (–0.540 to 0.143)	–	
		β_{k3}	–0.114 (–1.061 to 0.855)	–1.226 (–2.203 to –0.246)	–	
		β_{k4}	0.125 (–0.896 to 1.152)	–0.129 (–0.586 to 0.337)	–	
		$d_{k,grass}$	–0.715 (–1.052 to –0.416)	–0.211 (–0.383 to –0.050)	0.504 (0.169 to 0.873)	
		$d_{k,Parietaria}$	–0.440 (–0.967 to 0.092)	–0.508 (–0.958 to –0.058)	–0.068 (–0.761 to 0.619)	
		$d_{k,tree}$	–0.365 (–0.771 to 0.041)	–0.410 (–0.712 to –0.114)	–0.045 (–0.550 to 0.453)	
		$d_{k,Alternaria}$	–0.829 (–1.734 to 0.067)	–1.437 (–2.399 to –0.472)	–0.608 (–1.933 to 0.710)	
		$d_{k,ragweed}$	–0.591 (–1.575 to 0.381)	–0.340 (–0.771 to 0.095)	0.251 (–0.809 to 1.325)	
		σ^2	0.094 (0.024 to 0.209)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

c The DIC (pD) of the null model when the same number of studies is included in the meta-analysis is reported within square brackets

d For Drachenberg (2001, SLIT)[91] the data used were combined scores for allergen types (AT) TREE and GRASS. However, when the effect of different AT was explored via meta-regression, separate scores for the two allergen types were used. Therefore, the number of studies in the analysis is 60 instead of 59.

TABLE 60 Probabilistic analysis for MSs [probability (%) that treatment *k* is the best under different modelling assumptions]

	Placebo	SCIT	SLIT
Fixed effect (51)	00.0	>99	00.0
Random effect (51)	00.0	98.4	01.6
Age group of participants (51)			
Child	00.0	68.1	31.9
Adult	01.8	43.1	55.1
Year of publication (51)			
2000	00.0	96.9	03.1
2005	00.0	90.6	09.4
2010	00.1	64.6	35.3
Duration (48)			
Low	00.0	50.9	49.1
Medium	00.0	75.6	24.3
High	00.0	99.1	00.9
MAC (37)			
<5 µg	00.0	15.1	84.9
5–20 µg	00.0	95.3	04.7
>20 µg	00.0	90.4	09.6
Allergen type (52)			
Grass	00.0	99.8	00.2
Parietaria	00.1	42.1	57.9
Tree	00.0	43.0	57.0
Alternaria	00.0	18.0	82.0
Ragweed	00.8	67.8	31.4

TABLE 61 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (*d*) –SMS

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo:[a] direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	15	d_k	–0.414 (–0.499 to –0.328)	–0.389 (–196.20 to 193.70)	0.024 (–195.80 to 194.10)	94 (16)
Random effects (no covariates) **null model**	15	d_k	–0.440 (–0.579 to –0.326)	–0.127 (–196.20 to 196.70)	0.313 (–195.80 to 197.10)	95 (20)
		σ^2	0.017 (0.0 to 0.086)			
Random effects (age of participants)	15	β_k	0.206 (–0.155 to 0.604)	–0.012 (–195.50 to 195.10)	–	95 (20)
		$d_{k,child}$	–0.258 (–0.616 to 0.097)	–0.170 (–277.60 to 274.30)	0.089 (–277.30 to 274.70)	
		$d_{k,adult}$	–0.464 (–0.616 to –0.346)	–0.157 (–196.90 to 196.20)	0.307 (–196.40 to 196.70)	
		σ^2	0.019 (0.0 to 0.097)			
Random effects (year of publication)	15	β_k	0.010 (–0.011 to 0.032)	0.337 (–195.60 to 196.40)	–	96 (21)
		$d_{k,2000}$	–0.513 (–0.716 to –0.331)	–1.606 (–1005.0 to 994.80)	–1.093 (–1004.0 to 995.30)	
		$d_{k,2005}$	–0.461 (–0.605 to –0.338)	0.079 (–196.30 to 195.80)	0.540 (–195.80 to 196.20)	
		$d_{k,2010}$	–0.409 (–0.566 to –0.276)	1.764 (–998.50 to 1003.0)	2.173 (–998.10 to 1003.0)	
		σ^2	0.020 (0.0 to 0.101)			
Random effects (duration[b])	12	β_{k1}	–0.016 (–0.544 to 0.387)	–0.109 (–195.40 to 195.40)	–	97 (18) [95 (17)]
		β_{k2}	–0.106 (–0.427 to 0.253)	0.092 (–196.0 to 195.10)	–	
		$d_{k,<6months}$	–0.387 (–0.668 to –0.160)	0.288 (–196.10 to 197.70)	0.676 (–195.70 to 198.10)	
		$d_{k,6–12months}$	–0.404 (–0.915 to –0.079)	0.180 (–275.0 to 279.10)	0.583 (–274.60 to 279.40)	
		$d_{k,>12months}$	–0.494 (–0.736 to –0.272)	0.380 (–276.60 to 278.70)	0.874 (–276.10 to 279.20)	
		σ^2	0.037 (0.0 to 0.210)			

Medication scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo:[a] direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT[a]: indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	10	β_{k1}	0.169 (–0.257 to 0.668)	–0.189 (–196.60 to 194.90)	–	75 (16) [75 (15)]
		β_{k2}	–0.244 (–0.855 to 0.403)	0.094 (–195.0 to 196.40)	–	
		$d_{k,<5\mu g}$	–0.508 (–0.911 to –0.180)	–0.004 (–197.40 to 197.90)	0.505 (–196.90 to 198.40)	
		$d_{k,5-6\mu g}$	–0.340 (–0.638 to –0.061)	–0.192 (–278.30 to 277.40)	0.148 (–278.0 to 277.80)	
		$d_{k,>20\mu g}$	–0.753 (–1.285 to –0.251)	0.091 (–277.10 to 280.20)	0.843 (–276.50 to 280.90)	
		σ^2	0.061 (0.0 to 0.338)			
Random effects (AT)	15	β_{k1}	–0.586 (–1.075 to –0.109)	0.359 (–194.90 to 197.30)	–	93 (22)
		β_{k2}	0.028 (–0.321 to 0.371)	0.039 (–196.40 to 198.10)	–	
		β_{k3}	–0.847 (–1.655 to –0.040)	–0.129 (–195.70 to 195.70)	–	
		β_{k4}	–0.149 (–0.679 to 0.374)	0.418 (–195.10 to 194.60)	–	
		$d_{k,grass}$	–0.387 (–0.512 to –0.269)	0.236 (–195.30 to 195.40)	0.623 (–194.90 to 195.70)	
		$d_{k,Parietaria}$	–0.973 (–1.447 to –0.509)	0.595 (–276.60 to 276.20)	1.568 (–275.70 to 277.10)	
		$d_{k,tree}$	–0.359 (–0.688 to –0.042)	0.274 (–278.10 to 277.80)	0.633 (–277.90 to 278.20)	
		$d_{k,Alternaria}$	–1.234 (–2.035 to –0.439)	0.107 (–275.90 to 277.50)	1.341 (–274.70 to 278.70)	
		$d_{k,ragweed}$	–0.536 (–1.059 to –0.028)	0.654 (–279.10 to 277.90)	1.189 (–278.60 to 278.40)	
		σ^2	0.011 (0.0 to 0.059)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively.

b A number of studies were missing for NoSym <ref> and for Duration <ref>.

TABLE 62 Probabilistic analysis for SMSs [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (15)	00.0	50.2	49.8
Random effect (15)	00.0	50.2	49.8
Age group of participants (15)			
Child	02.9	47.1	50.0
Adult	00.0	50.2	49.8
Year of publication (15)			
2000	00.0	49.8	50.2
2005	00.0	50.4	49.7
2010	00.0	50.3	49.7
Duration (12)			
Low	00.1	50.2	49.7
Medium	00.5	49.8	49.8
High	00.0	50.4	49.6
MAC (10)			
<5 µg	00.2	50.0	49.9
5–20 µg	00.7	49.2	50.0
>20 µg	00.2	49.8	50.0
Allergen type (15)			
Grass	00.0	50.3	49.7
Parietaria	00.0	50.4	49.6
Tree	00.7	49.5	49.8
Alternaria	00.1	50.3	49.7
Ragweed	01.0	49.5	49.5

TABLE 63 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-QoL

QoL scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Fixed effects (no covariates)	15	d_k	–0.532 (–0.658 to –0.405)	–0.146 (–0.236 to –0.056)	0.386 (0.231 to 0.541)	43 (17)
Random effects (no covariates) **null model**	15	d_k	–0.580 (–0.892 to –0.280)	–0.197 (–0.498 to 0.089)	0.383 (–0.042 to 0.804)	–6 (27)
		σ^2	0.132 (0.041 to 0.342)			
Random effects (age of participants)	15	β_k	0.119 (–196.0 to 196.40)	–0.122 (–0.996 to 0.779)	–	–6 (27)
		$d_{k,child}$	–0.465 (–196.50 to 195.90)	–0.304 (–1.117 to 0.518)	0.161 (–196.0 to 196.40)	
		$d_{k,adult}$	–0.584 (–0.911 to –0.270)	–0.182 (–0.530 to 0.147)	0.402 (–0.062 to 0.864)	
		σ^2	0.149 (0.043 to 0.402)			
Random effects (year of publication)	15	β_k	–0.014 (–0.218 to 0.188)	0.039 (–0.170 to 0.267)	–	–5 (28)
		$d_{k,2000}$	–0.510 (–1.620 to 0.602)	–0.582 (–2.834 to 1.481)	–0.072 (–2.585 to 2.256)	
		$d_{k,2005}$	–0.581 (–0.926 to –0.247)	–0.387 (–1.525 to 0.659)	0.194 (–0.986 to 1.30)	
		$d_{k,2010}$	–0.651 (–1.691 to 0.364)	–0.193 (–0.532 to 0.137)	0.459 (–0.620 to 1.554)	
		σ^2	0.168 (0.048 to 0.467)			
Random effects (duration)	15	β_{k1}	0.462 (–1.082 to 2.002)	–0.085 (–1.087 to 0.975)	–	–4 (28)
		β_{k2}	0.571 (–0.745 to 1.869)	–0.260 (–1.048 to 0.576)	–	
		$d_{k,<6months}$	–1.096 (–2.327 to 0.146)	–0.113 (–0.616 to 0.343)	0.983 (–0.363 to 2.288)	
		$d_{k,6–12months}$	–0.634 (–1.562 to 0.297)	–0.198 (–1.113 to 0.719)	0.436 (–0.872 to 1.742)	
		$d_{k,>12months}$	–0.525 (–0.936 to –0.120)	–0.373 (–1.027 to 0.280)	0.152 (–0.617 to 0.925)	
		σ^2	0.197 (0.045 to 0.612)			

continued

TABLE 63 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-QoL (*continued*)

QoL scores						
Model (covariate included in the model)	***n***	**Parameter**	**SCIT vs placebo[a]: direct comparisons (*k* = '2'), posterior mean (95% CrI)**	**SLIT vs placebo[a]: direct comparisons (*k* = '3'), posterior mean (95% CrI)**	**SLIT vs SCIT:[a] indirect comparison (*k* = '32'), posterior mean (95% CrI)**	**DIC (pD)**
Random effects (MAC)	10	β_{k1}	–0.062 (–1.441 to 1.261)	–36.910 (–135.70 to 60.710)	–	1 (23) [–3 (18)]
		β_{k2}	–0.068 (–1.418 to 1.279)	–36.570 (–135.30 to 61.020)	–	
		$d_{k,<5\mu g}$	–0.587 (–1.767 to 0.593)	36.640 (–60.920 to 135.40)	37.220 (–60.470 to 136.0)	
		$d_{k,5–6\mu g}$	–0.649 (–1.354 to –0.007)	–0.274 (–0.889 to 0.332)	0.375 (–0.508 to 1.315)	
		$d_{k,>20\mu g}$	–0.655 (–1.303 to –0.008)	0.063 (–0.820 to 0.782)	0.718 (–0.393 to 1.670)	
		σ^2	0.260 (0.015 to 1.0)			
Random effects (allergen type)	15	β_{k1}	–0.159 (–0.899 to 0.585)	0.104 (–195.30 to 194.80)[b]	–	–5 (28)
		β_{k2}	0.393 (–195.20 to 196.20)[b]	–0.816 (–1.849 to 0.223)	–	
		β_{k3}	0.460 (–196.20 to 195.10)[b]	–0.157 (–195.20 to 194.0)[b]	–	
		β_{k4}	–0.629 (–1.853 to 0.591)	–0.030 (–195.50 to 197.20)[b]	–	
		β_{k5}	–0.304 (–1.319 to 0.723)	–0.017 (–195.80 to 195.90)[b]		
		$d_{k,grass}$	–0.461 (–0.891 to –0.037)	–0.127 (–0.445 to 0.196)	0.334 (–0.197 to 0.868)	
		$d_{k,Parietaria}$	–0.620 (–1.224 to –0.009)	–0.022 (–195.40 to 194.80)	0.597 (–194.80 to 195.30)	
		$d_{k,tree}$	–0.068 (–195.80 to 195.80)	–0.943 (–1.926 to 0.046)	–0.875 (–196.70 to 194.80)	
		$d_{k,Alternaria}$	–0.001 (–196.70 to 194.70)	–0.284 (–195.30 to 193.80)	–0.283 (–275.80 to 277.0)	
		$d_{k,ragweed}$	–1.090 (–2.237 to 0.050)	–0.157 (–195.60 to 197.10)	0.933 (–194.70 to 198.0)	
		$d_{k,Salsola\ kali}$	–0.765 (–1.696 to 0.164)	–0.143 (–195.90 to 195.80)	0.622 (–195.10 to 196.60)	
		σ^2	0.143 (0.038 to 0.420)			

a Differences d_k relative to the comparison of A vs B, need to be interpreted as $Y_A - Y_B$, where Y_A and Y_B are the score for treatment A and B, respectively..

b Such a wide CrI is due to the fact that there is no study reporting such covariate that can inform that parameter.

TABLE 64 Probabilistic analysis for QoL scores [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effect (15)	00.0	>99	00.0
Random effect (15)	00.0	96.4	03.6
Age group of participants (15)			
Child	10.5	50.0	39.5
Adult	00.0	95.9	04.1
Year of publication (15)			
2000	05.0	45.0	49.9
2005	00.0	64.5	35.5
2010	01.2	81.0	17.8
Duration (15)			
Low	01.3	92.6	06.1
Medium	02.6	76.1	21.3
High	00.2	66.8	33.0
MAC (10)			
<5 µg	10.9	68.3	20.9
5–20 µg	00.6	83.3	16.2
>20 µg	01.2	91.3	07.5
Allergen type (15)			
Grass	00.5	90.2	09.3
Parietaria	01.2	49.1	49.8
Tree	01.5	49.7	48.8
Alternaria	25.0	37.4	37.6
Ragweed	01.5	48.9	49.6
Salsola kali	02.5	47.8	49.7

TABLE 65 Meta-regression parameters estimates (alphas and betas), random-effect parameter estimates (σ^2), probability of *k*th treatment is best (*p*-best) and estimated standardised score differences (d)-RQLQ scores

RQLQ scores						
Covariate (no studies)	***n***	**Parameter**	**SCIT vs placebo**	**SLIT vs placebo**	**SLIT vs SCIT (indirect comparison)**	**DIC (pD)**
Fixed effects	12	d_k	–0.740 (–0.920 to –0.560)	0.071 (–0.010 to 0.151)	0.811 (0.614 to 1.007)	49 (14)
Random effects	12	d_k	–0.764 (–1.116 to –0.425)	–0.247 (–0.729 to 0.156)	0.517 (–0.071 to 1.045)	–2 (26)
		σ^2	0.155 (0.033 to 0.494)			
Age of participants	12	β_k	–0.023 (–195.20 to 195.40)	–0.047 (–196.70 to 195.80)	–	–2 (21)
		$d_{k,child}$	–0.788 (–196.10 to 194.60)	–0.294 (–197.10 to 195.60)	0.493 (–276.90 to 278.70)	
		$d_{k,adult}$	–0.765 (–1.115 to –0.421)	–0.248 (–0.734 to 0.159)	0.517 (–0.085 to 1.051)	
		σ^2	0.158 (0.033 to 0.506)			
Year of publication	12	β_k	–0.034 (–0.280 to 0.216)	0.133 (–0.169 to 0.475)	–	–1 (22)
		$d_{k,2000}$	–0.588 (–1.962 to 0.763)	–1.526 (–4.797 to 1.357)	–0.939 (–4.488 to 2.230)	
		$d_{k,2005}$	–0.758 (–1.162 to –0.370)	–0.860 (–2.466 to 0.558)	–0.102 (–1.748 to 1.365)	
		$d_{k,2010}$	–0.928 (–2.154 to 0.306)	–0.193 (–0.756 to 0.338)	0.735 (–0.634 to 2.074)	
		σ^2	0.221 (0.044 to 0.734)			
Duration	12	β_{k1}	0.202 (–1.426 to 1.853)	–0.212 (–195.10 to 194.80)	–	1 (22)
		β_{k2}	0.393 (–0.986 to 1.763)	–0.182 (–1.092 to 1.039)	–	
		$d_{k,<6months}$	–1.094 (–2.395 to 0.206)	–0.144 (–1.107 to 0.518)	0.950 (–0.686 to 2.364)	
		$d_{k,6–12months}$	–0.892 (–1.909 to 0.138)	–0.355 (–195.20 to 194.60)	0.536 (–194.30 to 195.20)	
		$d_{k,>12months}$	–0.70 (–1.170 to –0.251)	–0.326 (–1.034 to 0.388)	0.374 (–0.454 to 1.228)	
		σ^2	0.226 (0.006 to 0.946)			

RQLQ scores						
Covariate (no studies)	***n***	**Parameter**	**SCIT vs placebo**	**SLIT vs placebo**	**SLIT vs SCIT (indirect comparison)**	**DIC (pD)**
MAC	10	β_{k1}	–0.309 (–138.70 to 137.60)	0.008 (–138.50 to 139.60)	–	4 (19) [1 (17)]
		β_{k2}	–0.230 (–196.80 to 195.50)	0.411 (–195.60 to 197.40)	–	
		$d_{k,<5\mu g}$	–0.546 (–138.40 to 137.90)	–0.171 (–139.80 to 138.30)	0.375 (–195.10 to 196.20)	
		$d_{k,5–6\mu g}$	–0.855 (–1.237 to –0.475)	–0.162 (–0.782 to 0.303)	0.692 (–0.046 to 1.281)	
		$d_{k,>20\mu g}$	–0.775 (–239.60 to 240.10)	0.240 (–238.80 to 240.70)	1.015 (–337.90 to 341.10)	
		σ^2				
Allergen type	12	β_{k1}	–0.121 (–0.987 to 0.780)	0.710 (–195.20 to 196.10)		–1 (22)
		β_{k2}	–0.128 (–195.90 to 195.90)	–1.222 (–2.588 to 0.152)		
		β_{k3}	0.014 (–194.60 to 195.0)	0.439 (–196.60 to 196.40)		
		β_{k4}	–0.416 (–1.741 to 0.937)	–0.140 (–195.50 to 194.70)		
		β_{k5}	–0.117 (–1.276 to 1.059)	–0.253 (–196.50 to 194.30)		
		$d_{k,grass}$	–0.685 (–1.213 to –0.171)	–0.109 (–0.637 to 0.411)	0.576 (–0.154 to 1.316)	
		$d_{k,Parietaria}$	–0.806 (–1.511 to –0.081)	0.602 (–195.40 to 195.90)	1.407 (–194.60 to 196.60)	
		$d_{k,tree}$	–0.813 (–196.60 to 195.20)	–1.330 (–2.597 to –0.062)	–0.518 (–196.60 to 195.30)	
		$d_{k,Alternaria}$	–0.671 (–195.50 to 194.40)	0.330 (–196.70 to 196.40)	1.001 (–276.20 to 276.10)	
		$d_{k,ragweed}$	–1.101 (–2.327 to 0.144)	–0.249 (–195.70 to 194.70)	0.852 (–194.50 to 195.50)	
		$d_{k,Salsola\ kali}$	–0.802 (–1.858 to 0.251)	–0.361 (–196.60 to 194.30)	0.440 (–195.70 to 195.20)	
		σ^2	0.196 (0.032 to 0.771)			

TABLE 66 Probabilistic analysis for RQLQ scores [probability (%) that treatment *k* is the best under different modelling assumptions]

Model (covariate included in the model)	Placebo	SCIT	SLIT
Fixed effects (12)	00.0	>99	00.0
Random effects (12)	00.0	96.2	03.8
Age group of participants (12)			
Child	24.7	37.8	37.5
Adult	00.0	96.0	04.0
Year of publication (12)			
2000	02.8	26.9	70.3
2005	00.0	46.3	53.7
2010	01.5	86.8	11.8
Duration (12)			
Low	01.5	88.9	09.6
Medium	01.9	48.3	49.8
High	00.1	85.8	14.0
MAC (10)			
<5 µg	24.9	37.7	37.4
5–20 µg	00.0	97.0	03.0
>20 µg	24.8	37.7	37.5
Allergen type (12)			
Grass	00.3	94.7	04.9
Parietaria	00.9	49.6	49.5
Tree	01.0	49.7	49.3
Alternaria	24.8	37.9	37.3
Ragweed	01.9	48.4	49.7
Salsola kali	03.0	47.3	49.8

Appendix 4 Study selection process

The study selection process is shown in *Figure 30*. For many RCTs, more than one publication was identified (e.g. additional abstracts, different outcomes or data at different time points reported in separate publications). The numbers above relate to numbers of publications rather than individual RCTs, except where highlighted. Reasons for exclusion are listed in *Appendix 5*; only excluded studies published in 2006 or after (post Cochrane reviews search dates) have been listed. One of the main reasons for exclusion was a lack of double-blinding. There were some discrepancies between studies that were included or excluded in the Cochrane reviews and in this report. Reasons for this are also listed in *Appendix 5*. It may be owing to the fact that our inclusion and exclusion criteria were more detailed, whereas the ones in the Cochrane reviews were slightly broader.

There were also some publications that may have been relevant, but were not identified in the Cochrane reviews (or in their excluded studies list). Many of these appeared to be duplicate publications (e.g. in abstract form) of included studies, but there were some that potentially should have been included. It was beyond the remit of this report to look at these studies in detail.

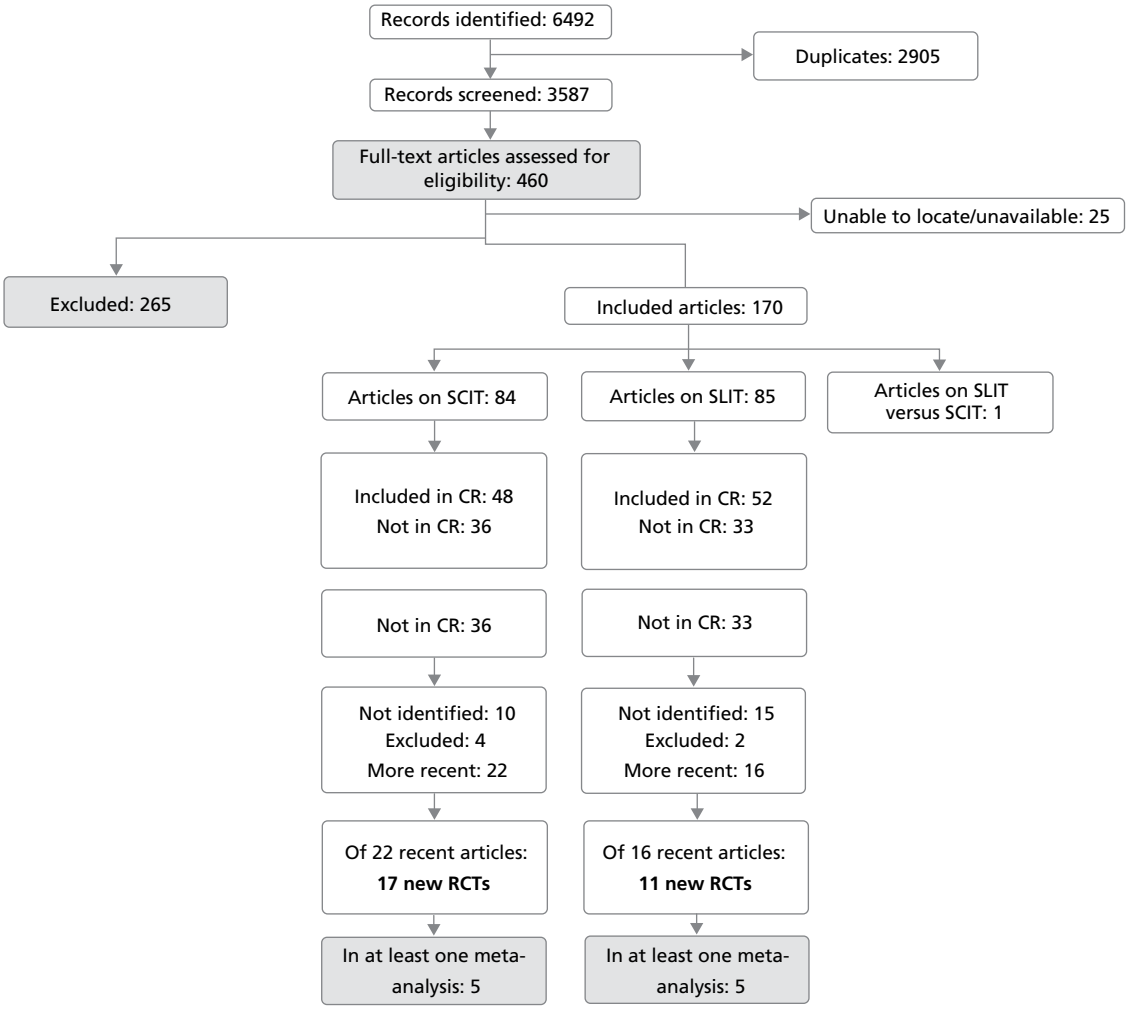

FIGURE 30 Study selection process.

Given the vast overlap between studies included in this report and the Cochrane reviews, and the consistency of direction of effect for different subgroups, it is unlikely that the discrepancies or missing studies noted above would have any significant impact on study results.

All included studies had at least one English-language publication associated with them. Some of the excluded studies were in other languages: German papers were translated by one of the authors, Polish papers by a Polish colleague, and Spanish or Portuguese papers by two of the authors with the help of a dictionary. Some reports in other languages (e.g. Dutch) were clearly reviews or comments. There were no potentially relevant papers identified after the Cochrane reviews search dates that could not be sufficiently translated to make a decision on inclusion/exclusion.

Appendix 5 Reasons for exclusion and discrepancies between included/excluded studies in Cochrane reviews and this report

Studies on pollen allergy included in relevant Cochrane reviews but excluded from this review

Study	Reason for exclusion
Armentia-Medina A, Blanco Quiros A, Martin-Santos JM, Alvarez Cuesta E, Moneo Goiri I, Carreira P, *et al*. Rush immunotherapy with a standardized Bermuda grass pollen extract. *Ann Allergy* 1989;**63**:127–35	Only 8 out of 30 patients with a history of allergic rhinitis
Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000;**55**:1142–7	Includes some children with asthma only, not SAR; results not separable for SAR children only
Grammer LC, Shaughnessey MA, Shaughnessy JJ, Patterson R, Grammer LC, Shaughnessey MA, *et al*. Asthma as a variable in a study of immunotherapy for allergic rhinitis. *J Allergy Clin Immunol* 1984;**73**:557–60	Placebo and untreated treatment groups combined in the analysis, so not all patients double-blinded
Lizaso Bacaicoa MT, Garcia BE, Gomez B, Zabalegui A, Rodriguez MJ, Tabar AI. [Treatment of allergy to mushrooms.] *Anales del Sistema Sanitario de Navarra* 2003;**26**(Suppl. 2):129–37	Not all participants had SAR
Meriney DK, Kothari H, Chinoy P, Grieco MH. The clinical and immunologic efficacy of immunotherapy with modified ragweed extract (allergoid) for ragweed hay fever. *Ann Allergy* 1986;**56**:34–8	Not all patients treatment naive
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	Children with SAA only (with or without rhinoconjunctivitis)
Paraskevopoulos G, Jacobson M, Carr V, Calderon M, Till SJ, Francis JN, *et al*. Grass pollen injection immunotherapy: time course of suppression of allergen-induced late phase skin response. *J Allergy Clin Immunol* 2005;**115**:S266	No relevant symptom or QoL-related outcomes
Sabbah A, Hassoun S, Lesellin J, Andre C, Sicard H. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass-pollen extract. *Allergy* 1994;**49**:309–13	Around half of patients not treatment naive

Other excluded studies (post 2005)

Study	Reason for exclusion
Agostinis F, Foglia C, Bruno ME, Falagiani P. Efficacy, safety and tolerability of sublingual monomeric allergoid in tablets given without up-dosing to pediatric patients with allergic rhinitis and/or asthma due to grass pollen. *Eur Ann Allergy Clin Immunol* 2009;**41**:177–80	Not double blind
Agostinis F, Forti S, Di BF. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. *Allergy* 2010;**65**:410–11	Transcutaneous administration, not sublingual or subcutaneous

Study	Reason for exclusion
Al Ahmed N, Arifhodzic N, Al Ahmed M. Comparison of clinical efficacy and preventive role between subcutaneous and sublingual immunotherapy in children with seasonal allergic rhinitis. *Allergy* 2010;**65**(XXIX EAACI Congress of the European Academy of Allergy and Clinical Immunology, London, UK, 5–9 June 2010):1550	Not double blind
Ali I, Goksal K, Ozan B, Gulsen D. Long-term allergen-specific immunotherapy correlates with long-term allergen-specific immunological tolerance. *Adv Ther* 2008;**25**:29–36	Retrospective evaluation
Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Mailing HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy* 2006;**61**:1–20	Review
Ariano R, Incorvaia C, La GS, Marcucci F, Pajno G, Sensi L, *et al*. Safety of sublingual immunotherapy started during the pollen season. *Curr Med Res Opin* 2009;**25**:103–7	Not double blind
Asturias JA, Ferrer A, Arilla MC, Andreu C, Madariaga B, Martinez A. Tolerance and immunological changes of chemically modified allergen vaccine of Parietaria judaica in accelerated schedules. *Clin Exp Allergy* 2007;**147**:491–6	Not double blind
Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX® for the prevention of seasonal grass pollen induced rhinoconjunctivitis: a Northern European perspective. *Clin Exp Allergy* 2007;**37**:772–9	CEA
Bartosikova L, Necas J, Bartosik T, Pavlik M, Fránová J. [Contribution of allergen immunotherapy using Phostal in the treatment of seasonal allergic rhinitis (two years of use)]. *Ceska Slov Farm* 2008;**57**:99–102	Not double blind
Bell MC, Jones SM. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *Pediatrics* 2009;**124**:S152	Comment on other study (Wahn *et al*.[26])
Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G, *et al*. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol* 2006;**97**:615–21	EE
Berto P, Frati F, Incorvaia C, Cadario G, Contiguglia R, Di Gioacchino M, *et al*. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin* 2008;**24**:261–6	Cost comparison
Bochenska-Marciniak M, Tworek D, Kupczyk M, Bogacka E, Kuprys Lipinska I, Kuna P. The effectiveness of allergen immunotherapy depending on the regimen on rhinoconjunctivitis and asthma symptoms in allergy to grass pollen. Abstract. *Am J Respir Crit Care Med* 2009;**179**[April (Meeting Abstracts):A2781 [Monday, Section B31]	Not placebo controlled
Bordignon V, Burastero SE. Multiple daily administrations of low-dose sublingual immunotherapy in allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2006; **97**:158–63	Not double blind
Bowser C, Erstein DP, Silverberg JI, Nowakowski M, Joks R. Correlation of plasma complement split product levels with allergic respiratory disease activity and relation to allergen immunotherapy. *Ann Allergy Asthma Immunol* 2010;**104**:42–9	Not RCT
Burastero SE, Mistrello G, Paolucci C, Breda D, Roncarolo D, Zanotta S, *et al*. Clinical and immunological correlates of pre-co-seasonal sublingual immunotherapy with birch monomeric allergoid in patients with allergic rhinoconjunctivitis. *Int J Immunopathol Pharmacol* 2009;**22**:343–52	Not double blind or RCT
Calderon M, Brandt T. Treatment of grass pollen allergy: focus on a standardized grass allergen extract: Grazax. *Therapeut Clin Risk Manag* 2008;**4**:1255–60	Review
Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy* 2007;**62**:958–61	Post hoc analysis of three trials

Study	Reason for exclusion
Can D, Tanac R, Demir E, Gulen F, Veral A. Efficacy of pollen immunotherapy in seasonal allergic rhinitis. *Pediatr Int* 2007;**49**:64–9	Not double blind
Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX® for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007;**101**:1885–94	Cost-effectiveness study
Ciprandi G, Sormani MP, Cirillo I, Tosca M. Upper respiratory tract infections and sublingual immunotherapy: preliminary evidence. *Ann Allergy Asthma Immunol* 2009;**102**:262–3	Not an RCT
Corren J, Lemay M, Lin YM, Rozga L, Randolph RK. Clinical and biochemical effects of a combination botanical product (ClearGuard™) for allergy: a pilot randomized double-blind placebo-controlled trial. *Nutrition J* 2008;**7**	Single-dose tablet taken for 3 days only
D'Anneo RW, Arena A, Garnmeri E, Bruno ME, Fallagiani P, Riva G, *et al*. *Parietaria* sublingual allergoid immunotherapy with a co-seasonal treatment schedule. *Allergol Immunopathol* 2008;**36**:79–84	Not double blind
Didier A, Montagut A, Fadef R, Melac M. Immunological Biomarkers of Grass Allergen Tablets in Grass Pollen Rhinoconjunctivitis Patients. *J Allergy Clin Immunol* 2008;**121**(American Academy of Allergy, Asthma and Immunology, 64th Annual Meeting, Philadelphia, PA, USA, 14–18 March, 2008):Abstract 478	No relevant outcomes reported
Durham SR. Allergen immunotherapy (desensitisation) for allergic diseases. *Clin Med* 2006;**6**:348–51	Review
Durham SR. Sublingual immunotherapy: reply. *J Allergy Clin Immunol* 2007;**119**:515–17	Author reply/letter
Durham SR, Birk AO, Andersen JS. Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy* 2011;**66**:120–3	Secondary analysis of data
Ellis AK, Ratz JD, Chowdry C, Day JH. Controlled allergen challenge clinical trials: impact upon seasonal allergic rhinitis symptoms? [P362]. *Ann Allergy Asthma Immunol* 2009;**103**:A139	Not seasonal exposure (controlled allergen challenge)
Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 2006;**61**:198–201	Discontinuation study
Friedlander S, Friedlander AS. Clinical effects of ragweed antigen emulsion. A double-blind study. *J Allergy* 1962;**33**:412–22	Does not appear to be randomised (comparative study)
Halken S, Agertoft L, Seidenberg J, Bauer C-P, Payot F, Martin-Munoz MF, *et al* .Five-grass pollen 300-IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol* 2010;**21**:970–6	Further report of Wahn *et al*.[26] (included in Cochrane review of SLIT); appears to contain no new data, although some more detailed analysis of AE data
Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, Montagut A *et al.* Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol* 2009;**124**:471–7	Symptoms not measured during natural exposure (allergen challenge chamber)
Horiguchi S, Okamoto Y, Yonekura S, Okawa T, Yamamoto H, Kunii N, *et al*. A randomized controlled trial of sublingual immunotherapy for Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2008;**146**:76–84	Not double blind
Howland WC, Hamilton RG, Holdich T. Effect of ultra short course subcutaneous immunotherapy on specific IgG and IgE levels compared with placebo in patients with ragweed pollen-allergic rhinoconjunctivitis. Abstract 17. *Ann Allergy Asthma Immunol* 2009;**103**:A23	No relevant outcomes reported
Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, *et al*. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;**62**:943–8	Open follow-up study of RCT

Study	Reason for exclusion
James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, *et al*. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011;**127**:509–16	Discontinuation study
Jutel M, Cromwell O. Clinical results from vaccination with recombinant grass pollen allergens. *Clin Dev Immunol* 2006;**13**:389–94.	Further analysis of Jutel 2005, included in Cochrane review
Keiding H, Jorgensen KP. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin* 2007;**23**:1113–20	Cost-effectiveness analysis
Keith P. Significant improvements in quality of life following mpl-adjuvanted ultra short course subcutaneous immunotherapy (uSCIT) in patients with seasonal grass pollen allergy. Abstract 219. *J Allergy Clin Immunol* 2009;**123**:S61	No relevant outcomes reported
Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. *Pediatr Allergy Immunol* 2006;**17**:396–407	Not double blind
Klunker S, Saggar LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR, *et al*. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: Inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007;**120**:688–95	No relevant outcomes reported
Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, *et al*. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy* 2009;**39**:271–9	Comparison of SIT plus omalizumab vs SIT only
Larenas-Linnemann D. Briefings from ACAAI 2008 annual meeting. The Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology, Seattle, WA, USA, 6–11 November, 2008. *Therapy* 2009;**6**:279–83	Review
Leonardi S, Spicuzza L, La RM. High-dose sublingual immunotherapy in children at 8-year follow-up. *Clin Exp Allergy* 2009;**102**:259–60	Discontinuation study
Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, *et al*. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy* 2009;**39**:387–93	Subgroup analysis of included RCTs
Martinez-Canavate Burgos A, Vallenzuella-Soria A, Rojo-Hernandez A. Immunotherapy with *Alternaria alternata*: present and future. *Allergol Immunopathol* 2007;**35**:259–63	Review
Martínez Cócera C, Sastre J, Cimarra M, Quirce S, Fernández Rivas M, Enríquez Matas A, *et al*. Immunotherapy with a *Phleum pratense* allergen extract induces an immune response to a grass-mix allergen extract. *J Investig Allergol Clin Immunol* 2010;**20**:13–19.	Not double blind
Mauro M, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. *Eur Ann Allergy Clin Immunol* 2007;**39**:119–22	Not double blind
McCormack PL, Wagstaff AJ. Ultra-short-course seasonal allergy vaccine (Pollinex® Quattro). *Drugs* 2006;**66:**931–8	Review
Milani M, Leonardi A, Pozzan M, Pecora S. Two years specific sublingual immunotherapy with alternative extracts. Abstract 493. *J Allergy Clin Immunol* 2008;**21**:S127	Not double blind
Mösges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol* 2010;**21**:1135–8	Report only on subgroup of children with asthma
Naspitz CK, Warner JO. Children are pharmaco-therapeutic orphans. *Pediatr Allergy Immunol* 2010;**21**:249–50	Editorial

Study	Reason for exclusion
Nasser S, Vestenbaek U, Beriot MA, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008; **63**:1624–9	Cost-effectiveness study
Niederberger V, Reisinger J, Valent P, Krauth MT, Pauli G, van HM, *et al*. Vaccination with genetically modified birch pollen allergens: immune and clinical effects on oral allergy syndrome. *J Allergy Clin Immunol* 2007;**119**:1013–16	Relates to food allergy
Nieminen K, Valovirta E, Savolainen J. Clinical outcome and IL–17, IL–23, IL–27 and FOXP3 expression in peripheral blood mononuclear cells of pollen-allergic children during sublingual immunotherapy. *Pediatr Allergy Immunol* 2010;**21**:E174–84	Secondary analysis of data
Nunes C, Ladeira S. Pre-seasonal Specific Immunotherapy in rhino-conjunctivitis versus placebo. *J Allergy Clin Immunol* 2010;**125**:AB236	Not double blind
Nunes C, Ladeira S. Pre-seasonal specific short-term immunotherapy versus placebo in seasonal rhino-conjunctivitis. *Rev Port Imunoalergol* 2010;**18**:39–56	Not double blind
Panzner P, Petras M, Sykora T, Lesna IK, Liska M. Both sublingual and supralingual routes of administration are effective in long-term allergen-specific immunotherapy. *Allergy Asthma Proc* 2011;**32**:142–50	Not double blind
Passali D, Mösges R, Passali GC, Passali FM, Ayoko G, Bellussi L. Safety, tolerability and efficacy of sublingual allergoid immunotherapy with three different shortened up-dosing administration schedules. *Acta Otorhinolaryngol Ital* 2010;**30**:131–7	Not double blind
Patel P, Salapatek AMF. Pollinex® Quattro: a novel and well-tolerated, ultra short-course allergy vaccine. *Expert Rev Vaccine* 2006;**5**:617–29	Review
Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, *et al*. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006;**97**:141–8	Review
Petersen KD, Gyrd-Hansen D, Linneberg A, Dahl R, Larsen JN, Lowenstein H, *et al*. Willingness to pay for allergy-vaccination among Danish patients with respiratory allergy. *Int J Technol Assess Health Care* 2010;**26**:20–9.	Economic study
Pfaar O, Klimek L, Fischer I, Sieber J, Amoroso S, Aguilar CM, *et al*. Safety of two cluster schedules for subcutaneous immunotherapy in allergic rhinitis or asthma patients sensitized to inhalant allergens. *Int Arch Allergy Immunol* 2009;**150**:102–8	Open-label study (safety)
Piconi S, Trabattoni D, Rainone V, Borgonovo L, Passerini S, Rizzardini G, *et al*. Immunological effects of sublingual immunotherapy: clinical efficacy is associated with modulation of programmed cell death ligand 1, IL–10, and IgG4. *J Immunol* 2010;**185**:7723–30	Not double blind. Different treatment schedules compared
Pilette C, Nouri-Aria KT, Jacobson MR, Wilcock LK, Detry B, Walker SM, *et al*. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. *J Immunol* 2007;**178**:4658–66	No relevant outcomes reported
Pokladnikova J, Krcmova I, Vlcek J. Economic evaluation of sublingual vs subcutaneous allergen immunotherapy. *Clin Exp Allergy* 2008;**100**:482–9	EE based on open-label study
Pozzan M, Milani M. Efficacy of sublingual specific immunotherapy in patients with respiratory allergy to *Alternaria alternata*: A randomised, assessor-blinded, patient-reported outcome, controlled 3-year trial. *Curr Med Res Opin* 2010;**26**:2801–6	Not double blind
Pree I, Reisinger J, Focke M, Vrtala S, Pauli G, van HM, *et al*. Analysis of epitope-specific immune responses induced by vaccination with structurally folded and unfolded recombinant Bet v 1 allergen derivatives in man. *J Immunol* 2007;**179**:5309–16	No relevant outcomes (in vitro study)
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	Not standard SIT

Study	Reason for exclusion
Railey MD, Adair MA, Burks AW. Allergen immunotherapy for allergic rhinitis. *Curr Allergy Asthma Rep* 2008;**8**:1–3	Comment
Rak S, Heinrich C, Scheynius A. Comparison of nasal immunohistology in patients with seasonal rhinoconjunctivitis treated with topical steroids or specific allergen immunotherapy. *Allergy* 2005;**60**:643–9	Not placebo controlled with rescue medication (SIT + placebo steroids vs placebo SIT + steroids)
Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. *Allergol Immunopathol* 2007;**35**:44–51	Not double blind
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	SAA, not rhinitis
Roder E, Berger MY, de Groot H, van Wijk RG. Sublingual immunotherapy in youngsters: adherence in a randomized clinical trial. *Clin Exp Allergy* 2008;**38**:1659–67	Analysis of adherence data from trial reported elsewhere
Rodriguez F, Boquete M, Ibanez MD, Torre-Martinez F, Tabar AI. Once daily sublingual immunotherapy without updosing: a new treatment schedule. *Int Arch Allergy Immunol* 2006;**140**:321–6	Results for patients with SAR not separable
Rolinck-Werninghaus C, Keil T, Kopp M, Zielen S, Schauer U, von Berg A, *et al*. Specific IgE serum concentration is associated with symptom severity in children with seasonal allergic rhinitis. *Allergy* 2008;**63**:1339–44	RCT of omalizumab vs placebo
Romaniuk LI, DuBuske IV, DuBuske LM. Comparative efficacy of subcutaneous immunotherapy, sublingual immunotherapy and combined subcutaneous and sublingual immunotherapy in patients with seasonal allergic rhinitis and cross-reactive food allergy. Abstract 82. *J Allergy Clin Immunol* 2009;**123**:S25	Results for patients with SAR with not separable from those with food allergy
Rossi RE, Monasterolo G, Coco G, Silvestro L, Operti D. Evaluation of serum IgG4 antibodies specific to grass pollen allergen components in the follow up of allergic patients undergoing subcutaneous and sublingual immunotherapy. *Vaccine* 2007;**25**:957–64	Not double blind
Sager A, Braeutigam M, Badorrek P, Krug N. Efficacy of a rush immunotherapy with a depigmented polymerized extract of grass pollen using an environmental challenge chamber (ECC). Abstract 485. *J Allergy Clin Immunol* 2008;**21**:S125	No natural exposure-allergen chamber
Serra P, Martino M, Muggianu E, Corrias C, Manconi P, Milani M. Efficacy of SQ-standardised grass allergy immunotherapy tablet treatment on basophil activation test in subjects with grass pollen induced rhinoconjunctivitis. *Allergy* 2010;**65**(XXIX, EAACI, Congress of the European Academy of Allergy and Clinical Immunology, London, UK, 5–9 June 2010):684	No relevant outcomes
Simons FER, HayGlass KT. Immunotherapy with a ragweed vaccine [2]. *New Eng J Med* 2007;**356**:86–7	Correspondence
Sjolin I, Haugaard L, Kopp T, Jansen A, Brüning H, Smedegaard AB, *et al*. High patient compliance on a once daily treatment regimen with the hay fever drug Grazax. *J Allergy Clin Immunol* 2008;**121**(American Academy of Allergy, Asthma and Immunology 64th Annual Meeting, Philadelphia, PA, USA, 14–18 March, 2008, S128):Abstract 495	Not double blind
Skripak J, Wood RA. 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. Commentary. *Pediatrics* 2006;**118**:S22	Comment on another study
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	Patients with SAA
Stosovic R, Bogic M, Tomic-Spiric V. Long-term efficacy and safety of sublingual immunotherapy in seasonal allergic rhinitis. *Allergy* 2008;**63** (XXVII EAACI, Congress of the European Academy of Allergology and Clinical Immunology, Barcelona, Spain, 7–11 June, 2008):Abstract 1065	Not double blind

Study	Reason for exclusion
Thien F. Sublingual immunotherapy with a grass allergen tablet improved symptoms and quality of life in allergic rhinoconjunctivitis. *Evid Base Med* 2006;**11**:173	Commentary
Wahn U, Bauer C, Agertoft L, Melac M, Le Gall M. Agreement of efficacy assessments for five grass pollen sublingual immunotherapy (SLIT) tablets in children and adolescents with grass pollen rhinoconjunctivitis and with or without mild asthma. Abstract 214. *J Allergy Clin Immunol* 2009;**123**:S59	Secondary analysis of data
Williams A, Henzgen M, Rajakulasingam K, Williams A, Henzgen M, Rajakulasingam K. Additional benefit of a third year of specific grass pollen allergoid immunotherapy in patients with seasonal allergic rhinitis. *Eur Ann Allergy Clin Immunol* 2007;**39**:123–6	Open-label continuation of trial
Zuberbier T, Sussman G. Epidemiological characteristics and allergen sensitisation patterns in subjects with intermittent allergic rhinitis in the international ACCEPT1 study in association with GA2LEN. *Allergy* 2008;**63** (XXVII EAACI, Congress of the European Academy of Allergology and Clinical Immunology, Barcelona, Spain, 7–11 June 2008):Abstract	Not SIT

Unobtainable studies (reference incorrect or inaccurate and therefore unable to locate, or British Library unable to supply at the time of ordering)

Arbesman CE. Hyposensitization therapy including repository: a double-blind study *J Allergy Clin Immunol* 1964;**35**:12–17

Arbesman CE, Reisman RE, Kunz ML. Clinical and immunologic evaluation of a purified fraction of ragweed pollen (delta). A double-blind study. *J Allergy Clin Immunol* 1965;**36**:29–38

Ariano R, Panzani RC, Augeri G. Efficacy and safety of oral immunotherapy in respiratory allergy to *Parietaria judaica* pollen. A double-blind study. *J Investig Allergol Clin Immunol* 1998;**8**:155–60

Bachert C. New Clinical Documentation on Alk Grass Allergen Tablet. *Drugs of Today* 2008;**44**:57–60

Basomba A. [Immunotherapy in pollenosis: a double-blind study.] *Rev Espanol Alergol Inmunol Clin* 1991;**6**:22–7

Corthay P, Gumowski PI, Bodmer R, Clot B. Efficacy of sublingual versus subcutaneous immunotherapy to pollen allergens after 3 consecutive years of treatment. Annual Meeting of the Swiss Society for Allergology and Immunology, 1996

Durham SR, Hamid QA. The effect of immunotherapy on allergen induced late responses. *Arbeiten aus dem Paul Ehrlich Institut zu Frankfurt a M* 1997;33–9

Frank E, Williams A, Cromwell O, Atkinson P, Rajakulasingam K. Effectiveness of a pre-seasonal allergoid immunotherapy in patients with seasonal allergic rhinitis due to grass pollen. *J Allergy Clin Immunol* 2001;**107**:S260 POSTER no. 851 (Tuesday 20 March). American Association of Asthma, Allergy & Immunology, 57th Annual Meeting, 2001

Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. *J Am Med Assoc* 1967;**201**:915–17

Hordijk GJ, Antvelink JB, Luwema RA. A placebo controlled study on the efficacy of sublingual immunotherapy with standardized grass pollen allergens (Oralgen). XVI Congress of the European Rhinologic Society; VIII Congress of the International Rhinologic Society, Ghent, Belgium, 7–13 June 1996:150

Khinchi MS, Poulsen LK, Carat F, Andre C, Malling HJ. Clinical efficacy of sublingual-swallow and subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis due to birch pollen. A double-blind, double-dummy placebo-controlled study. *Allergy* 2000;**54**:24

Klimek L, Pfaar O, Sieber J, Amoroso S, Carmen MA, Sges R. A prospective trial to evaluate the safety of two cluster regimens in subcutaneous immunotherapy in patients with allergic rhinitis and mild or moderate allergic asthma to grass pollen, tree pollen or mites. *Allergy* 2006;**61**:Abstract (XXV Congress of the European Academy of Allergology and Clinical Immunology)

Leonardi S, Arena A, Bruno ME, Cannaò PM, D'Anneo RW, Falagiani P, *et al*. Olea sublingual allergoid immunotherapy administered with two different treatment regimens. *Allergy Asthma Proc* 2010;**31**:e25–9

Matuska J. Cluster immunotherapy. SR theophylline in prevention of systemic reactions. *Eur Respir J* 2001;**18**:430

Monzon S, Venturini M, Colas C, Lezaun A, Casanovas M, Reichelt C, *et al*. Specific immunotherapy with modified *Salsola kali* extract: preliminary results. *Alergol Inmunol Clin* 2003;**18**:20–4

Poddubikova AM, Kostinov MP. [Immunovac-VP4 vaccine used in complex allergen-specific immunotherapy of patients with hay fever.] *Zh Mikrobiol Epidemiol Immunobiol* 2010;44–8

Polosa R, Ligotti F, Mangano G, Mastruzzo C, Sarva M, Spicuzza L, *et al*. Seasonal variability in BHR and sputum cells count in subjects with rhinitis and effect of 3 years' specific immunotherapy. *American Thoracic Society 99th International Conference* 2003;A031. Poster

Pravettoni V, Pastroello E, Qualizza R, Codecasa L, Vassellatti D. Double blind placebo controlled study of specific immunotherapy (ITS) with absorbed aluminum hydroxide allergoid in grass-pollen induced rhinitis. *J Allergy Clin Immunol* 1987;**79**:Abstract (American Academy of Allergy and Immunology 43rd Annual Meeting, Washington DC, 19–25 February 1987)

Rak S, Stender A, Dahl R. Confirmed clinical safety and efficacy of grass allergen tablets. *Eur Respir J* 2005;**26** (15th European Respiratory Society Annual Congress, Copenhagen, Denmark, 17–21 September, 2005):Abstract

Russello M, Maurol M, Incorvaia C, D'Ingianna E, Gazzola GB. Subcutaneous and sublingual immunotherapy in birch pollinosis: a comparison of efficacy and safety. *Allergy* 2004;**59**(XXIII Congress of the European Academy of Allergology and Clinical Immunology, Amsterdam, The Netherlands, 12–16 June 2004):Abstract

Torres Lima M, Wilson DR, Roberts A, Walker SM, Durham SR. Grass pollen sublingual immunotherapy (SLIT) for seasonal rhinoconjunctivitis: a randomised controlled trial. *J Allergy Clin Immunol* 2001;**107**:837

Torres Lima M, Wilson DR, Pitkin L, Roberts A, Nouri-Aria KT, Jacobson M, *et al*. Grass pollen immunotherapy (SLIT) for seasonal rhinoconjunctivitis: a randomised controlled trial. *Clin Exp Allergy* 2001;**31**:42

Valovirta E. PAT: the Preventive Allergy Treatment study design and preliminary results. *Wiener Medizinische Wochenschrift* 1999;**149**:442–3

Walker S. Immunotherapy for pollen allergy. International Primary Care Respiratory Conference, 9–11 June, St Neots, UK 2000;**9**:S27. Abstract 065

Yuksel H, Tanac R, Gousseinov A, Demir E. Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy. *J Investig Allergol Clin Immunol* 1999;**9**:305–13

Studies not identified in Cochrane reviews

Subcutaneous immunotherapy

Reference	Details
Bachert C. [Influence of specific immunotherapy on inflammation of the nasal mucosa.] *Allergo J* 1997;**6**:157–8	Appears to be report of study reported elsewhere but unclear. Thirty-four patients. Patient-related outcomes reported
Crimi N, Li GF, 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	Possible duplicate of studies listed as excluded in Cochrane review (non-relevant outcomes.) In this study, SSs and MSs are presented. Thirty patients
Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. Clinical results. *Allergy* 1986;**41**:131–40	Duplicate of Karlsson *et al.* 1986 listed as excluded in Cochrane review, as not SAR. Study is in *Cladosporium herbarum*, a mould; authors mention July–September as peak mould season, so does appear to have seasonal aspect
Durham SR, Varney V, Gaga M, Frew AJ, Jacobson M, Kay AB. Immunotherapy and allergic inflammation. *Clin Exp Allergy* 1991;**21**:206–10	Duplicate of study included in Cochrane review (Varney 1991)
Frew AJ, Powell RJ, Durham SR. Alutard SQ grass demonstrates clinical efficacy in subjects with seasonal allergic rhinoconjunctivitis in a large-scale double-blind placebo controlled study of specific allergy vaccination (the AVANZ study). Abstract 317. *J Allergy Clin Immunol* 2004;**113**:S105	Abstract of study included in Cochrane review (Frew *et al.* 2006[161])
Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J, Horst M *et al*. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. *J Allergy Clin Immunol* 1990;**85**:460–72	Appears to be relevant RCT in 24 patients. Unclear if published elsewhere
Jean F, Bousquet J, Hejjaoui A, Guerin B, Maasch HJ, Michel FB. Double-blind placebo controlled rush immunotherapy trial with grass-pollen allergen and allergoid. *J Allergy Clin Immunol* 1985;**75**:164	Abstract. Likely duplicate of study included in Cochrane review
Munro-Ashman D, McEwen H, Feinberg JG. The patient self (P-S) test. Demonstration of a rise in blocking antibodies after treatment with Allpyral. *Int Arch Allergy Appl Immunol* 1971;**40**:448–53	Appears to be relevant RCT in 21 patients
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	Duplicate publication of Crimi *et al.* 2004, listed above
Rozniecka M, Kowalski M, Grzegorczyk J, Wojciechowska B, Sliwinska-Kowalska M, Rozniecki J. [Characteristics of hay fever during pollen season with regard to the influence of specific immunotherapy. I. Clinical course and biochemical changes in nasal lavage.] *Pneumonol Alergol Pol* 1995;**63**:135–43	Appears to be relevant RCT in 27 patients

Sublingual immunotherapy

Reference	Details
Amar SM, Harbeck R, Sills M, O'Brien H, Nelson HS. The response to sublingual immunotherapy with grass pollen extract administered as a single extract or as part of a multi-allergen extract in patients with seasonal allergic rhinitis caused by grass pollen. *J Allergy Clin Immunol* 2009;**123**(American Academy of Allergy, Asthma and Immunology 65th Annual Meeting. Washington, USA, 13–17 March 2009):Abstract 277	Further abstract of Amar 2009 included in Cochrane review
Ariano R, Panzani RC, Mistrello G. Efficacy of sublingual coseasonal immunotherapy with a monomeric allergoid in Cupressaceae pollen allergy: preliminary data. *Eur Ann Allergy Clin Immunol* 2005;**37**:103–8	Not identified in Cochrane review; 30 patients
Dahl R, Kapp A, Colombo G, de Monchy JGR, Rak S, Emminger W, *et al*. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2008;**121**:512–18	Further publication of GT–08 trial; not listed as included study, but mentioned in text
de Blay F, Barnig C, Kanny G, Purohit A, Leynadier F, De Lara JMT, *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	Full text of abstract included in Cochrane review
Horak F, Siegfried J, Worm M, Melac M, Didier A. Clinical efficacy of sublingual immunotherapy (SLIT) with grass pollen tablets in patients with rhinoconjunctivitis throughout the pollen season and at peak pollen. *Allergy* 2008;**63**(XXVII EAACI Congress of the European Academy of Allergology and Clinical Immunology, Barcelona, Spain, 7–11 June 2008):Abstract 586	Abstract of Didier *et al*.[24] included in Cochrane review
Horiguchi S, Okamoto Y, Yonekura S, Okawa T, Kunii N, Yamamoto H, *et al.* [Lowered effectiveness of immunotherapy for cypress pollinosis by using Japanese cedar pollen extract.] *Jp J Allergol* 2008;**57**:558–61	Japanese paper identified as likely to be included after preliminary translation. Full translation not obtained
Larsen TH, Poulsen LK, Melac M, Combebias A, Andre C, Malling HJ. Safety and tolerability of grass pollen tablets in sublingual immunotherapy: a phase-1 study. *Allergy* 2006;**61**:1173–6	Not identified in Cochrane review; 30 patients
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 updosing. *J Investig Allergol Clin Immunol* 2007;**17**:399–405	Not identified in Cochrane review; 105 patients
Mösges R, Brüning H, Hessler HJ, Götz 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	Not identified in Cochrane review; 105 patients
Palma-Carlos AG, Santos AS, Branco-Ferreira M, Pregal AL, Palma-Carlos ML. Monoid sublingual immunotherapy. *Eur Ann Allergy Clin Immunology* 2006;**38**:87–9	Likely duplicate publication of Palma-Carlos 2006 in Cochrane review
Rak S, Yang WH, Pedersen MR, Durham SR. Once-daily sublingual allergen-specific immunotherapy improves quality of life in patients with grass pollen-induced allergic rhinoconjunctivitis: A double-blind, randomised study. *Qual Life Res* 2007;**16**:191–201	Report of Durham 2006 included in Cochrane review
Roder E, Berger MY, Hop WCJ, de GH, Gerth van Wijk R. Efficacy of sublingual immunotherapy (SLIT) with grass pollen allergen in children and adolescents. *J Allergy Clin Immunol* 2006;**117**(American Academy of Allergy, Asthma and Immunology 62nd Annual Meeting, Miami Beach, FL, USA, 3–7 March 2006:S89): Abstract 346	Duplicate of study in Cochrane review
Sieber J, Merk H, Ott H. Seasonal sublingual immunotherapy is efficacious in allergic rhinitis from the first treatment season on also under high grass pollen exposure: the ECRIT study. *Allergy* 2008;**63**(XXVII EAACI Congress of the European Academy of Allergology and Clinical Immunology, Barcelona, Spain, 7–11 June 2008):Abstract 597	Abstract of included study

Reference	Details
Valovirta E, Ljorring C, Jacobsen L. Double-blind, placebo-controlled dose-response study of clinical efficacy and safety of sublingual immunotherapy (SLIT) with tree pollen extract in children suffering from tree pollen induced hay fever with or without SAA. *Allergy* 2003;**58**(XXII Congress of the European Academy of Allergology and Clinical Immunology)	Likely abstract of included study
Worm M. Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. *Eur Ann Allergy Clin Immunology* 2006;**38**:355–60	Not identified in Cochrane review; 188 patients.

Studies excluded from Cochrane review but meeting our inclusion criteria (not included in this report as not part of update)

Subcutaneous immunotherapy

Reference	Details
Polosa R, Li Gotti F, Mangano G, Mastruzzo C, Pistorio MP, Crimi N. Monitoring of seasonal variability in bronchial hyper-responsiveness and sputum cell counts in non-asthmatic subjects with rhinitis and effect of specific immunotherapy. *Clin Exp Allergy* 2003;**33**:873–81	Excluded from Cochrane review as 'other outcomes investigated'. Do give symptom/medication scores, but not usable in meta-analysis
Varney VA, Hamid QA, Gaga M, Ying S, Jacobson M, Frew AJ, *et al*. Influence of grass-pollen immunotherapy on cellular infiltration and cytokine messenger-RNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993;**92**:644–51	Excluded from Cochrane review as 'other outcomes investigated'. Do give symptom/medication scores, but not usable in meta-analysis
Weyer A, Donat N, L'Heritier C, Juilliard F, Pauli G, Soufflet B, *et al.* Grass pollen hyposensitization versus placebo therapy. I. Clinical effectiveness and methodological aspects of a pre-seasonal course of desensitization with a four-grass pollen extract. *Allergy* 1981;**36**:309–17	Excluded from Cochrane review as different immunotherapy preparations used. 'The first five doses were administered as aqueous preparations, whereas the 12 subsequent higher doses were injected in their $AlOH_3$-adsorbed form in order to avoid systemic reactions'
Fontana VJ, Holt LE Jr, Mainland D, Fontana VJ, Holt LEJ, Mainland D. Effectiveness of hyposensitization therapy in ragweed hay-fever in children. *J Am Med Assoc* 1966;**195**:985–92	Excluded from Cochrane review as no standardised allergen extract

Sublingual immunotherapy

Reference	Details
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	Excluded from Cochrane review as 'additional data not available'. States that 1–20 drops of extract dropped on to pieces of bread, which were held sublingually for 2 minutes
Van Niekerk CH, De Wet JI, Van Niekerk CH, De Wet JI. Efficacy of grass-maize pollen oral immunotherapy in patients with seasonal hay-fever: a double-blind study. *Clin Allergy* 1987;**17**:507–13	Excluded from Cochrane review as 'not SLIT'; states in paper that 1–15 drops taken sublingually, kept in the mouth for at least 1 minute then swallowed

Appendix 6 Main study characteristics and risk of bias

Subcutaneous immunotherapy compared with placebo

Casale 2006[159]

Study design	DBPC RCT
Population symptoms	AR (no asthma)
Treatment naive	No 'recent immunotherapy'. 19.5% had previously received SIT
n, age	159 patients (aged between 18 and 50 years); 79 active (two groups, IT with or without omalizumab), 80 placebo (two groups, placebo with or without omalizumab)
Intervention details	*Allergen:* ragweed Nine weeks' pretreatment with active/placebo omalizumab; rush IT with six injections over 3–5 hours with short ragweed extract (ALK-Abelló), 0.012 µg Amb a 1, up to 1.2 µg Amb a 1. Then increasing doses weekly for 4 weeks to 8 µg, followed by 8 weeks of maintenance doses of 12 µg (12 weeks total, including ragweed season)
Outcomes	SSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Placebo with increasing concentrations of histamine in order to maintain blinding
Incomplete outcome data	Low risk
Support for judgement	All patients accounted for. Intention-to-treat (ITT) analysis performed
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Overall, 19.5% previously received SIT, slight imbalance between treatment arms

Ceuppens 2009[160]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis (no or mild asthma)
Treatment naive	Yes. No previous SIT
n, age	62 adults (aged 18–65 years); 31 active, 31 placebo
Intervention details	*Allergen:* birch Glutaraldehyde-modified birch pollen extract adsorbed on to $AlOH_3$ (purethal birch) – 500 µg extract/ml; 52 µg Bet v1 content/ml. Weekly induction (0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml); three fortnightly doses of 0.5 ml; maintenance dose 0.5 ml at monthly interval for total of 18–22 months
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'Placebo preparations injected subcutaneously'
Incomplete outcome data	Low risk
Support for judgement	Dropouts (4/62; three in active group, one in placebo group) not included in results
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Patients all treatment naive

Chakraborty 2006[30]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis or allergic asthma or both
Treatment naive	Yes. No previous SIT
n, age	35 patients (aged 20–59 years); 18 active, 17 placebo
Intervention details	*Allergen:* date sugar palm Standardised allergen extract *Phoenix sylvestris* (date sugar palm); weekly induction phase for 24 weeks from 0.05 µg to 0.5 µg Fr IIa (fraction 11a of *P. sylvestris*); maintenance phase for 18 months at 2-weekly intervals with 0.5–1 µg Fr IIa. Dose reduced 20–40% in symptomatic patients during pollen season
Outcomes	SMSs, global measure of overall severity
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'Both the subjects and the administering personnel were blinded as to the composition of the injection vials'
Incomplete outcome data	Low risk
Support for judgement	All patients completed the study
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	History of IT an exclusion criterion

Charpin 2007[142]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis (possibly associated with moderate asthma)
Treatment naive	Yes. No previous SIT
n, age	40 adults (aged 24–66 years); 22 active, 18 placebo
Intervention details	*Allergen*: cypress Standardised *Juniperus ashei* (cypress) extract (Stallergènes); 54 μg Jun a1 major allergen/ml in 100-index of reactivity (IR) extract. Adsorbed on to $AlOH_3$. Induction phase fortnightly injections followed by maintenance phase at maximum tolerated dose for 15 months (frequency not reported), covering two pollen seasons. Maximum dose of Jun a1 injected was 16.2 μg
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Matched placebo containing histamine
Incomplete outcome data	Unclear risk
Support for judgement	Fairly high number of dropouts (8/22 active and 4/18 placebo); similar reasons for dropout. Not included in 'intention-to-treat (ITT) population'
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	All patients were treatment naive

Colas 2006[143]

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	Unclear, but no IT during last 4 years
n, age	63 adults (aged 18–50 years, mean 33 years); 41 active, 19 placebo
Intervention details	*Allergen*: Russian thistle Depigmented and glutaraldehyde polymerised extract of *S. kali* adsorbed to $AlOH_3$. Cluster schedule: first day 0.1, 0.25 and 0.5 ml × 45-μg extract/ml; 1 week later, 0.1, 0.25 and 0.5 ml × 450 μg/ml; then, starting 1 month later, one injection per month totalling 12 maintenance doses 0.5 ml × 450 μg/ml. Cumulative dose of Sal k 1 during trial was 597.65 μg
Outcomes	SSs, MSs, QoL, AEs, global assessment of health
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	'The placebo contained the identical solution as the experimental product, but without active ingredient; the presentation and dosage schedules were identical'
Incomplete outcome data	Low risk
Support for judgement	3/63 patients (two active, one placebo) dropped out prior to pollen season and not due to AEs; not included in analyses
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 4 years, but previous history unknown

Creticos 2006[144]

Study design	DBPC RCT
Population symptoms	AR
Treatment naive	Unclear. Exclusion criteria stated that no IT within last 5 years, but 20% were allowed to have had treatment > 5 years ago
n, age	25 adults (aged 23–60 years); 14 active, 11 placebo
Intervention details	*Allergen*: ragweed Preseasonal, six injections at weekly intervals, with dose from 0.06 to 12.0 µg AIC (Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate)
Outcomes	SSs, MSs, rhinitis-VAS, QoL, AEs (all listed as secondary outcomes)
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Random block design provided by Immune Tolerance Network statistical and clinical coordinating centre
Allocation concealment	Low risk
Support for judgement	Blinded coordinator used internet system to receive blinded treatment code
Blinding of participants/personnel	Low risk
Support for judgement	Full details of blinding given in a web appendix
Incomplete outcome data	High risk
Support for judgement	6/14 (active) and 9/11 (placebo) completed year 2; most analyses used only those that had completed. Also used subgroups who reached target dose in analysis
Free of selective reporting	Unclear risk
Support for judgement	All outcomes listed in methodology accounted for in results, although not very detailed. Some further information in web appendix
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years, but some patients may have had previous SIT

DuBuske 2011[145]

Study design	DBPC RCT
Population symptoms	Moderate to severe AR and/or conjunctivitis
Treatment naive	Excluded if previous treatment unless >3 years ago and with initial success but subsequent symptom recurrence
n, age	1028 adults (aged 18–59 years); 514 active, 514 placebo
Intervention details	*Allergen*: Thirteen-grass mix Grass MATA monophosphoryl lipid (MPL), Pollinex Quattro, Pollinex Complete; Allergy Therapeutics UK. Ultra-short course SCIT – four increasing dose injections [300, 800, 2000, 2000 standardised units (SU)] 13-grass-pollen allergoid mixture in L-tyrosine depot plus 50 µg MPL. Given at approximately weekly intervals pre-season
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Interactive voice randomisation system. Performed in blocks at study and site level
Allocation concealment	Low risk
Support for judgement	Interactive voice randomisation system
Blinding of participants/personnel	Low risk
Support for judgement	Placebo appeared identical apart from active ingredient
Incomplete outcome data	Low risk
Support for judgement	Intention-to-treat (ITT) analysis performed for primary efficacy analysis. Missing data imputed using matched-pair technique. Similar numbers dropped out in both treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Excluded if previous treatment unless >3 years ago and with initial success but subsequent symptom recurrence

Francis 2008[146]

Study design	DBPC RCT
Population symptoms	Moderate to severe AR with poor symptom control
Treatment naive	No details
n, age	18 adults (mean age between 30 and 37 years); 12 active, 6 placebo
Intervention details	*Allergen*: timothy grass Modified cluster regimen: weekly visits for 2 months, with two injections per visit in increasing dosage from 100 to 100,000 standardised quality units (SQ-Us) of timothy grass pollen (whole extract, Alutard SQ, ALK-Abelló). Maintenance dose monthly up to 1 year of 1 ml 100,000 SQ-U (20 µg Phl p5) but reduced by 40% z1 during pollen season
Outcomes	Overall clinical assessment, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Low risk
Support for judgement	Placebo with histamine and identical in appearance
Incomplete outcome data	Low risk
Support for judgement	Appears that all participants included in analysis
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Hoiby 2010[148]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without allergic asthma
Treatment naive	No details
n, age	61 adults, adolescents and children (51/5/5, respectively; aged 7–69 years); active 31, placebo 30
Intervention details	*Allergen*: birch Depigoid (Laboratorios LETI SI) standardised depigmented, glutaraldehyde-polymerised *Betula alba* adsorbed on to $AlHO_3$. Updosing at 7-day intervals: 0.2 ml 100 depigmented, glutaraldehyde-polymerised pollen (DPP)/ml, 0.5 ml 100 DPP/ml, 0.2 ml 1000 DPP/ml, 0.5 ml 1000 DPP/ml; maintenance dose 0.5 ml 10,000 DPP/ml every 6 weeks for 18 months; maintenance dose corresponded to 30 μg Bet v 1 before polymerisation
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	'Within study centres patients were allocated to the treatment in ascending order'
Blinding of participants/personnel	Low risk
Support for judgement	'No visible difference between placebo and Depigoid® vials.' No histamine, but very few reactions in total so unlikely to have interfered with blinding
Incomplete outcome data	Unclear risk
Support for judgement	A 'modified' intention-to-treat (ITT) population was used excluding patients who did not reach maintenance dose, those who did not receive at least one dose during 2006 pollen season and those who did not adhere to study protocol. One patient unaccounted for. Primary analysis conducted on 45/61 patients. All 61 patients accounted for in safety results
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Kettner 2007[149] (abstract only)

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	211 patients (age range not stated); 108 active, 103 placebo
Intervention details	*Allergen*: birch rBet v 1-FV recombinant birch extract, dosage increased to 80 µg then maintained 1.5 years (frequency of injections not stated)
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	Results reported for 'full analysis set' only
Free of selective reporting	Unclear risk
Support for judgement	Full methodology not reported, so unclear how many outcome investigated
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Klimek 2010[150] (abstract only)

Study design	DBPC RCT
Population symptoms	No details
Symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	148 patients (age range not stated); 112 active, 36 placebo
Intervention details	*Allergen*: grasses and rye Coseasonal. Updosing with six injections up to 10,000 SQ-U (Alutard SQ grasses and rye, ALK-Abelló) with 1–3 injection intervals, then two injections of 10,000 SQ-U after 14 and 28 days
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	No details
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Kuna 2011[152]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	Yes. No previous IT
n, age	50 children and adolescents (aged 5–18); active 30, placebo 20
Intervention details	*Allergen*: *Alternaria* $AlOH_3$-adsorbed, standardised *A. alternata* extract 100% (8 μg/ml Alt a 1 in maintenance dose) (Allergopharma) – updosing: 14 injections weekly or fortnightly. Maintenance dose: 1 ml 35,000 therapeutic units (TUs)/ml or highest tolerated dose every 4–6 weeks for up to 3 years
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated random number tables
Allocation concealment	Low risk
Support for judgement	Code concealed by manufacturer
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo containing histamine indistinguishable from active treatment. All personnel at the study site were blinded
Incomplete outcome data	Unclear risk
Support for judgement	Dropouts = 4/30 active and 1/20 placebo. Reason for dropout was difficulties with timings of study for all. Not stated whether 'intention to treat (ITT)' or other
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	No previous SIT

Ljorring 2009[153] (abstract only)

Study design	DBPC RCT
Population symptoms	Grass-allergic patients. No further details
Treatment naive	No details
n, age	162 patients. Age and allocation not reported
Intervention details	*Allergen*: grass Alutard SQ® grass, 100,000 SQ-U (ALK-Abelló); 1 year. No further details on treatment schedule
Outcomes	SMSs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	Numbers in analysis not reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history not reported

Pauli 2008[154]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	Yes. No previous IT
n, age	*n* = 147 (aged 18–50 years); active 98 (three groups), placebo 36
Intervention details	*Allergen*: birch One of three $AlOH_3$-adsorbed extracts: birch pollen extract, natural Bet v 1, recombinant Bet v 1, standardised for Bet v 1 concentration (Stallergènes). Build-up starting 6 months before pollen season by weekly injections from 0.1 ml of 0.5 µg/ml, increasing weekly to 0.3 ml of 50 µg/ml or maximum tolerated dose. Maintenance dose reached at least 7 weeks before pollen season was 15 µg Bet v 1 then given monthly for 2 years
Outcomes	SSs, MSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	'Minimisation method considering symptom severity and degree of birch sensitisation'
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding	Low risk
Support for judgement	Placebo containing histamine to maintain blinding
Incomplete outcome data	Low risk
Support for judgement	Between 24% and 27% withdrew from each arm of the four groups, none for AEs. Intention-to-treat (ITT) analysis performed where possible
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	Previous SIT considered major protocol violation (*n* = 1)

Pfaar 2010[155]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis with or without asthma
Treatment naive	No details
n, age	184 adults (aged 18–65 years, mean 38 years); 137 active, 47 placebo
Intervention details	*Allergen*: birch, hazel and alder Depigoid® (Laboratorios LETI) standardised depigmented, glutaraldehyde-polymerised tree pollen extract (33% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *B. alba*) adsorbed on to $AlOH_3$. Updosing at 7-day intervals: 0.2 ml 100 DPP/ml, 0.5 ml 100 DPP/ml, 0.2 ml 1000 DPP/ml, 0.5 ml 1000 DPP/ml; maintenance dose 0.5 ml 10,000 DPP/ml every 6 weeks for 18 months; maintenance dose corresponded to 11.0 µg Bet v 1 before polymerisation
Outcomes	SSs, MSs, SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo medication was identical in appearance'
Incomplete outcome data	High risk
Support for judgement	Primary outcomes analysed on intention-to-treat (ITT) and per protocol basis. Secondary outcomes (including SSs and MSs) on per protocol basis only
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear
Support for judgement	Previous SIT history not reported

Powell 2007[156]

Further report of Frew 2006[161] included in Cochrane review, see reported as abstract Krishna 2006.[151]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis inadequately controlled with medication in previous years
Treatment naive	No SIT in previous 5 years
n, age	410 adults (18–60 years, mean 38 years); 203 high dose, 104 medium dose, 103 placebo
Intervention details	*Allergen*: timothy grass Alutard SQ® *P. pratense* 10,000 SQ-U (2 µg Phl p 5) or 100,000 SQ-U (20 µg Phl p 5) (ALK-Abelló); updosing 15 injections (two/visit) over 8 weeks; maintenance phase every 6 ± 2 weeks for approximately 12 months
Outcomes	QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Generated by ALK-Abelló
Allocation concealment	Low risk
Support for judgement	ALK-Abelló maintained sequence; investigators allocated sequential randomisation number from sequence
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo and active medication were indistinguishable'
Incomplete outcome data	Low risk
Support for judgement	387/410 completed study (169, 87, 91). All randomised subjects included in analysis [intention to treat (ITT)]
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results (note: not all outcomes reported in this publication)
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years, but unclear if ever treated with SIT

Sahin 2011[157] (abstract only)

Study design	DBPC RCT
Population symptoms	AR and/or conjunctivitis
Treatment naive	No details
n, age	121 adults (aged 18–60 years), 61 active, 59 placebo (1 dropout)
Intervention details	*Allergen*: grass and rye Highly polymerised allergen extract mixture of grass and rye pollen (Clustoid), two injections/day for initiation phase (cluster schedule) then once per month for maintenance (length of treatment not clear)
Outcomes	SSs, MSs, global evaluation by patients, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/personnel	Unclear risk
Support for judgement	No details
Incomplete outcome data	Unclear risk
Support for judgement	No details
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Previous SIT history not reported

Ventura 2009[158]

Note: this study has as treatment arms SLIT, SCIT and placebo; there is no direct comparison between SLIT and SCIT.

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis
Treatment naive	Unclear (not in treatment at time of study)
n, age	*n* = 20 adults (18–55 years); active *n* = 10, placebo *n* = 10
Intervention details	*Allergen*: cypress 300 IR/ml *J. ashei* extract adsorbed on to aluminium hydroxide phosphate (StaloralR, Stallergènes Sa). Jun a1 MAC 76 μg/ml of the 100-index of reactivity (IR) allergen extract; daily allergen dose in maintenance of 228 μg/ml Twelve-week induction phase with weekly injections and maintenance phase of 9 months with monthly injections
Outcomes	SSs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated code
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding participants/ personnel	Low risk
Support for judgement	The placebo had the same appearance and taste as SLIT. No further details
Incomplete outcome data	Low risk
Support for judgement	Data for all 20 patients reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Sublingual immunotherapy compared with placebo

Blaiss 2011[189]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis; 26% history of asthma, 89% multisensitised
Treatment naive	Unclear
n, age	*n* = 345, active *n* = 149, placebo *n* = 158 Children aged 5–17 years; mean age 12.3 years
Intervention details	*Allergen*: timothy grass Once-daily sublingual *P. pratense* grass AIT (allergen immunotherapy tablet) 75,000 SQ-T, 15 µg Phl p5 (Schering Plough) started 16 weeks before pollen season and continued throughout season (23 weeks total)
Outcomes	SMSs, SSs, MSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	External computer-generated randomisation; stratified by study site and asthma status
Allocation concealment	Low risk
Support for judgement	External randomisation group using an interactive voice response system
Blinding of participants/ personnel	Low risk
Support for judgement	'Subjects and investigators were blinded to treatment by using a matching placebo in identical packaging to the grass AIT treatment. Blinding was maintained until data were locked'
Incomplete outcome data	Unclear risk
Support for judgement	345 randomised; intention-to-treat (ITT) population *n* = 307 (all randomised patients with at least one data entry). Missing data not imputed. Discontinuations 14.6% intervention group and 6.5% placebo group
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear
Support for judgement	SIT history of patients not reported

Cortellini 2010[190]

Study design	DBPC RCT
Population symptoms	Moderate/severe persistent rhinitis with or without intermittent asthma
Treatment naive	Yes
n, age	*n* = 27, adolescents and adults (age 14–42); active *n* = 15, placebo *n* = 12
Intervention details	*Allergen*: *Alternaria* Build-up phase lasted 15 days, starting with one drop from 100-Ru vial, increasing daily by one drop, up to five drops. Repeated with 1000-RU (radioallergosorbent test units) vial and 10,000-RU vial until maintenance dose reached. Maintenance dose was five drops of glycerinated extract, 10,000 RU/ml Alt a 1 (1.5 µg/ml) (Anallergo) every other day for 10 months (January to October)
Outcomes	SSs, MSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'The placebo was indistinguishable by taste and aspect from the active SLIT.' 'Blinding was maintained until the last patient had completed the study'
Incomplete outcome data	Low risk
Support for judgement	Analysis performed on per-protocol population, not 'intention to treat (ITT)' but only one dropout of 27 randomised
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Low risk
Support for judgement	No previous SIT

Didier 2011[25]

Preliminary results also in Didier 2010 abstract.[199]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis
Treatment naive	No details
n, age	*n* = 633, adults (18–50 years) 2 active (*n* = 207 in both groups), 1 placebo arm (*n* = 219)
Intervention details	*Allergen*: five-grass mix Daily 300-index of reactivity (IR) five-grass pollen tablet (Oralair): either 4 or 2 months' preseasonal treatment, then during the pollen season. Treatment over three consecutive pollen seasons
Outcomes	SSs (adjusted for rescue medication use), SMSs, individual symptoms scores, symptoms and medication-free days, QoL, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	No details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	The 2-month group received placebo during the time the 4-month group was receiving their active treatment to maintain blinding
Incomplete outcome data	Unclear risk
Support for judgement	All a patients analyses performed on patients who had at least one dose of investigational product and who had at least one measurement during the pollen season. Frequency of discontinuations was similar between the three groups. Dropouts due to AEs were more frequent in active treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Durham 2011[32] (GT–08 trial), Durham 2010,[200] Dahl 2008[270] and Dahl 2006[93]

Note: This study was identified in the Cochrane review; we report on more recent publications with longer follow-up data.

Study design	DBPC RCT
Population symptoms	Significant allergic rhinoconjunctivitis
Treatment naive	Unclear (but no grass pollen SIT within last 10 years or any other allergen within last 5 years)
n, age	$n = 634$ (mean age around 34 ± 10 years)
Intervention details	*Allergen*: timothy grass Grazax® [*P. pratense* 75,000 SQ-T (standardised quality units tablet)/2800 BAU (bioequivalent allergy unit) (ALK-Abelló)]. Treatment started 16 weeks before pollen season and continued daily for 3 years (approximately 15 µg) then 2-year follow-up
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Stated only that patients were randomised but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo tablet similar in taste, smell and appearance. All personnel associated with the study remained blinded
Incomplete outcome data	Unclear risk
Support for judgement	Analyses for all randomised patients where data were available. No imputation of missing data. Similar completion rates at years 1 and 2, and similar reasons for withdrawals. Further loss to follow-up after year 1, as some sites closed and some patients chose not to participate
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Patients may have had previous SIT (but not in last 10/5 years for grass or other allergen SIT, respectively)

Fujimura 2011[191]

Study design	DBPC RCT
Population symptoms	Moderate or severe symptoms of pollinosis
Treatment naive	Yes
n, age	*n* = 103 adults (age 16–73); active *n* = 58, placebo *n* = 45
Intervention details	*Allergen*: Japanese cedar Standardised Japanese cedar pollen extract (Torii Pharmaceuticals). Updosing from 0.2 ml of 20 Japanese Allergy Unit (JAU)/ml, increasing by 0.2 ml/day for 5 days per week. Maintenance dose was 1.0 ml of 2000 JAU/ml given once weekly over 2 years (two pollen seasons)
Outcomes	SMSs, AEs, QoL
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Random numbers table generated by personnel not directly involved in study
Allocation concealment	Low risk
Support for judgement	Allocation by personnel not directly involved in study
Blinding of participants/ personnel	Unclear risk
Support for judgement	Stated that study was double blind for two seasons; follow-up season was single blind
Incomplete outcome data	Low-risk SMSs, high-risk-QoL data
Support for judgement	Both intention-to-treat (ITT) and on-treatment analysis performed but only on-treatment analysis results presented for QoL data
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Yes
Support for judgement	No previous SIT

Horak 2009[202]

Further publication of study reported in Didier 2007[24] (included in Cochrane review). Horak 2009[202] includes further data on QoL not reported in Didier 2007.[24]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis
Treatment naive	Yes
n, age	*n* = 628 adults (aged 18–45 years); four groups: *n* = 157 given 100 IR, *n* = 155 given 300 IR, *n* = 160 given 500 IR, *n* = 156 given placebo
Intervention details	*Allergen*: five-grass mix 100-index of reactivity (IR), 300-IR or 500-IR standardised lyophilised five-grass pollen tablet (300 IR/ml approximately = 25 mg/ml allergen extracts). Daily tablet. Five days' titration period from 100 IR to assigned dose. Maintenance approximately 4 months prior to pollen season and throughout pollen the season
Outcomes	SSs, QoL, medication-free days, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	Double blind; blinding maintained during induction phase by giving all patients two tables (presumably using placebo to make up difference), with one tablet from day 6
Incomplete outcome data	Unclear risk
Support for judgement	Only patients with complete data sets included in intention-to-treat (ITT) population (569/628, 91%). Discontinuations due to AE only in active treatment groups. Overall, slightly more withdrawals from active groups
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for; note that clinical outcomes reported in Didier 2007 (in Cochrane review). Additional data in this publication only QoL
Free of other bias?	Yes
Support for judgement	All patients treatment naive

Nelson 2011[192]

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis with or without asthma
Treatment naive	Unclear (but stated that no SIT in last 5 years)
n, age	*n* = 438 adults (18–65); active *n* = 213, placebo *n* = 207
Intervention details	*Allergen*: timothy grass Once-daily 2800 BAU standardised *P. pratense*, 75,000 SQ-T, approximately 15 µg Phl p5 (Schering Plough), starting 16 weeks preseasonal plus coseasonal, throughout the pollen season. No build-up dosing
Outcomes	SSs, MSs, SMSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation schedule
Allocation concealment	Low risk
Support for judgement	External randomisation group using an interactive voice-response system
Blinding of participants/ personnel	Low risk
Support for judgement	'Double-blinding (subjects and investigators) was established by use of a matching placebo tablet.' 'Blinding was maintained until the database was locked'
Incomplete outcome data	Low risk
Support for judgement	391/439 with at least one post-treatment diary entry analysed. Similar numbers and reasons for discontinuation in both treatment arms
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results.
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 5 years)

Panizo 2010[193]

Study design	DBPC RCT
Population symptoms	Rhinitis with or without asthma
Treatment naive	Unclear (but not in last 5 years)
Participant details	$n = 78$ adults (18–65); active = 52, placebo $n = 26$
Intervention details	*Allergen*: timothy grass Daily Grazax® 75,000 SQ-T for at least 8 weeks preseasonal, plus coseasonal, throughout the season
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Stated that patients were randomised but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo similar in taste, smell and physical appearance'
Incomplete outcome data	Low risk (for AE outcome)
Support for judgement	All patients included in safety analysis
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT but no SIT in previous 5 years

Pfaar 2011[194]

Study design	DBPC RCT
Population symptoms	Seasonal allergy symptoms
Treatment naive	Unclear (but stated that no SIT in last 3 years)
n, age	*n* = 80 adults (18–65 years); active *n* = 64 (four groups with different doses, *n* = 16 in each), placebo *n* = 16 (four in each group)
Intervention details	*Allergen*: timothy grass Extract of 12 mixed-grass pollens (Allergy Therapeutics, B2 grass mixture), standardised by major allergen, *P. pratense* Phl p 1 ± adjuvant MPL • Group 1: 9.45 µg *P. pratense* • Group 2: 9.45 µg *P. pratense* + 21 µg MPL (monophosphoryl lipid A) • Group 3: 9.5 µg *P. pratense* + 52.5 µg MPL • Group 4: 19 µg *P. pratense* + 52.5 µg MPL Eight-week treatment period; periods varied for the four groups (preseasonal for three, postseasonal for one)
Outcomes	AEs
Risk of bias	
Adequate sequence generation	Unclear risk
Support for judgement	Patients were described as randomised, but no further details
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo solutions contained buffered glycerine solution and flavouring to match the active SLIT'
Incomplete outcome data	Low risk
Support for judgement	All subjects accounted for
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 3 years)

Reich 2011[195]

Study design: RCT	DBPC RCT
Objective diagnosis	Yes
Population symptoms	Moderate to severe rhinoconjunctivitis; 41% with history of asthma
Treatment naive	Unclear (but no SIT in last 5 years)
n, age	*n* = 276, active *n* = 219, placebo *n* = 57 Mean age 35 years
Intervention details	*Allergen*: timothy grass Once daily sublingual *P. pratense* grass AIT 75,000 SQ-T, 2800 BAU (Grazax®, ALK) for 8–10 weeks during pollen season
Outcomes	MSs, AEs, global evaluation
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer generated block randomisation. Randomisation list generated by trial-independent statistician
Allocation concealment	Low risk
Support for judgement	Sealed randomisation code envelopes. Patients assigned lowest available randomisation numbers
Blinding of participants/ personnel	Low risk
Support for judgement	'Investigators and patients were blinded throughout the trial.' Matching placebo with taste, smell and appearance similar to the active extract. Drug codes broken only after completion of trial
Incomplete outcome data	Low risk
Support for judgement	All randomised patients included in analyses
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	History of SIT in previous 5 years an exclusion criterion, but unclear if any patients had ever received SIT

Skoner 2010[196]

Study design	DBPC RCT
Population symptoms	Moderate to severe allergic rhinoconjunctivitis
Treatment naive	Unclear (but no SIT for ragweed in last 3 years)
n, age	*n* = 115 adults (aged 18–50 years); *n* = 39 medium dose, *n* = 36 high dose, *n* = 40 placebo
Intervention details	*Allergen*: ragweed Preliminary dosing at first visit: up to four incremental doses of short ragweed pollen extract standardised for Amb a 1 content (medium-dose group 0, 0.48, 1.7 and 4.8 µg Amb a 1; high-dose group 0, 4.8, 17 and 48 µg extract). Maximum tolerated dose used. Daily dose of maintenance dose. Mean maximum tolerated dose was 3.21 (1.64) µg and 30.54 (16.14) µg in medium- and high-dose groups. Average cumulative dose 498 (185) µg/ml and 4941 (1487) µg/ml Pre-and coseasonal treatment. Average duration 17 weeks (±3)
Outcomes	SMSs, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Central block randomisation with stratification based on asthma diagnosis
Allocation concealment	Low risk
Support for judgement	Sequentially numbered containers, pharmacy control and central randomisation
Blinding of participants/ personnel	Low risk
Support for judgement	Placebo masked with colouring
Incomplete outcome data	Unclear risk
Support for judgement	Patients with missing data excluded from analysis. Data for 90% of patients. Similar proportions missing from different groups, but no reasons stated
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for
Free of other bias?	Unclear risk
Support for judgement	Some patients may have had previous SIT (but no SIT in previous 3 years)

Ventura 2009[158]

Note: this study has as treatment arms SLIT, SCIT and placebo; there is no direct comparison between SLIT and SCIT.

Study design	DBPC RCT
Population symptoms	Allergic rhinoconjunctivitis
Treatment naive	Unclear (not in treatment at time of study)
n, age	*n* = 20 adults (18–55 years); active *n* = 10, placebo *n* = 10
Intervention details	*Allergen*: cypress 300 IR/ml *J. ashei* extract as glycerol saline solution (StaloralR). Daily allergen dose of 228 μg/ml 30-day induction, 11 months' maintenance; drops self-administered three times per week
Outcomes	SSs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated code
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	The placebo had the same appearance and taste as SLIT
Incomplete outcome data	Low risk
Support for judgement	Data for all 20 patients reported
Free of selective reporting	Low risk
Support for judgement	All outcomes listed in methodology accounted for in results
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Voltolini 2010[197]

Study design	DBPC RCT
Population symptoms	Moderate/severe persistent rhinitis and slight intermittent to moderate asthma
Treatment naive	No details
n, age	*n* = 24 adults (mean ages 44 and 40 years in active and placebo groups, respectively); active *n* = 14, placebo *n* = 10
Intervention details	*Allergen*: birch Allergen extract of birch at 10 IR/ml and 300 IR/ml (Stallergènes) Build-up from 10 index of reactivity (IR) over 11 days to maintenance dose of 300 IR then daily for 4 months, repeated over two consecutive years
Outcomes	SSs, MSs, asthma days/severity, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Computer-generated randomisation list
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'Placebo vials matched the active treatment in colour and flavour'
Incomplete outcome data	Low risk
Support for judgement	Analysis of completers only, but only one patient lost to follow-up in each group (reason not stated)
Free of selective reporting	High risk
Support for judgement	MSs measured but not reported. Treatment over two seasons but data reported after 1 year only. SSs recorded for three symptoms but reported for two only
Free of other bias?	Unclear risk
Support for judgement	SIT history of patients not reported

Subcutaneous immunotherapy compared with sublingual immunotherapy

Khinchi 2004[210]

Study design	DBPC RCT
Population symptoms	Rhinoconjunctivitis uncontrolled by conventional pharmacotherapy
Treatment naive	No SIT within last 5 years
n, age	71 adults (20–58 years); 23 SLIT, 24 SCIT and 15 placebo
Intervention details	*Allergen*: birch Birch pollen extract standardised in terms of major allergen Bet v 1 administered as glycerine-saline solution (SLIT, Staloral®) or adsorbed on calcium phosphate (SCIT, Phostal®) *SLIT*: 30-day induction phase, maintenance phase 21–23 months. Drops every other day held under tongue for 2 minutes. Dose between 0.0164 and 49.2 μg *SCIT*: 12-week induction phase (weekly injections) with 0.0164 μg, monthly maintenance phase 3.28 μg
Outcomes	SSs, MSs, QoL, AEs
Risk of bias	
Adequate sequence generation	Low risk
Support for judgement	Allocation by minimisation
Allocation concealment	Unclear risk
Support for judgement	No details
Blinding of participants/ personnel	Low risk
Support for judgement	'All study personnel and participants were blinded to treatment assignment for the 2-year duration of treatment in the study.' Placebo preparations included caramelised sugar for SLIT to ensure identical visual appearance and histamine dihydrochloride for injections to ensure induction of local reactions for SCIT
Incomplete outcome data	Unclear risk
Support for judgement	Similar numbers of withdrawals in the three groups. Only patients completing first treatment season included in statistical calculations. Results not reported in a way that is consistent with most other studies
Free of selective reporting	Unclear risk
Support for judgement	All outcomes listed in methodology accounted for in results. Second season is not included in the evaluation of efficacy (owing to low pollen counts)
Free of other bias?	Unclear risk
Support for judgement	No SIT in previous 5 years but previous treatment history unknown

Appendix 7 Results of subgroup analyses

Subcutaneous immunotherapy

Comparison 1 Subcutaneous immunotherapy compared with placebo, all studies

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	17	1184	SMD (IV, random, 95% CI)	–0.65 (–0.85 to –0.45)
2 MSs	16	1103		–0.55 (–0.75 to –0.34)
3 SMSs	8	617		–0.48 (–0.67 to –0.29)

IV, inverse variance.

Comparison 2 Subcutaneous immunotherapy compared with placebo, adults

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	16	1140	SMD (IV, random, 95% CI)	–0.68 (–0.89 to –0.47)
2 MSs	15	1059		–0.53 (–0.75 to –0.32)

IV, inverse variance.

Comparison 3 Subcutaneous immunotherapy compared with placebo, <6 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	5	274	SMD (IV, random, 95% CI)	–1.29 (–2.10 to –0.49)
2 MSs	2	143		–0.34 (–0.68 to –0.01)
3 SMSs	3	221		–0.47 (–0.91 to –0.02)

IV, inverse variance.

Comparison 4 Subcutaneous immunotherapy compared with placebo, 6–12 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	2	309	SMD (IV, random, 95% CI)	–0.54 (–0.78 to –0.29)
2 MSs	3	332		–0.46 (–0.69 to –0.23)

IV, inverse variance.

Comparison 5 Subcutaneous immunotherapy compared with placebo, >12 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	8	442	SMD (IV, random, 95% CI)	–0.51 (–0.70 to –0.32)
2 MSs	9	469		–0.67 (–1.06 to –0.29)
3 SMSs	3	253		–0.51 (–0.76 to –0.25)

IV, inverse variance.

Comparison 6 Subcutaneous immunotherapy compared with placebo, major allergen content <5 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	3	228	SMD (IV, random, 95% CI)	–0.43 (–0.69 to –0.16)
2 MSs	2	147		–0.31 (–0.63 to 0.02)
3 SMSs	3	228		–0.39 (–0.70 to –0.07)

IV, inverse variance.

Comparison 7 Subcutaneous immunotherapy compared with placebo, major allergen content 5–20 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	5	231	SMD (IV, random, 95% CI)	–0.54 (–0.80 to –0.27)
2 MSs	6	254		–0.45 (–0.70 to –0.20)

IV, inverse variance.

Comparison 8 Subcutaneous immunotherapy compared with placebo, >20 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	3	341	SMD (IV, random, 95% CI)	–1.06 (–2.08 to –0.05)
2 MSs	2	305		–0.55 (–0.96 to –0.13)

IV, inverse variance.

Comparison 9 Subcutaneous immunotherapy compared with placebo, grass pollen

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	9	552	SMD (IV, random, 95% CI)	–0.64 (–0.91 to –0.37)
2 MSs	8	483		–0.77 (–1.22 to –0.33)
3 SMSs	5	435		–0.43 (–0.62 to –0.24)

IV, inverse variance.

Comparison 10 Subcutaneous immunotherapy compared with placebo, Parietaria

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	3	353	SMD (IV, random, 95% CI)	–1.15 (–2.09 to –0.21)
2 MSs	2	318		–0.43 (–0.67 to –0.20)
3 SMSs	2	77		–0.96 (–1.44 to –0.49)

IV, inverse variance.

Comparison 11 Subcutaneous immunotherapy compared with placebo, tree

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	4	235	SMD (IV, random, 95% CI)	–0.46 (–0.72 to –0.20)
2 MSs	4	235		–0.34 (–0.60 to –0.09)

IV, inverse variance.

Comparison 12 Subcutaneous immunotherapy compared with placebo, QoL

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
All studies	8	955	SMD (IV, random, 95% CI)	–0.53 (–0.66 to –0.39)
Duration >12 months	6	662		–0.47 (–0.63 to –0.31)
MAC 5–20μg	3	381		–0.52 (–0.74 to –0.31)
MAC >20μg	3	379		–0.65 (–0.87 to –0.43)
Grass pollen	4	561		–0.44 (–0.61 to –0.26)
Parietaria pollen	2	316		–0.63 (–0.87 to –0.39)
RQLQ	8	955	MD (IV, random, 95% CI)	–0.74 (–0.92 to –0.56)

IV, inverse variance.

Sublingual immunotherapy

Comparison 13 Sublingual immunotherapy compared with placebo, all studies

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	42	4819	SMD (IV, random, 95% CI)	–0.33 (–0.42 to –0.25)
2 MSs	35	3779		–0.27 (–0.37 to –0.17)
3 SMSs	6	1394		–0.40 (–0.55 to –0.25)

IV, inverse variance.

Comparison 14 Sublingual immunotherapy compared with placebo, adults

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	33	3476	SMD (IV, random, 95% CI)	–0.38 (–0.49 to –0.27)
2 MSs	27	2604		–0.35 (–0.47 to –0.23)
3 SMSs	5	1087		–0.44 (–0.62 to –0.27)

IV, inverse variance.

Comparison 15 Sublingual immunotherapy compared with placebo, children

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	9	1343	SMD (IV, random, 95% CI)	–0.24 (–0.35 to –0.13)
2 MSs	8	1175		–0.08 (–0.25 to 0.08)

IV, inverse variance.

Comparison 16 Sublingual immunotherapy compared with placebo, <6 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	15	1882	SMD (IV, random, 95% CI)	–0.34 (–0.47 to –0.20)
2 MSs	14	1517		–0.33 (–0.47 to –0.19)
3 SMSs	2	376		–0.31 (–0.51 to –0.11)

IV, inverse variance.

Comparison 17 Sublingual immunotherapy compared with placebo, 6–12 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	15	1539	SMD (IV, random, 95% CI)	–0.31 (–0.47 to –0.16)
2 MSs	13	1223		–0.31 (–0.53 to –0.08)
3 SMSs	2	417		–0.66 (–1.63 to 0.30)

IV, inverse variance.

Comparison 18 Sublingual immunotherapy compared with placebo, >12 months

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	12	1398	SMD (IV, random, 95% CI)	–0.35 (–0.52 to –0.18)
2 MSs	8	1039		–0.16 (–0.31 to –0.01)
3 SMSs	2	601		–0.48 (–0.64 to –0.31)

IV, inverse variance.

Comparison 19 Sublingual immunotherapy compared with placebo, major allergen content <5 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	6	229	SMD (IV, random, 95% CI)	–0.53 (–1.03 to –0.03)
2 MSs	5	194		–0.63 (–1.08 to –0.18)

IV, inverse variance.

Comparison 20 Sublingual immunotherapy compared with placebo, major allergen content 5–20 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	13	2287	SMD (IV, random, 95% CI)	–0.29 (–0.37 to –0.20)
2 MSs	12	2285		–0.18 (–0.30 to –0.05)
3 SMSs	3	985		–0.32 (–0.45 to –0.19)

IV, inverse variance.

Comparison 21 Sublingual immunotherapy compared with placebo, major allergen content >20 µg

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	12	1088	SMD (IV, random, 95% CI)	–0.33 (–0.48 to –0.18)
2 MSs	10	708		–0.26 (–0.47 to –0.06)

IV, inverse variance.

Comparison 22 Sublingual immunotherapy compared with placebo, grass pollen

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	26	4045	SMD (IV, random, 95% CI)	–0.31 (–0.39 to –0.22)
2 MSs	19	3005		–0.20 (–0.31 to –0.08)
3 SMSs	4	1299		–0.36 (–0.48 to –0.24)

IV, inverse variance.

Comparison 23 Sublingual immunotherapy compared with placebo, ragweed

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	3	244	SMD (IV, random, 95% CI)	–0.44 (–0.48 to –0.18)
2 MSs	3	244		–0.34 (–0.60 to –0.09)

IV, inverse variance.

Comparison 24 Sublingual immunotherapy compared with placebo, Parietaria

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	4	124	SMD (IV, random, 95% CI)	–0.27 (–0.62 to 0.09)
2 MSs	4	124		–0.49 (–0.85 to –0.13)

IV, inverse variance.

Comparison 25 Sublingual immunotherapy compared with placebo, tree

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 SSs	9	380	SMD (IV, random, 95% CI)	–0.42 (–0.77 to –0.06)
2 MSs	9	380		–0.38 (–0.62 to –0.13)

IV, inverse variance.

Comparison 26 Sublingual immunotherapy compared with placebo, QoL

Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
1 All studies	7	1878	SMD (IV, random, 95% CI)	–0.37 (–0.52 to –0.22)
2 Adults	6	1658		–0.39 (–0.56 to –0.21)
3 < 6 months	4	908		–0.45 (–0.74 to –0.17)
4 > 12 months	2	601		–0.37 (–0.54 to –0.21)
5 MAC 5–20 μg	2	507		–0.32 (–0.49 to –0.14)
6 MAC > 20 μg	2	323		–0.70 (–0.93 to –0.48)
7 RQLQ	4	924	MD (IV, random, 95% CI)	–0.34 (–0.49 to –0.18)

IV, inverse variance.

Subcutaneous immunotherapy

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Balda 1998[163]	6.56	10.43	49	9.07	8.19	56	8.7%	−0.27 (−0.65 to 0.12)
Bodtger 2002[169]	2.2	1	16	3.3	1.4	17	5.1%	−0.88 (−1.60 to −0.16)
Bousquet 1990[170]	63.6	32.5	20	108.6	33.2	18	5.1%	−1.34 (−2.05 to −0.63)
Brewczynski 1999[171]	59.5	32.6	10	122.4	85.13	8	3.3%	−0.98 (−1.97 to 0.02)
Charpin 2007[142]	3.3	2.42	14	5.06	2.66	14	4.7%	−0.67 (−1.44 to 0.09)
Corrigan 2005[164]	166.5	114.93	77	218	135.39	77	9.6%	−0.41 (−0.73 to −0.09)
Drachenberg 2001[91]	0.75	0.44	74	0.95	0.41	50	9.0%	−0.46 (−0.83 to −0.10)
Ferrer 2005[165]	0.44	0.32	22	0.8	0.54	20	5.8%	−0.81 (−1.44 to −0.17)
Frew 2006[161]	3.31	2.42	187	4.59	2.93	89	10.5%	−0.49 (−0.75 to −0.24)
Jutel 2005[166]	3.93	3.28	29	5.82	3.44	28	6.9%	−0.55 (−1.08 to −0.02)
Ortolani 1984[174]	2.01	0.57	8	5.86	1.63	7	1.5%	−3.06 (−4.69 to −1.43)
Ortolani 1994[167]	0.61	0.12	18	2.3	0.98	17	3.8%	−2.40 (−3.29 to −1.51)
Pauli 2008[154]	0	6.8	33	3.41	7.1	36	7.5%	−0.48 (−0.96 to −0.00)
Varney 1991[172]	1531	1875	19	2230	856	16	5.4%	−0.46 (−1.13 to 0.22)
Walker 2001[173]	−1212	2632	17	−115	1159	13	4.9%	−0.50 (−1.24 to 0.23)
Zenner 1997[168]	82.24	64.38	41	115.98	83.67	40	8.0%	−0.45 (−0.89 to −0.01)
Total (95% CI)			634			506	100.0%	−0.68 (−0.89 to −0.47)

Heterogeneity: $\tau^2=0.09$; $\chi^2=36.19$, df=15 ($p=0.002$); $I^2=59\%$
Test for overall effect: $z=6.32$ ($p<0.00001$)

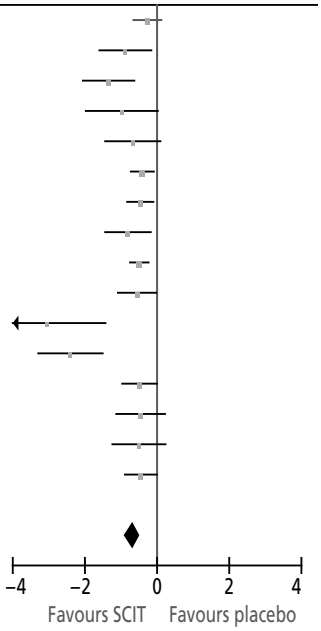

FIGURE 31 Subcutaneous immunotherapy vs placebo, adults, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Balda 1998[163]	9.03	16.03	49	13.63	19.67	56	9.3%	−0.25 (−0.64 to 0.13)
Bodtger 2002[169]	9.9	7	17	14.5	8.5	17	5.7%	−0.58 (−1.26 to 0.11)
Bousquet 1990[170]	38.6	37.6	20	66.4	51.7	18	6.0%	−0.61 (−1.26 to 0.05)
Brewczynski 1999[171]	17.2	10.4	10	36.8	35.46	8	3.6%	−0.76 (−1.73 to 0.22)
Charpin 2007[142]	3.98	4.15	14	5.23	4.41	14	5.2%	−0.28 (−1.03 to 0.46)
Corrigan 2005[164]	68.58	96.15	77	101.21	126.01	77	10.3%	−0.29 (−0.61 to 0.03)
Dolz 1996[175]	6	6.07	18	48.66	17.95	10	2.4%	−3.56 (−4.82 to −2.29)
Drachenberg 2001[91]	0.54	0.71	74	0.71	0.77	50	9.7%	−0.23 (−0.59 to 0.13)
Ferrer 2005[165]	0.35	0.47	22	0.92	1.73	20	6.4%	−0.45 (−1.06 to 0.16)
Frew 2006[161]	2.93	2.95	187	4.29	3.53	89	11.2%	−0.43 (−0.69 to −0.18)
Jutel 2005[166]	2.73	4.48	29	3.78	4.92	28	7.5%	−0.22 (−0.74 to 0.30)
Mirone 2004[176]	0.7	1.4	11	2.2	3.1	12	4.4%	−0.59 (−1.43 to 0.25)
Pauli 2008[154]	0	4.6	33	1.9	4.8	36	8.1%	−0.40 (−0.88 to 0.08)
Varney 1991[172]	2146	2513	19	14,491	15,066	16	5.3%	−1.17 (−1.89 to −0.44)
Walker 2001[173]	−1308	983	16	101	1899	13	4.9%	−0.94 (−1.71 to −0.16)
Total (95% CI)			596			464	100.0%	−0.53 (−0.75 to −0.32)

Heterogeneity: $\tau^2=0.09$; $\chi^2=33.54$, df=14 ($p=0.002$); $I^2=58\%$
Test for overall effect: $z=4.82$ ($p<0.00001$)

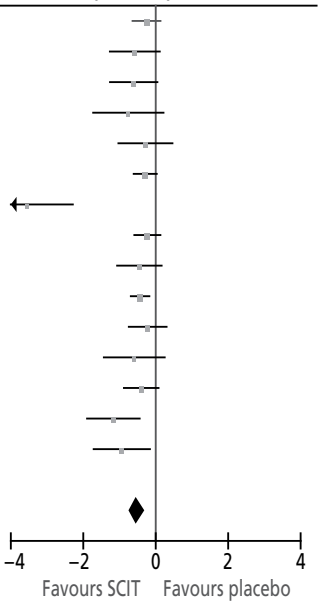

FIGURE 32 Subcutaneous immunotherapy vs placebo, adults, MSs.

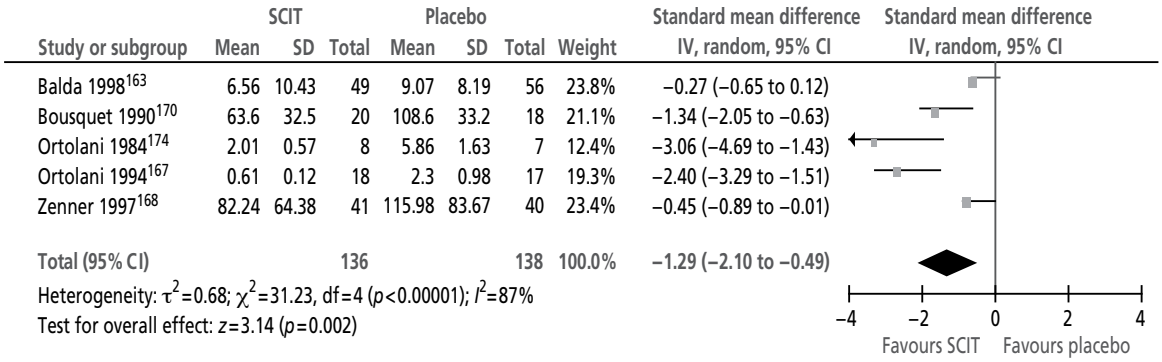

FIGURE 33 Subcutaneous immunotherapy vs placebo, <6 months, SSs.

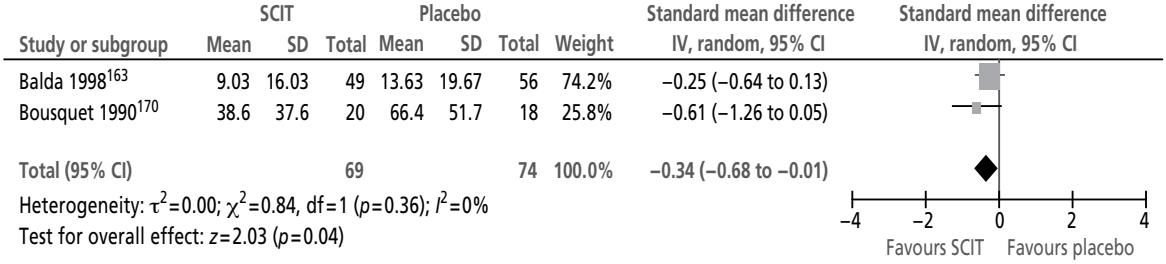

FIGURE 34 Subcutaneous immunotherapy vs placebo, <6 months, MSs.

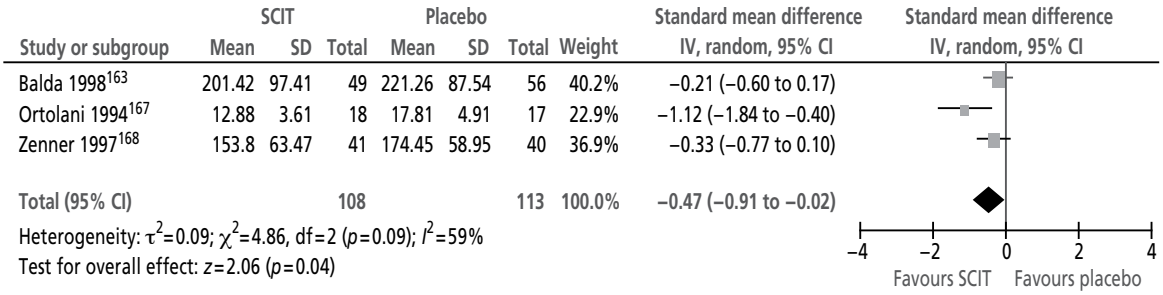

FIGURE 35 Subcutaneous immunotherapy vs placebo, <6 months, SMSs.

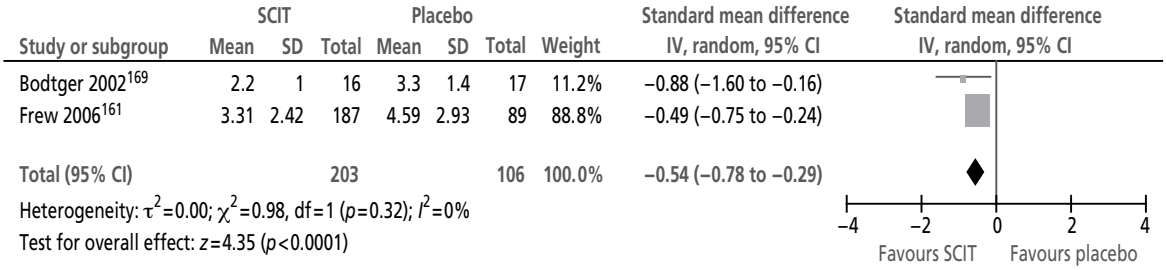

FIGURE 36 Subcutaneous immunotherapy vs placebo, 6–12 months, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Bodtger 2002[169]	9.9	7	17	14.5	8.5	17	11.2%	−0.58 (−1.26 to 0.11)
Frew 2006[161]	2.93	2.95	187	4.29	3.53	89	81.3%	−0.43 (−0.69 to −0.18)
Mirone 2004[176]	0.7	1.4	11	2.2	3.1	12	7.5%	−0.59 (−1.43 to 0.25)
Total (95% CI)			215			118	100.0%	−0.46 (−0.69 to −0.23)

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.26$, df=2 ($p=0.88$); $I^2=0\%$

Test for overall effect: $z=3.91$ ($p<0.0001$)

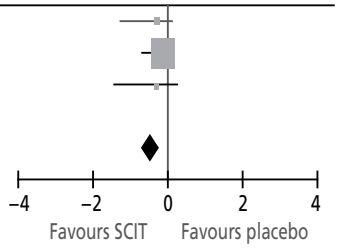

FIGURE 37 Subcutaneous immunotherapy vs placebo, 6–12 months, MSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Brewczynski 1999[171]	59.5	32.6	10	122.4	85.13	8	3.6%	−0.98 (−1.97 to 0.02)
Charpin 2007[142]	3.3	2.42	14	5.06	2.66	14	6.2%	−0.67 (−1.44 to 0.09)
Corrigan 2005[164]	166.5	114.93	77	218	135.39	77	35.6%	−0.41 (−0.73 to −0.09)
Ferrer 2005[165]	0.44	0.32	22	0.8	0.54	20	9.1%	−0.81 (−1.44 to −0.17)
Jutel 2005[166]	3.93	3.28	29	5.82	3.44	28	12.9%	−0.55 (−1.08 to −0.02)
Kuna 2011[152]	85	140	25	140	240	19	10.1%	−0.29 (−0.88 to 0.31)
Pauli 2008[154]	0	6.8	33	3.41	7.1	36	15.8%	−0.48 (−0.96 to −0.00)
Walker 2001[173]	−1212	2632	17	−115	1159	13	6.7%	−0.50 (−1.24 to 0.23)
Total (95% CI)			227			215	100.0%	−0.51 (−0.70 to −0.32)

Heterogeneity: $\tau^2=0.00$; $\chi^2=2.82$, df=7 ($p=0.90$); $I^2=0\%$

Test for overall effect: $z=5.21$ ($p<0.00001$)

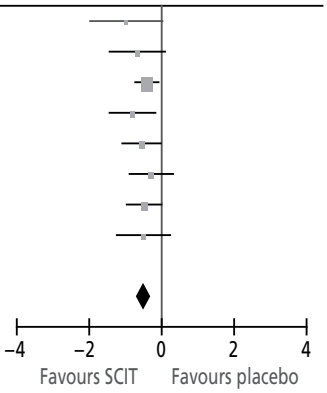

FIGURE 38 Subcutaneous immunotherapy vs placebo, >12 months, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Brewczynski 1999[171]	17.2	10.4	10	36.8	35.46	8	8.2%	−0.76 (−1.73 to 0.22)
Charpin 2007[142]	3.98	4.15	14	5.23	4.41	14	10.4%	−0.28 (−1.03 to 0.46)
Corrigan 2005[164]	68.58	96.15	77	101.21	126.01	77	15.3%	−0.29 (−0.61 to 0.03)
Dolz 1996[175]	6	6.07	18	48.66	17.95	10	6.0%	−3.56 (−4.82 to −2.29)
Ferrer 2005[165]	0.35	0.47	22	0.92	1.73	20	11.9%	−0.45 (−1.06 to 0.16)
Jutel 2005[166]	2.73	4.48	29	3.78	4.92	28	13.0%	−0.22 (−0.74 to 0.30)
Kuna 2011[152]	2.3	5	25	21.4	35	19	11.8%	−0.81 (−1.43 to −0.19)
Pauli 2008[154]	0	4.6	33	1.9	4.8	36	13.5%	−0.40 (−0.88 to 0.08)
Walker 2001[173]	−1308	983	16	101	1899	13	10.1%	−0.94 (−1.71 to −0.16)
Total (95% CI)			244			225	100.0%	−0.67 (−1.06 to −0.29)

Heterogeneity: $\tau^2=0.23$; $\chi^2=28.04$, df=8 ($p=0.0005$); $I^2=71\%$

Test for overall effect: $z=3.43$ ($p=0.0006$)

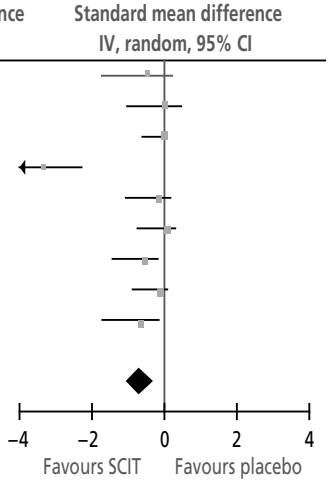

FIGURE 39 Subcutaneous immunotherapy vs placebo, >12 months, MSs.

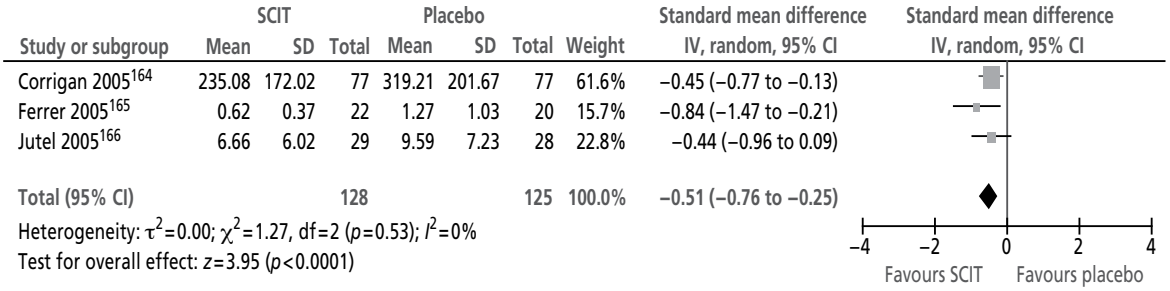

FIGURE 40 Subcutaneous immunotherapy vs placebo, >12 months, SMSs.

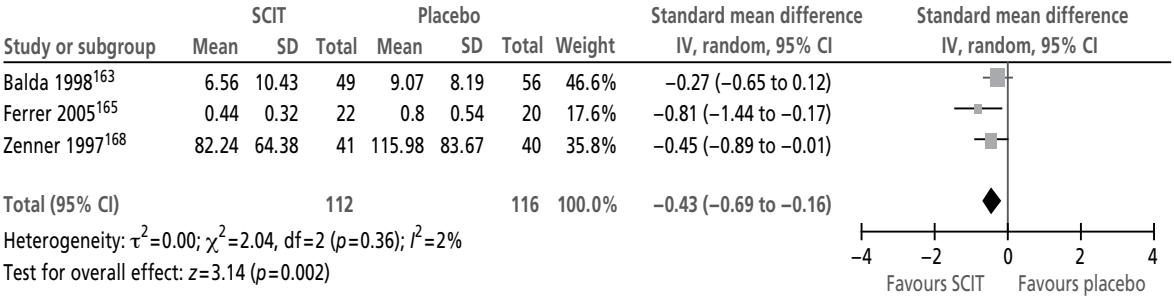

FIGURE 41 Subcutaneous immunotherapy vs placebo, <5μg, SSs.

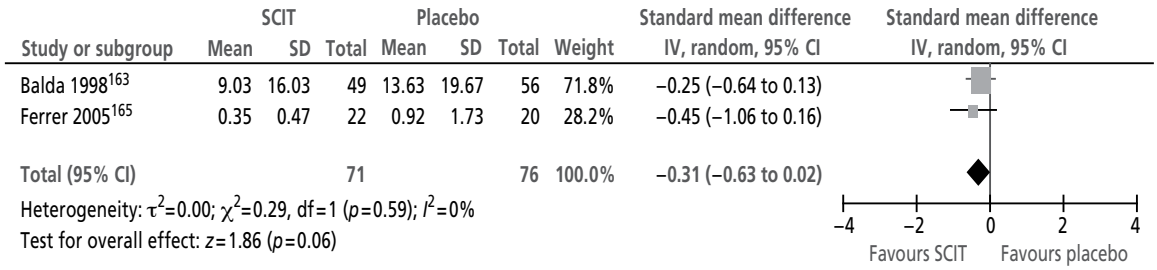

FIGURE 42 Subcutaneous immunotherapy vs placebo, <5μg, MS.

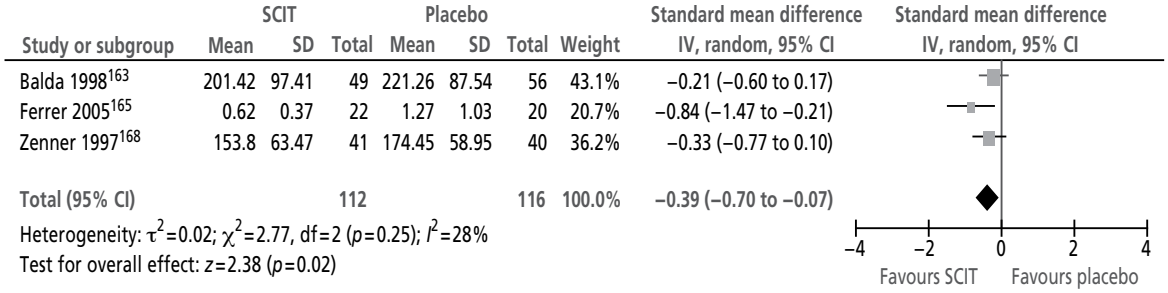

FIGURE 43 Subcutaneous immunotherapy vs placebo, <5μg, SMSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Bodtger 2002[169]	2.2	1	16	3.3	1.4	17	13.5%	−0.88 (−1.60 to −0.16)
Charpin 2007[142]	3.3	2.42	14	5.06	2.66	14	11.9%	−0.67 (−1.44 to 0.09)
Jutel 2005[166]	3.93	3.28	29	5.82	3.44	28	24.8%	−0.55 (−1.08 to −0.02)
Kuna 2011[152]	85	140	25	140	240	19	19.4%	−0.29 (−0.88 to 0.31)
Pauli 2008[154]	0	6.8	33	3.41	7.1	36	30.3%	−0.48 (−0.96 to −0.00)
Total (95% CI)			117			114	100.0%	−0.54 (−0.80 to −0.27)

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.71$, df=4 ($p=0.79$); $I^2=0\%$
Test for overall effect: $z=4.00$ ($p<0.0001$)

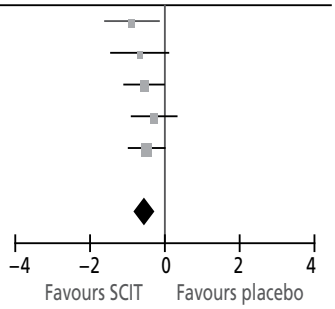

FIGURE 44 Subcutaneous immunotherapy vs placebo, 5–20 μg, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Bodtger 2002[169]	9.9	7	17	14.5	8.5	17	13.2%	−0.58 (−1.26 to 0.11)
Charpin 2007[142]	3.98	4.15	14	5.23	4.41	14	11.3%	−0.28 (−1.03 to 0.46)
Jutel 2005[166]	2.73	4.48	29	3.78	4.92	28	23.0%	−0.22 (−0.74 to 0.30)
Kuna 2011[152]	2.3	5	25	21.4	35	19	16.2%	−0.81 (−1.43 to −0.19)
Mirone 2004[176]	0.7	1.4	11	2.2	3.1	12	8.9%	−0.59 (−1.43 to 0.25)
Pauli 2008[154]	0	4.6	33	1.9	4.8	36	27.4%	−0.40 (−0.88 to 0.08)
Total (95% CI)			129			126	100.0%	−0.45 (−0.70 to −0.20)

Heterogeneity: $\tau^2=0.00$; $\chi^2=2.49$, df=5 ($p=0.78$); $I^2=0\%$
Test for overall effect: $z=3.54$ ($p=0.0004$)

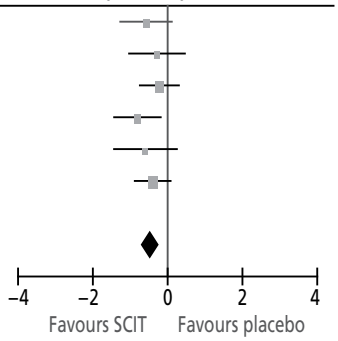

FIGURE 45 Subcutaneous immunotherapy vs placebo, 5–20 μg, MSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Frew 2006[161]	3.31	2.42	187	4.59	2.93	89	37.9%	−0.49 (−0.75 to −0.24)
Ortolani 1994[167]	0.61	0.12	18	2.3	0.98	17	29.9%	−2.40 (−3.29 to −1.51)
Walker 2001[173]	−1212	2632	17	−115	1159	13	32.3%	−0.50 (−1.24 to 0.23)
Total (95% CI)			222			119	100.0%	−1.06 (−2.08 to −0.05)

Heterogeneity: $\tau^2=0.69$; $\chi^2=16.37$, df=2 ($p=0.0003$); $I^2=88\%$
Test for overall effect: $z=2.06$ ($p=0.04$)

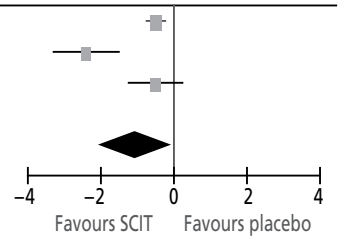

FIGURE 46 Subcutaneous immunotherapy vs placebo, >20 μg, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Frew 2006[161]	2.93	2.95	187	4.29	3.53	89	77.4%	−0.43 (−0.69 to −0.18)
Walker 2001[173]	−1308	983	16	101	1899	13	22.6%	−0.94 (−1.71 to −0.16)
Total (95% CI)			203			102	100.0%	−0.55 (−0.96 to −0.13)

Heterogeneity: $\tau^2=0.04$; $\chi^2=1.47$, df=1 ($p=0.23$); $I^2=32\%$
Test for overall effect: $z=2.58$ ($p=0.010$)

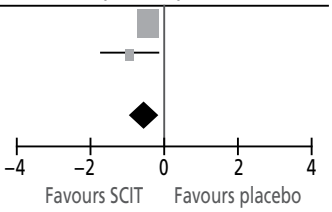

FIGURE 47 Subcutaneous immunotherapy vs placebo, >20μg, MSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Bousquet 1990[170]	63.6	32.5	20	108.6	33.2	18	9.2%	−1.34 (−2.05 to −0.63)
Brewczynski 1999[171]	59.5	32.6	10	122.4	85.13	8	5.7%	−0.98 (−1.97 to 0.02)
Corrigan 2005[164]	166.5	114.93	77	218	135.39	77	18.7%	−0.41 (−0.73 to −0.09)
Drachenberg 2001[91]	0.75	0.44	74	0.95	0.41	50	17.4%	−0.46 (−0.83 to −0.10)
Jutel 2005[166]	3.93	3.28	29	5.82	3.44	28	12.8%	−0.55 (−1.08 to −0.02)
Ortolani 1984[174]	2.01	0.57	8	5.86	1.63	7	2.5%	−3.06 (−4.69 to −1.43)
Varney 1991[172]	1531	1875	19	2230	856	16	9.8%	−0.46 (−1.13 to 0.22)
Walker 2001[173]	−1212	2632	17	−115	1159	13	8.8%	−0.50 (−1.24 to 0.23)
Zenner 1997[168]	82.24	64.38	41	115.98	83.67	40	15.1%	−0.45 (−0.89 to −0.01)
Total (95% CI)			295			257	100.0%	−0.64 (−0.91 to −0.37)

Heterogeneity: $\tau^2=0.07$; $\chi^2=15.84$, df=8 ($p=0.04$); $I^2=49\%$
Test for overall effect: $z=4.64$ ($p<0.00001$)

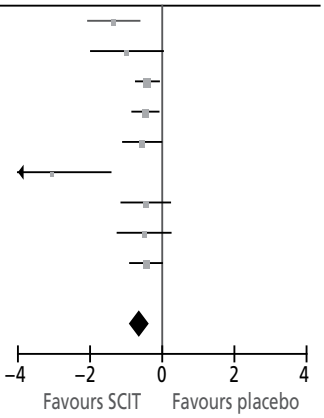

FIGURE 48 Subcutaneous immunotherapy vs placebo, grass pollen, SSs.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Bousquet 1990[170]	38.6	37.6	20	66.4	51.7	18	12.9%	−0.61 (−1.26 to 0.05)
Brewczynski 1999[171]	17.2	10.4	10	36.8	35.46	8	9.6%	−0.76 (−1.73 to 0.22)
Corrigan 2005[164]	68.58	96.15	77	101.21	126.01	77	16.3%	−0.29 (−0.61 to 0.03)
Dolz 1996[175]	6	6.07	18	48.66	17.95	10	7.3%	−3.56 (−4.82 to −2.29)
Drachenberg 2001[91]	0.54	0.71	74	0.71	0.77	50	15.9%	−0.23 (−0.59 to 0.13)
Jutel 2005[166]	2.73	4.48	29	3.78	4.92	28	14.3%	−0.22 (−0.74 to 0.30)
Varney 1991[172]	2146	2513	19	14,491	15,066	16	12.1%	−1.17 (−1.89 to −0.44)
Walker 2001[173]	−1308	983	16	101	1899	13	11.5%	−0.94 (−1.71 to −0.16)
Total (95% CI)			263			220	100.0%	−0.77 (−1.22 to −0.33)

Heterogeneity: $\tau^2=0.29$; $\chi^2=32.04$, df=7 ($p<0.0001$); $I^2=78\%$
Test for overall effect: $z=3.41$ ($p=0.0006$)

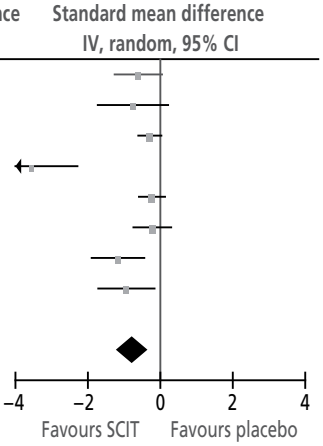

FIGURE 49 Subcutaneous immunotherapy vs placebo, grass pollen, MSs.

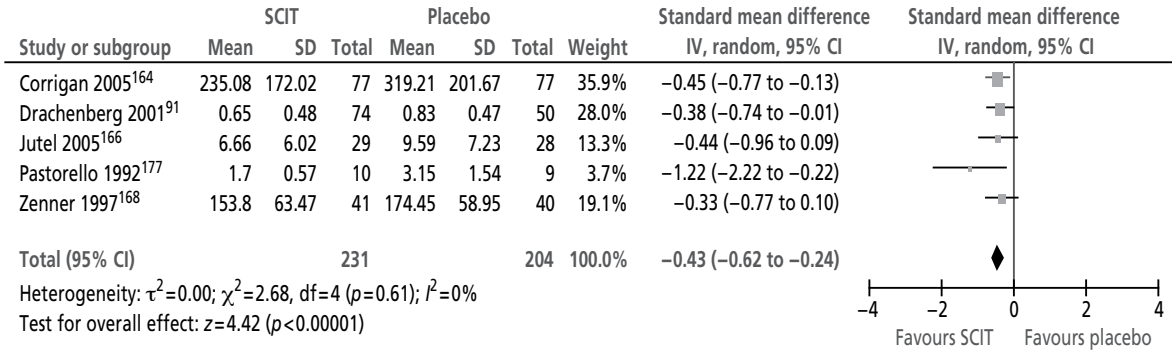

FIGURE 50 Subcutaneous immunotherapy vs placebo, grass pollen, SMSs.

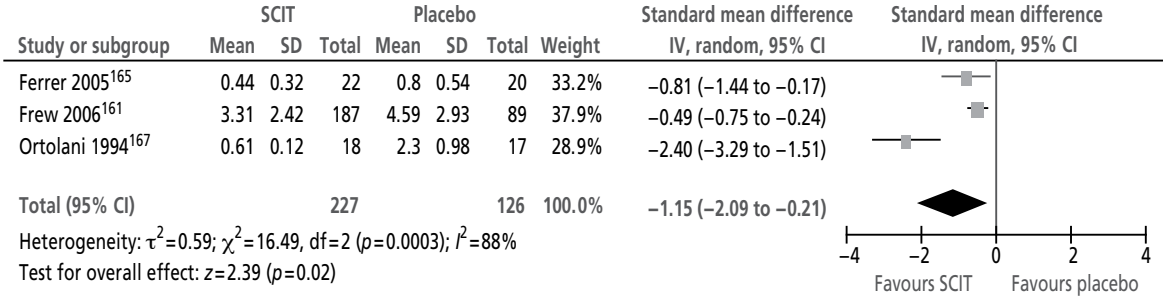

FIGURE 51 Subcutaneous immunotherapy vs placebo, *Parietaria*, SSs.

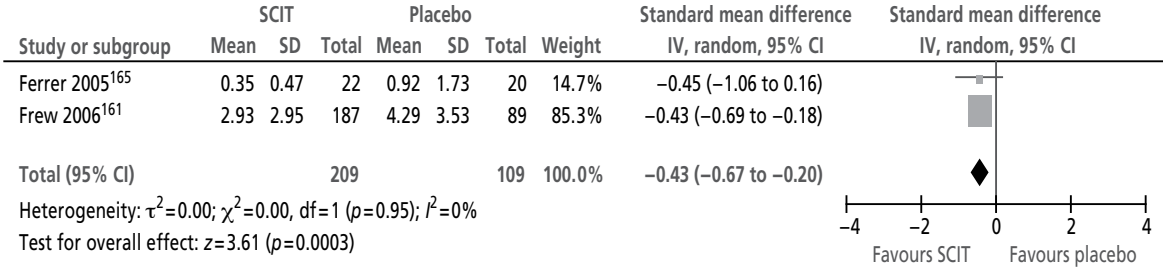

FIGURE 52 Subcutaneous immunotherapy vs placebo, *Parietaria*, MSs.

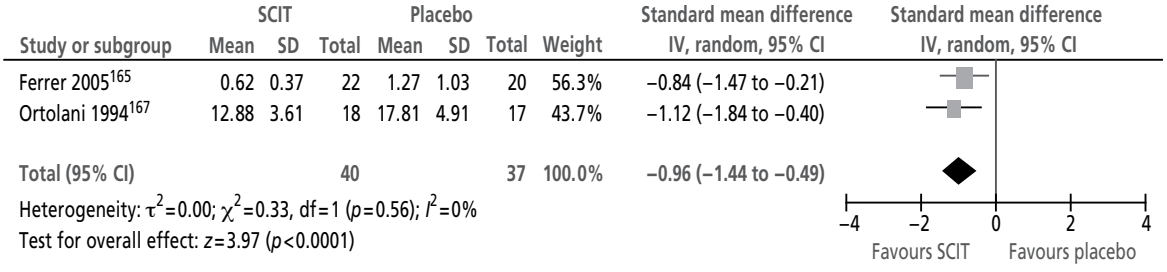

FIGURE 53 Subcutaneous immunotherapy vs placebo, *Parietaria*, SMSs.

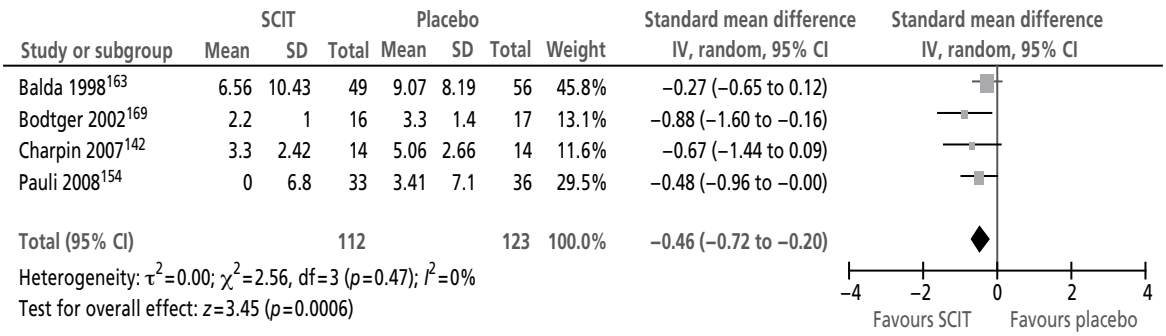

FIGURE 54 Subcutaneous immunotherapy vs placebo, tree pollen, SSs.

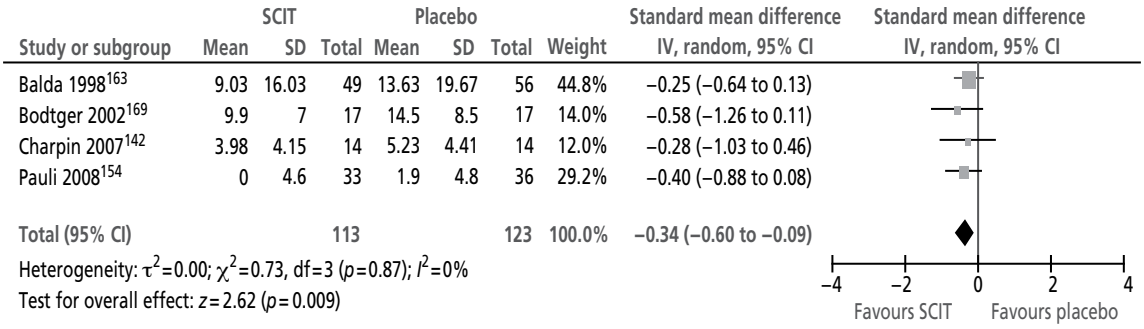

FIGURE 55 Subcutaneous immunotherapy vs placebo, tree pollen, MSs.

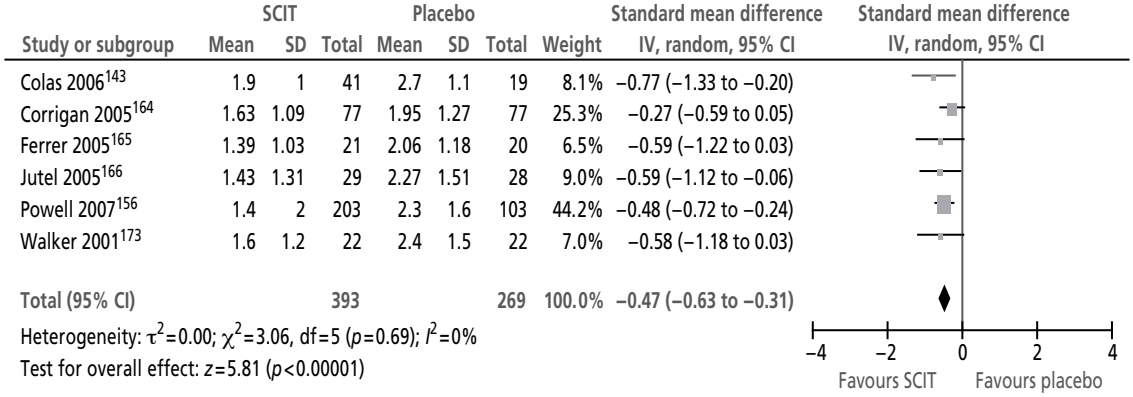

FIGURE 56 Subcutaneous immunotherapy vs placebo, QoL, >12 months.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Creticos 2006[146]	0.5	0.6	9	1.6	1.2	9	4.5%	−1.10 (−2.11 to −0.09)
Jutel 2005[166]	1.43	1.31	29	2.27	1.51	28	16.2%	−0.59 (−1.12 to −0.06)
Powell 2007[156]	1.4	2	203	2.3	1.6	103	79.3%	−0.48 (−0.72 to −0.24)
Total (95% CI)			241			140	100.0%	−0.52 (−0.74 to −0.31)

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.46$, df=2 ($p=0.48$); $I^2=0\%$
Test for overall effect: $z=4.80$ ($p<0.00001$)

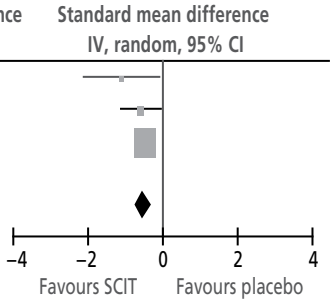

FIGURE 57 Subcutaneous immunotherapy vs placebo, QoL, major allergen content, 5–20 μg.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Colas 2006[143]	1.9	1	41	2.7	1.1	19	15.0%	−0.77 (−1.33 to −0.20)
Frew 2006[161]	1.4	1.42	183	2.29	1.34	92	72.1%	−0.64 (−0.89 to −0.38)
Walker 2001[173]	1.6	1.2	22	2.4	1.5	22	12.9%	−0.58 (−1.18 to 0.03)
Total (95% CI)			246			133	100.0%	−0.65 (−0.87 to −0.43)

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.22$, df=2 ($p=0.89$); $I^2=0\%$
Test for overall effect: $z=5.84$ ($p<0.00001$)

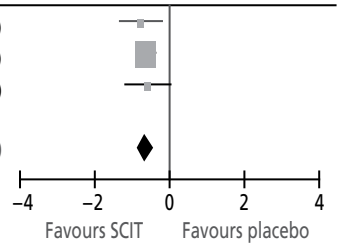

FIGURE 58 Subcutaneous immunotherapy vs placebo, QoL, major allergen content, >20 μg.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Corrigan 2005[164]	1.63	1.09	77	1.95	1.27	77	29.6%	−0.27 (−0.59 to 0.05)
Jutel 2005[166]	1.43	1.31	29	2.27	1.51	28	10.6%	−0.59 (−1.12 to −0.06)
Powell 2007[156]	1.4	2	203	2.3	1.6	103	51.7%	−0.48 (−0.72 to −0.24)
Walker 2001[173]	1.6	1.2	22	2.4	1.5	22	8.2%	−0.58 (−1.18 to 0.03)
Total (95% CI)			331			230	100.0%	−0.44 (−0.61 to −0.26)

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.71$, df=3 ($p=0.64$); $I^2=0\%$
Test for overall effect: $z=4.95$ ($p<0.00001$)

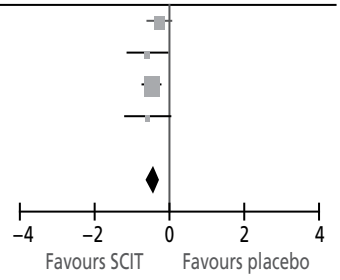

FIGURE 59 Subcutaneous immunotherapy vs placebo, QoL, grass.

Study or subgroup	SCIT Mean	SCIT SD	SCIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Ferrer 2005[165]	1.39	1.03	21	2.06	1.18	20	14.3%	−0.59 (−1.22 to 0.03)
Frew 2006[161]	1.4	1.42	183	2.29	1.34	92	85.7%	−0.64 (−0.89 to −0.38)
Total (95% CI)			204			112	100.0%	−0.63 (−0.87 to −0.39)

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.02$, df=1 ($p=0.90$); $I^2=0\%$
Test for overall effect: $z=5.21$ ($p<0.00001$)

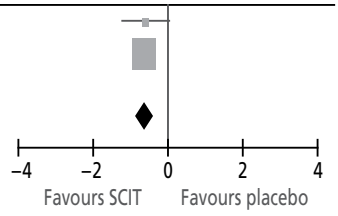

FIGURE 60 Subcutaneous immunotherapy vs placebo, QoL, *Parietaria*.

Sublingual immunotherapy

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	3.83	4.9	19	3.71	2.7	17	2.0%	0.03 (–0.63 to 0.68)
Andre 2003[95]	2.27	1.42	48	3.09	2.14	51	3.7%	–0.45 (–0.84 to –0.05)
Ariano 2001[96]	1.8	1.75	10	5.38	1.57	10	0.8%	–2.06 (–3.19 to –0.93)
Bowen 2004[97]	3.95	2.45	37	5.03	2.54	39	3.2%	–0.43 (–0.88 to 0.03)
Casanovas 1994[98]	5.46	3.56	9	10.98	7.1	6	0.8%	–1.00 (–2.11 to 0.12)
Cortellini 2010[190]	182	67	15	315	115	11	1.2%	–1.43 (–2.31 to –0.54)
D'Ambrosio 1999[99]	509	514.2	14	897.06	678.2	16	1.7%	–0.62 (–1.36 to 0.12)
Dahl 2006[100]	2.1	1.7	61	3.3	2.2	32	3.3%	–0.63 (–1.07 to –0.19)
de Blay 2003[101]	20.55	15.88	33	23.49	18.76	42	3.2%	–0.17 (–0.62 to 0.29)
Di Rienzo 2006[102]	0.4	0.3	18	0.8	0.5	14	1.6%	–0.98 (–1.72 to –0.23)
Didier 2007[24]	3.58	2.976	136	4.93	3.229	148	5.5%	–0.43 (–0.67 to –0.20)
Didier 2011[25]	2.67	3.63	149	4.03	3.71	165	5.7%	–0.37 (–0.59 to –0.15)
Drachenberg 2001[91]	29.5	24.2	37	36.4	30.4	12	2.0%	–0.26 (–0.92 to 0.39)
Dubakiene 2003[103]	0.48	0.3	47	0.64	0.43	53	3.7%	–0.42 (–0.82 to –0.03)
Durham 2006[104]	2.48	2.1	131	2.96	2.09	129	5.4%	–0.23 (–0.47 to 0.02)
Durham 2010[200]	2.7	2.1	142	3.7	2.1	115	5.4%	–0.47 (–0.72 to –0.23)
Feliziani 1995[105]	109.7	92.46	18	215.8	114.2	16	1.7%	–1.00 (–1.72 to –0.28)
Hordijk 1998[106]	3.21	3.05	35	5.13	3.6	36	3.0%	–0.57 (–1.04 to –0.09)
Lima 2002[107]	2494	2326	28	2465	1537	28	2.7%	0.01 (–0.51 to 0.54)
Nelson 2011[192]	3.83	4.07	184	4.69	4.32	207	6.0%	–0.20 (–0.40 to –0.01)
Ott 2009[108]	–1.02	4.54	123	1.32	4.54	60	4.6%	–0.51 (–0.83 to –0.20)
Palma-Carlos 2006[109]	31.15	32.61	17	55.86	50.48	16	1.8%	–0.57 (–1.27 to 0.13)
Panzner 2008[110]	111.35	114.91	20	321.6	211.22	15	1.6%	–1.26 (–2.00 to –0.52)
Passalacqua 1999[111]	189	113	15	191	108	15	1.7%	–0.02 (–0.73 to 0.70)
Peter 2009[112]	0.732	0.483	176	0.78	0.544	189	5.9%	–0.09 (–0.30 to 0.11)
Pfaar 2008[113]	146.2	123	42	236.2	133.6	48	3.4%	–0.69 (–1.12 to –0.27)
Pradalier 1999[114]	2.33	1.6	63	2.65	2	63	4.2%	–0.18 (–0.53 to 0.17)
Skoner 2010[196]	0.19	1.16	33	1	2.3	36	3.0%	–0.43 (–0.91 to 0.04)
Smith 2004[115]	2.58	2.48	45	2.32	1.67	51	3.7%	0.12 (–0.28 to 0.52)
Troise 1995[116]	87	76	15	102	58	16	1.8%	–0.22 (–0.92 to 0.49)
Vervloet 2006[117]	2.68	1.64	19	2.44	2.06	19	2.1%	0.13 (–0.51 to 0.76)
Voltolini 2001[197]	130	154	15	83	79	15	1.7%	0.37 (–0.35 to 1.10)
Wessner 2001[118]	0.32	0.26	14	0.51	0.38	18	1.7%	–0.56 (–1.27 to 0.16)
Total (95% CI)			1768			1708	100.0%	–0.38 (–0.49 to –0.27)

Heterogeneity: τ^2=0.04; χ^2=62.78, df=32 (p=0.0009); I^2=49%
Test for overall effect: z=6.94 (p<0.00001)

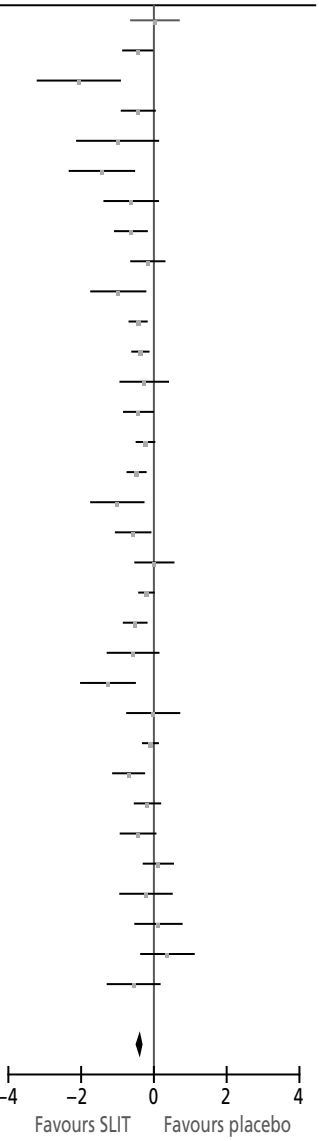

FIGURE 61 Sublingual immunotherapy vs placebo, adults, SSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	0.44	1.2	19	0.14	0.24	17	2.5%	0.33 (−0.33 to 0.99)
Andre 2003[95]	2.41	3.09	48	4	4.24	51	4.7%	−0.42 (−0.82 to −0.02)
Ariano 2001[96]	2.5	2.1	10	5.3	4.9	10	1.5%	−0.71 (−1.62 to 0.20)
Bowen 2004[97]	1.05	1.6	37	1.26	1.24	39	4.1%	−0.15 (−0.60 to 0.30)
Casanovas 1994[98]	1.69	2.46	9	2.13	2.22	6	1.2%	−0.17 (−1.21 to 0.86)
Cortellini 2010[190]	41	34	15	94	37	11	1.5%	−1.45 (−2.34 to −0.57)
D'Ambrosio 1999[99]	48.1	46.6	14	124.37	121	16	2.0%	−0.79 (−1.54 to −0.04)
Dahl 2006[100]	2.4	3.9	61	4.2	4.1	32	4.3%	−0.45 (−0.88 to −0.02)
de Blay 2003[101]	3.48	5.37	33	7.57	8.23	42	4.0%	−0.57 (−1.03 to −0.10)
Di Rienzo 2006[102]	3.2	0.7	18	4.9	1.5	14	1.8%	−1.48 (−2.28 to −0.68)
Didier 2011[25]	0.31	3.63	149	0.47	3.71	165	7.4%	−0.04 (−0.26 to 0.18)
Drachenberg 2001[91]	12.5	18.7	37	23.8	26.4	12	2.5%	−0.54 (−1.20 to 0.12)
Dubakiene 2003[103]	0.13	0.17	47	0.17	0.19	53	4.8%	−0.22 (−0.61 to 0.17)
Durham 2006[104]	1.4	2.13	131	2.03	2.39	129	7.0%	−0.28 (−0.52 to −0.03)
Durham 2010[200]	1.82	3.01	160	3.04	3.01	127	7.2%	−0.40 (−0.64 to −0.17)
Feliziani 1995[105]	24.06	25.72	18	75.9	50.3	16	2.0%	−1.29 (−2.04 to −0.54)
Hordijk 1998[106]	0.16	0.37	35	0.31	0.45	36	3.9%	−0.36 (−0.83 to 0.11)
Lima 2002[107]	2334	2616	28	2837	2052	28	3.4%	−0.21 (−0.74 to 0.31)
Nelson 2011[192]	1.25	2.71	184	1.7	2.88	207	7.8%	−0.16 (−0.36 to 0.04)
Ott 2009[108]	−0.28	11.55	123	−0.92	2.47	60	6.0%	0.07 (−0.24 to 0.38)
Palma-Carlos 2006[109]	15.38	32.98	17	44.57	65.05	16	2.3%	−0.56 (−1.26 to 0.14)
Passalacqua 1999[111]	42	49.5	15	83	65	15	2.1%	−0.69 (−1.43 to 0.05)
Pradalier 1999[114]	1.77	2.3	63	2.13	2.7	63	5.4%	−0.14 (−0.49 to 0.21)
Skoner 2010[196]	0.0003	1.64	33	0.63	1.06	36	3.8%	−0.46 (−0.93 to 0.02)
Troise 1995[116]	17	21	15	33	33	16	2.2%	−0.56 (−1.28 to 0.16)
Vervloet 2006[117]	3.39	3.94	19	4.71	5	19	2.6%	−0.29 (−0.93 to 0.35)
Voltolini 2001[197]	22	30	15	39	34	15	2.1%	−0.52 (−1.25 to 0.21)
Total (95% CI)			**1353**			**1251**	**100.0%**	**−0.35 (−0.47 to −0.23)**

Heterogeneity: $\tau^2=0.04$; $\chi^2=47.67$, df=26 ($p=0.006$); $I^2=45\%$
Test for overall effect: $z=5.76$ ($p<0.00001$)

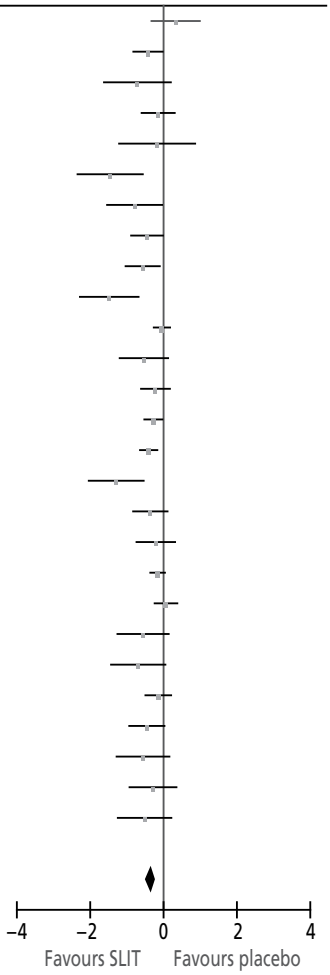

FIGURE 62 Sublingual immunotherapy vs placebo, adults, MSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Cortellini 2010[190]	231	113	15	414	173	11	3.8%	−1.26 (−2.12 to −0.39)
Didier 2011[25]	3.46	3.625	149	5.28	3.942	165	28.0%	−0.48 (−0.70 to −0.25)
Durham 2010[200]	0.17	0.19	160	0.26	0.19	127	26.7%	−0.47 (−0.71 to −0.24)
Nelson 2011[192]	5.08	5.4	184	6.39	4.8	207	31.0%	−0.26 (−0.46 to −0.06)
Skoner 2010[196]	0.19	2.32	33	1.63	2.99	36	10.5%	−0.53 (−1.01 to −0.05)
Total (95% CI)			**541**			**546**	**100.0%**	**−0.44 (−0.62 to −0.27)**

Heterogeneity: $\tau^2=0.02$; $\chi^2=6.82$, df=4 ($p=0.15$); $I^2=41\%$
Test for overall effect: $z=4.98$ ($p<0.00001$)

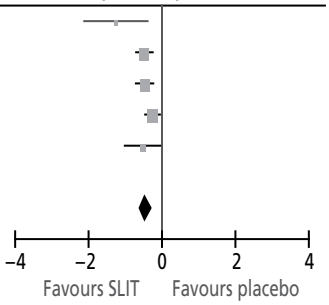

FIGURE 63 Sublingual immunotherapy vs placebo, adults, SMSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	3.71	4.88	149	4.91	5.03	158	22.9%	−0.24 (−0.47 to −0.02)
Bufe 2004[84]	1.54	0.77	68	1.59	0.96	64	9.9%	−0.06 (−0.40 to 0.28)
Bufe 2009[85]	2.67	2.38	117	3.17	2.14	121	17.8%	−0.22 (−0.48 to 0.03)
La Rosa 1999[86]	1.21	1.66	16	1.61	1.56	17	2.5%	−0.24 (−0.93 to 0.44)
Roder 2007[87]	2.45	1.48	91	2.74	1.66	77	12.5%	−0.18 (−0.49 to 0.12)
Rolinck-Werninghaus 2004[88]	13.71	23.12	39	12.66	21.65	38	5.8%	0.05 (−0.40 to 0.49)
Valovirta 2006[90]	1.5	1.4	27	2.2	1.4	29	4.1%	−0.49 (−1.03 to 0.04)
Vourdas 1998[89]	1.07	1.63	34	1.38	2.01	32	4.9%	−0.17 (−0.65 to 0.32)
Wahn 2009[26]	3.25	2.86	131	4.51	2.931	135	19.6%	−0.43 (−0.68 to −0.19)
Total (95% CI)			672			671	100.0%	−0.24 (−0.35 to −0.13)

Heterogeneity: $\tau^2=0.00$; $\chi^2=6.22$, df=8 ($p=0.62$); $I^2=0\%$
Test for overall effect: $z=4.37$ ($p<0.0001$)

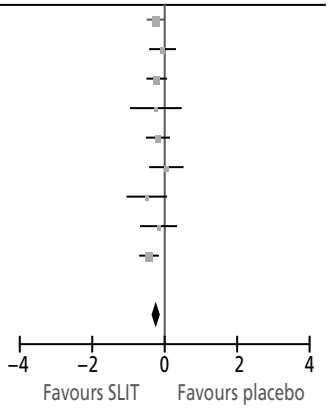

FIGURE 64 Sublingual immunotherapy vs placebo, children, SSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	0.91	3.66	149	1.33	2.51	158	19.9%	−0.13 (−0.36 to 0.09)
Bufe 2004[84]	0.24	0.19	68	0.18	0.019	64	13.2%	0.44 (0.09 to 0.78)
Bufe 2009[85]	2.13	3.48	117	2.53	3.03	121	17.9%	−0.12 (−0.38 to 0.13)
La Rosa 1999[86]	2.28	3.89	16	2.36	3.95	17	4.9%	−0.02 (−0.70 to 0.66)
Rolinck-Werninghaus 2004[88]	2.54	3.58	39	2.85	3.87	38	9.5%	−0.08 (−0.53 to 0.36)
Valovirta 2006[90]	2.9	3.4	27	3.9	4.6	29	7.5%	−0.24 (−0.77 to 0.28)
Vourdas 1998[89]	1.39	3.41	34	1.77	3.85	32	8.5%	−0.10 (−0.59 to 0.38)
Wahn 2009[26]	0.6	0.611	131	0.79	0.647	135	18.7%	−0.30 (−0.54 to −0.06)
Total (95% CI)			581			594	100.0%	−0.08 (−0.25 to 0.08)

Heterogeneity: $\tau^2=0.02$; $\chi^2=12.33$, df=7 ($p=0.09$); $I^2=43\%$
Test for overall effect: $z=0.99$ ($p=0.32$)

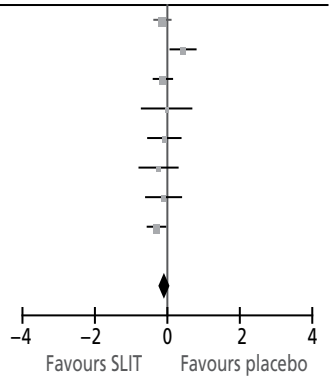

FIGURE 65 Sublingual immunotherapy vs placebo, children, MSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	3.71	4.88	149	4.91	5.03	158	12.2%	−0.24 (−0.47 to −0.02)
Bowen 2004[97]	3.95	2.45	37	5.03	2.54	39	5.9%	−0.43 (−0.88 to 0.03)
Casanovas 1994[98]	5.46	3.56	9	10.98	7.1	6	1.3%	−1.00 (−2.11 to 0.12)
Dahl 2006[93]	2.1	1.7	61	3.3	2.2	32	6.2%	−0.63 (−1.07 to −0.19)
Di Rienzo 2006[102]	0.4	0.3	18	0.8	0.5	14	2.7%	−0.98 (−1.72 to −0.23)
Dubakiene 2003[103]	0.48	0.3	47	0.64	0.43	53	7.0%	−0.42 (−0.82 to −0.03)
Durham 2006[104]	2.48	2.1	131	2.96	2.09	129	11.5%	−0.23 (−0.47 to 0.02)
Feliziani 1995[105]	109.7	92.46	18	215.8	114.2	16	2.9%	−1.00 (−1.72 to −0.28)
Hordijk 1998[106]	3.21	3.05	35	5.13	3.6	36	5.5%	−0.57 (−1.04 to −0.09)
Peter 2009[112]	0.732	0.483	176	0.78	0.544	189	13.0%	−0.09 (−0.30 to 0.11)
Pradalier 1999[114]	2.33	1.6	63	2.65	2	63	8.2%	−0.18 (−0.53 to 0.17)
Skoner 2010[196]	0.19	1.16	33	1	2.3	36	5.5%	−0.43 (−0.91 to 0.04)
Vervloet 2006[117]	2.68	1.64	19	2.44	2.06	19	3.6%	0.13 (−0.51 to 0.76)
Voltolini 2001[197]	130	154	15	83	79	15	2.9%	0.37 (−0.35 to 1.10)
Wahn 2009[26]	3.25	2.86	131	4.51	2.931	135	11.5%	−0.43 (−0.68 to −0.19)
Total (95% CI)			942			940	100.0%	−0.34 (−0.47 to −0.20)

Heterogeneity: $\tau^2=0.02$; $\chi^2=23.96$, df=14 ($p=0.05$); $I^2=42\%$

Test for overall effect: $z=4.94$ ($p<0.00001$)

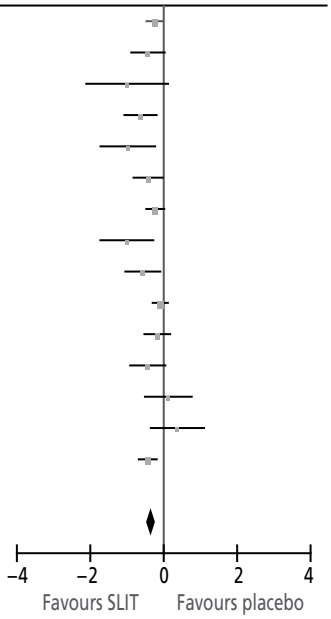

FIGURE 66 Sublingual immunotherapy vs placebo, <6 months, SSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	0.91	3.66	149	1.33	2.51	158	14.5%	−0.13 (−0.36 to 0.09)
Bowen 2004[97]	1.05	1.6	37	1.26	1.24	39	6.7%	−0.15 (−0.60 to 0.30)
Casanovas 1994[98]	1.69	2.46	9	2.13	2.22	6	1.7%	−0.17 (−1.21 to 0.86)
Dahl 2006[93]	2.4	3.9	61	4.2	4.1	32	7.1%	−0.45 (−0.88 to −0.02)
Di Rienzo 2006[102]	3.2	0.7	18	4.9	1.5	14	2.7%	−1.48 (−2.28 to −0.68)
Dubakiene 2003[103]	0.13	0.17	47	0.17	0.19	53	8.1%	−0.22 (−0.61 to 0.17)
Durham 2006[104]	1.4	2.13	131	2.03	2.39	129	13.5%	−0.28 (−0.52 to −0.03)
Feliziani 1995[105]	24.06	25.72	18	75.9	50.3	16	3.0%	−1.29 (−2.04 to −0.54)
Hordijk 1998[106]	0.16	0.37	35	0.31	0.45	36	6.4%	−0.36 (−0.83 to 0.11)
Pradalier 1999[114]	1.77	2.3	63	2.13	2.7	63	9.4%	−0.14 (−0.49 to 0.21)
Skoner 2010[196]	0.0003	1.64	33	0.63	1.06	36	6.2%	−0.46 (−0.93 to 0.02)
Vervloet 2006[117]	3.39	3.94	19	4.71	5	19	3.9%	−0.29 (−0.93 to 0.35)
Voltolini 2001[195]	22	30	15	39	34	15	3.1%	−0.52 (−1.25 to 0.21)
Wahn 2009[26]	0.6	0.611	131	0.79	0.647	135	13.6%	−0.30 (−0.54 to −0.06)
Total (95% CI)			766			751	100.0%	−0.33 (−0.47 to −0.19)

Heterogeneity: $\tau^2=0.02$; $\chi^2=19.96$, df=13 ($p=0.10$); $I^2=35\%$

Test for overall effect: $z=4.67$ ($p<0.00001$)

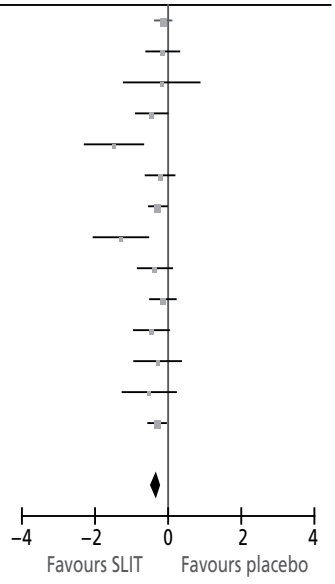

FIGURE 67 Sublingual immunotherapy vs placebo, <6 months, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	4.62	6.1	149	6.25	6.3	158	82.1%	−0.26 (−0.49 to −0.04)
Skoner 2010[196]	0.19	2.32	33	1.63	2.99	36	17.9%	−0.53 (−1.01 to −0.05)
Total (95% CI)			182			194	100.0%	−0.31 (−0.51 to −0.11)

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.97$, df=1 ($p=0.32$); $I^2=0\%$
Test for overall effect: $z=2.98$ ($p=0.003$)

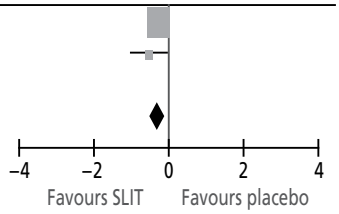

FIGURE 68 Sublingual immunotherapy vs placebo, <6 months, SMSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	3.83	4.9	19	3.71	2.7	17	4.3%	0.03 (−0.63 to 0.68)
Andre 2003[95]	2.27	1.42	48	3.09	2.14	51	8.4%	−0.45 (−0.84 to −0.05)
Ariano 2001[96]	1.8	1.75	10	5.38	1.57	10	1.7%	−2.06 (−3.19 to −0.93)
Bufe 2004[84]	1.54	0.77	68	1.59	0.96	64	9.9%	−0.06 (−0.40 to 0.28)
Bufe 2009[85]	2.67	2.38	117	3.17	2.14	121	12.6%	−0.22 (−0.48 to 0.03)
Cortellini 2010[190]	182	67	15	315	115	11	2.6%	−1.43 (−2.31 to −0.54)
D'Ambrosio 1999[99]	509	514.2	14	897.06	678.2	16	3.5%	−0.62 (−1.36 to 0.12)
de Blay 2003[101]	20.55	15.88	33	23.49	18.76	42	7.1%	−0.17 (−0.62 to 0.29)
Didier 2007[25]	3.58	2.976	136	4.93	3.229	148	13.3%	−0.43 (−0.67 to −0.20)
Drachenberg 2001[91]	29.5	24.2	37	36.4	30.4	12	4.3%	−0.26 (−0.92 to 0.39)
Nelson 2011[192]	3.83	4.07	184	4.69	4.32	207	14.6%	−0.20 (−0.40 to −0.01)
Passalacqua 1999[111]	189	113	15	191	108	15	3.7%	−0.02 (−0.73 to 0.70)
Troise 1995[116]	87	76	15	102	58	16	3.8%	−0.22 (−0.92 to 0.49)
Vourdas 1998[89]	1.07	1.63	34	1.38	2.01	32	6.6%	−0.17 (−0.65 to 0.32)
Wessner 2001[118]	0.32	0.26	14	0.51	0.38	18	3.7%	−0.56 (−1.27 to 0.16)
Total (95% CI)			759			780	100.0%	−0.31 (−0.47 to −0.16)

Heterogeneity: $\tau^2=0.03$; $\chi^2=23.94$, df=14 ($p=0.05$); $I^2=42\%$
Test for overall effect: $z=4.03$ ($p<0.0001$)

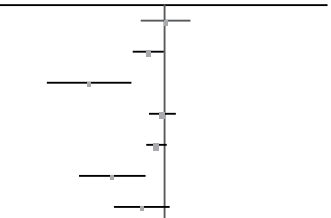

FIGURE 69 Sublingual immunotherapy vs placebo, 6–12 months, SSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	0.44	1.2	19	0.14	0.24	17	6.3%	0.33 (−0.33 to 0.99)
Andre 2003[95]	2.41	3.09	48	4	4.24	51	9.7%	−0.42 (−0.82 to −0.02)
Ariano 2001[96]	2.5	2.1	10	5.3	4.9	10	4.2%	−0.71 (−1.62 to 0.20)
Bufe 2004[84]	0.24	0.19	68	0.18	0.019	64	10.5%	0.44 (0.09 to 0.78)
Bufe 2009[85]	2.13	3.48	117	2.53	3.03	121	11.9%	−0.12 (−0.38 to 0.13)
Cortellini 2010[190]	41	34	15	94	37	11	4.4%	−1.45 (−2.34 to −0.57)
D'Ambrosio 1999[99]	48.1	46.6	14	124.37	121	16	5.5%	−0.79 (−1.54 to −0.04)
de Blay 2003[101]	3.48	5.37	33	7.57	8.23	42	8.7%	−0.57 (−1.03 to −0.10)
Drachenberg 2001[91]	12.5	18.7	37	23.8	26.4	12	6.3%	−0.54 (−1.20 to 0.12)
Nelson 2011[192]	1.25	2.71	184	1.7	2.88	207	12.6%	−0.16 (−0.36 to 0.04)
Passalacqua 1999[111]	42	49.5	15	83	65	15	5.5%	−0.69 (−1.43 to 0.05)
Troise 1995[116]	17	21	15	33	33	16	5.7%	−0.56 (−1.28 to 0.16)
Vourdas 1998[89]	1.39	3.41	34	1.77	3.85	32	8.5%	−0.10 (−0.59 to 0.38)
Total (95% CI)			609			614	100.0%	−0.31 (−0.53 to −0.08)

Heterogeneity: τ^2=0.09; χ^2=34.63, df=12 (p=0.0005); I^2=65%
Test for overall effect: z=2.70 (p=0.007)

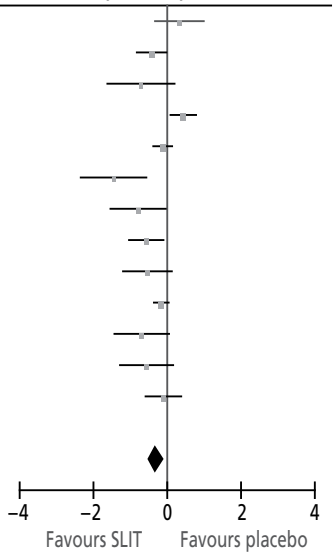

FIGURE 70 Sublingual immunotherapy vs placebo, 6–12 months, MSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Cortellini 2010[190]	231	113	15	414	173	11	40.8%	−1.26 (−2.12 to −0.39)
Nelson 2011[192]	5.08	5.4	184	6.39	4.8	207	59.2%	−0.26 (−0.46 to −0.06)
Total (95% CI)			199			218	100.0%	−0.66 (−1.63 to 0.30)

Heterogeneity: τ^2=0.40; χ^2=4.90, df=1 (p=0.03); I^2=80%
Test for overall effect: z=1.35 (p=0.18)

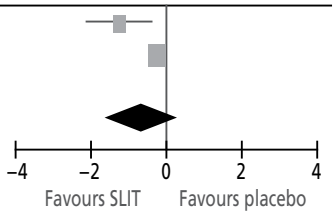

FIGURE 71 Sublingual immunotherapy vs placebo, 6–12 months, SMSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Didier 2011[25]	2.67	3.63	149	4.03	3.71	165	13.8%	−0.37 (−0.59 to −0.15)
Durham 2010[200]	2.7	2.1	142	3.7	2.1	115	13.0%	−0.47 (−0.72 to −0.23)
La Rosa 1999[86]	1.21	1.66	16	1.61	1.56	17	4.5%	−0.24 (−0.93 to 0.44)
Lima 2002[107]	2494	2326	28	2465	1537	28	6.5%	0.01 (−0.51 to 0.54)
Ott 2009[108]	−1.02	4.54	123	1.32	4.54	60	11.1%	−0.51 (−0.83 to −0.20)
Palma-Carlos 2006[109]	31.15	32.61	17	55.86	50.48	16	4.3%	−0.57 (−1.27 to 0.13)
Panzner 2008[110]	111.35	114.91	20	321.6	211.22	15	4.0%	−1.26 (−2.00 to −0.52)
Pfaar 2008[113]	146.2	123	42	236.2	133.6	48	8.3%	−0.69 (−1.12 to −0.27)
Roder 2007[87]	2.45	1.48	91	2.74	1.66	77	11.4%	−0.18 (−0.49 to 0.12)
Rolinck-Werninghaus 2004[88]	13.71	23.12	39	12.66	21.65	38	7.9%	0.05 (−0.40 to 0.49)
Smith 2004[115]	2.58	2.48	45	2.32	1.67	51	8.9%	0.12 (−0.28 to 0.52)
Valovirta 2006[90]	1.5	1.4	27	2.2	1.4	29	6.4%	−0.49 (−1.03 to 0.04)
Total (95% CI)			739			659	100.0%	−0.35 (−0.52 to −0.18)

Heterogeneity: τ^2=0.04; χ^2=22.47, df=11 (p=0.02); I^2=51%
Test for overall effect: z=4.11 (p<0.0001)

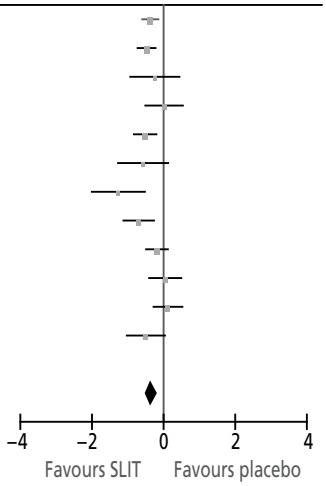

FIGURE 72 Sublingual immunotherapy vs placebo, >12 months, SSs.

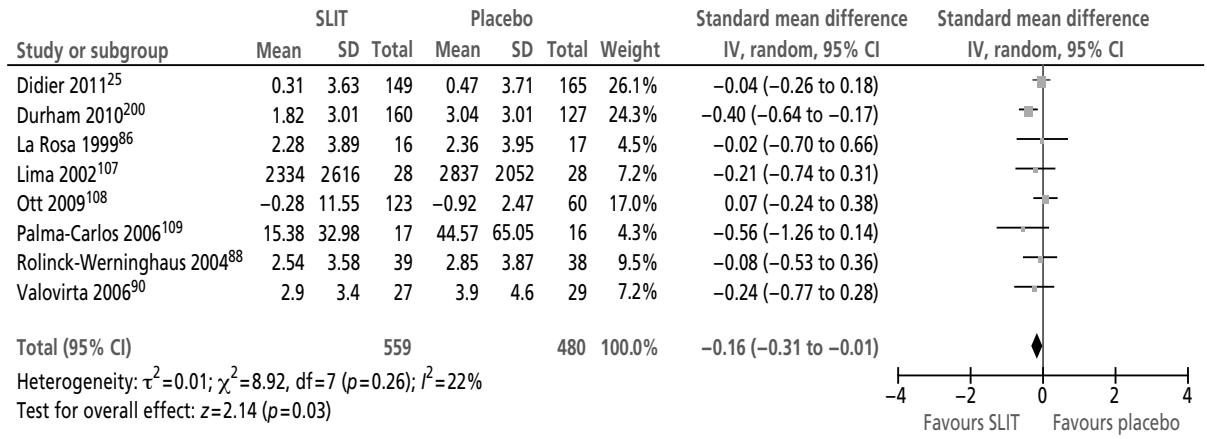

FIGURE 73 Sublingual immunotherapy vs placebo, >12 months, MSs.

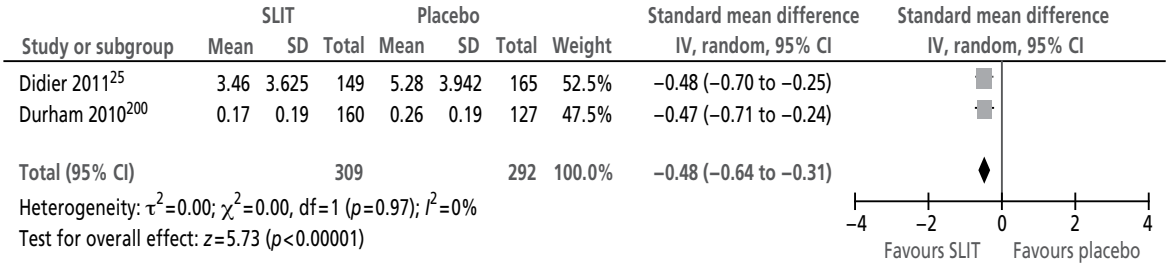

FIGURE 74 Sublingual immunotherapy vs placebo, >12 months, SMSs.

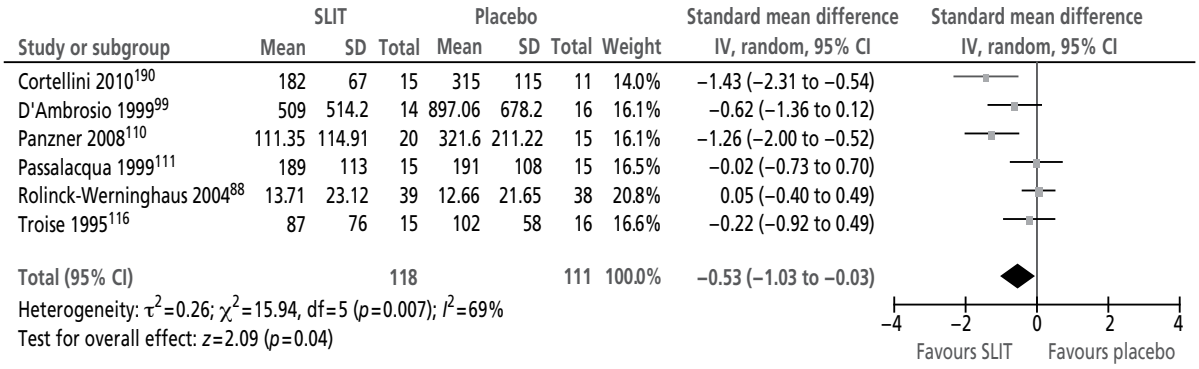

FIGURE 75 Sublingual immunotherapy vs placebo, major allergen content, <5μg, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Cortellini 2010[190]	41	34	15	94	37	11	15.4%	−1.45 (−2.34 to −0.57)
D'Ambrosio 1999[99]	48.1	46.6	14	124.37	121	16	18.6%	−0.79 (−1.54 to −0.04)
Passalacqua 1999[111]	42	49.5	15	83	65	15	18.8%	−0.69 (−1.43 to 0.05)
Rolinck-Werninghaus 2004[88]	2.54	3.58	39	2.85	3.87	38	27.8%	−0.08 (−0.53 to 0.36)
Troise 1995[116]	17	21	15	33	33	16	19.4%	−0.56 (−1.28 to 0.16)
Total (95% CI)			98			96	100.0%	−0.63 (−1.08 to −0.18)

Heterogeneity: $\tau^2=0.14$; $\chi^2=8.64$, df=4 ($p=0.07$); $I^2=54\%$
Test for overall effect: $z=2.74$ ($p=0.006$)

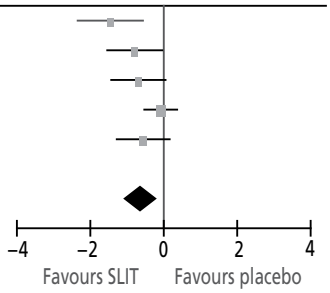

FIGURE 76 Sublingual immunotherapy vs placebo, major allergen content, <5μg, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	3.83	4.9	19	3.71	2.7	17	1.6%	0.03 (−0.63 to 0.68)
Blaiss 2011[189]	3.71	4.88	149	4.91	5.03	158	13.6%	−0.24 (−0.47 to −0.02)
Bufe 2004[84]	1.54	0.77	68	1.59	0.96	64	5.9%	−0.06 (−0.40 to 0.28)
Bufe 2009[85]	2.67	2.38	117	3.17	2.14	121	10.6%	−0.22 (−0.48 to 0.03)
Dahl 2006[100]	2.1	1.7	61	3.3	2.2	32	3.6%	−0.63 (−1.07 to −0.19)
Drachenberg 200[91]	29.5	24.2	37	36.4	30.4	12	1.6%	−0.26 (−0.92 to 0.39)
Dubakiene 2003[103]	0.48	0.3	47	0.64	0.43	53	4.4%	−0.42 (−0.82 to −0.03)
Durham 2006[104]	2.48	2.1	131	2.96	2.09	129	11.6%	−0.23 (−0.47 to 0.02)
Durham 2010[200]	2.7	2.1	142	3.7	2.1	115	11.1%	−0.47 (−0.72 to −0.23)
Nelson 2011[192]	3.83	4.07	184	4.69	4.32	207	17.4%	−0.20 (−0.40 to −0.01)
Pradalier 1999[114]	2.33	1.6	63	2.65	2	63	5.6%	−0.18 (−0.53 to 0.17)
Wahn 2009[26]	3.25	2.86	131	4.51	2.931	135	11.6%	−0.43 (−0.68 to −0.19)
Wessner 2001[118]	0.32	0.26	14	0.51	0.38	18	1.4%	−0.56 (−1.27 to 0.16)
Total (95% CI)			1163			1124	100.0%	−0.29 (−0.37 to −0.20)

Heterogeneity: $\tau^2=0.00$; $\chi^2=11.29$, df=12 ($p=0.50$); $I^2=0\%$
Test for overall effect: $z=6.78$ ($p<0.00001$)

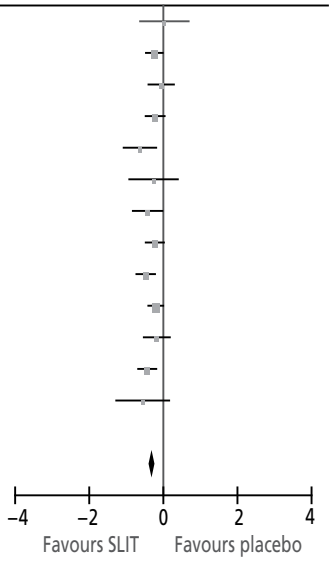

FIGURE 77 Sublingual immunotherapy vs placebo, major allergen content, 5–20μg, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	0.44	1.2	19	0.14	0.24	17	3.0%	0.33 (–0.33 to 0.99)
Blaiss 2011[189]	0.91	3.66	149	1.33	2.51	158	11.4%	–0.13 (–0.36 to 0.09)
Bufe 2004[84]	0.24	0.19	68	0.18	0.019	64	7.6%	0.44 (0.09 to 0.78)
Bufe 2009[85]	2.13	3.48	117	2.53	3.03	121	10.3%	–0.12 (–0.38 to 0.13)
Dahl 2006[100]	2.4	3.9	61	4.2	4.1	32	5.8%	–0.45 (–0.88 to –0.02)
Drachenberg 2001[91]	12.5	18.7	37	23.8	26.4	12	3.0%	–0.54 (–1.20 to 0.12)
Dubakiene 2003[103]	0.13	0.17	47	0.17	0.19	53	6.5%	–0.22 (–0.61 to 0.17)
Durham 2006[104]	1.4	2.13	131	2.03	2.39	129	10.7%	–0.28 (–0.52 to –0.03)
Durham 2010[200]	1.82	3.01	160	3.04	3.01	127	11.0%	–0.40 (–0.64 to –0.17)
Nelson 2011[192]	1.25	2.71	184	1.7	2.88	207	12.3%	–0.16 (–0.36 to 0.04)
Pradalier 1999[114]	1.77	2.3	63	2.13	2.7	63	7.5%	–0.14 (–0.49 to 0.21)
Wahn 2009[26]	0.6	0.611	131	0.79	0.647	135	10.8%	–0.30 (–0.54 to –0.06)
Total (95% CI)			1167			1118	100.0%	–0.18 (–0.30 to –0.05)

Heterogeneity: τ^2=0.02; χ^2=22.58, df=11 (p=0.02); I^2=51%
Test for overall effect: z=2.76 (p=0.006)

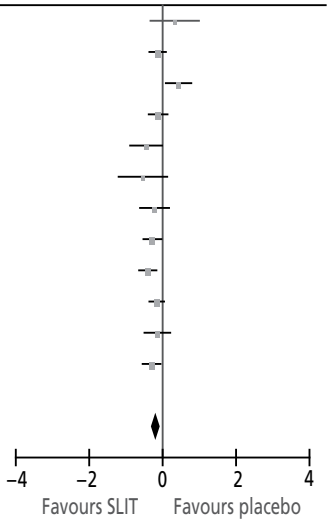

FIGURE 78 Sublingual immunotherapy vs placebo, major allergen content, 5–20μg, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	4.62	6.1	149	6.25	6.3	158	31.7%	–0.26 (–0.49 to –0.04)
Durham 2010[200]	0.17	0.19	160	0.26	0.19	127	29.0%	–0.47 (–0.71 to –0.24)
Nelson 2011[192]	5.08	5.4	184	6.39	4.8	207	39.2%	–0.26 (–0.46 to –0.06)
Total (95% CI)			493			492	100.0%	–0.32 (–0.45 to –0.19)

Heterogeneity: τ^2=0.00; χ^2=2.24, df=2 (p=0.33); I^2=11%
Test for overall effect: z=4.71 (p<0.00001)

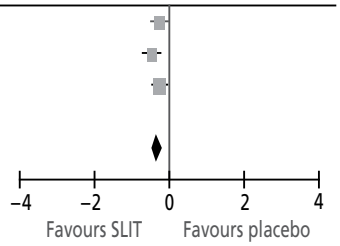

FIGURE 79 Sublingual immunotherapy vs placebo, major allergen content, 5–20μg, SMSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Andre 2003[95]	2.27	1.42	48	3.09	2.14	51	9.9%	–0.45 (–0.84 to –0.05)
Bowen 2004[97]	3.95	2.45	37	5.03	2.54	39	8.2%	–0.43 (–0.88 to 0.03)
Di Rienzo 2006[102]	0.4	0.3	18	0.8	0.5	14	3.6%	–0.98 (–1.72 to –0.23)
Didier 2007[24]	3.58	2.976	136	4.93	3.229	148	18.2%	–0.43 (–0.67 to –0.20)
La Rosa 1999[86]	1.21	1.66	16	1.61	1.56	17	4.2%	–0.24 (–0.93 to 0.44)
Lima 2002[107]	2494	2326	28	2465	1537	28	6.6%	0.01 (–0.51 to 0.54)
Ott 2009[108]	–1.02	4.54	123	1.32	4.54	60	13.5%	–0.51 (–0.83 to –0.20)
Skoner 2010[196]	0.19	1.16	33	1	2.3	36	7.6%	–0.43 (–0.91 to 0.04)
Smith 2004[115]	2.58	2.48	45	2.32	1.67	51	9.8%	0.12 (–0.28 to 0.52)
Valovirta 2006[90]	1.5	1.4	27	2.2	1.4	29	6.4%	–0.49 (–1.03 to 0.04)
Vervloet 2006[117]	2.68	1.64	19	2.44	2.06	19	4.7%	0.13 (–0.51 to 0.76)
Vourdas 1998[89]	1.07	1.63	34	1.38	2.01	32	7.4%	–0.17 (–0.65 to 0.32)
Total (95% CI)			564			524	100.0%	–0.33 (–0.48 to –0.18)

Heterogeneity: τ^2=0.02; χ^2=14.97, df=11 (p=0.18); I^2=27%
Test for overall effect: z=4.32 (p<0.0001)

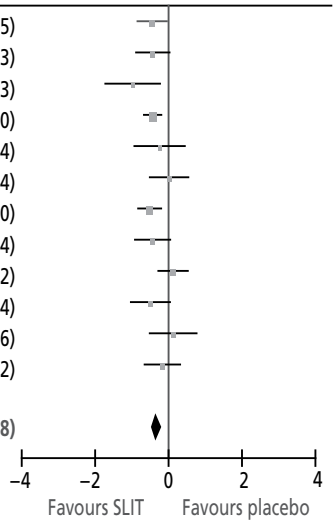

FIGURE 80 Sublingual immunotherapy vs placebo, major allergen content, >20μg, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Andre 2003[95]	2.41	3.09	48	4	4.24	51	12.9%	−0.42 (−0.82 to −0.02)
Bowen 2004[97]	1.05	1.6	37	1.26	1.24	39	11.4%	−0.15 (−0.60 to 0.30)
Di Rienzo 2006[102]	3.2	0.7	18	4.9	1.5	14	5.3%	−1.48 (−2.28 to −0.68)
La Rosa 1999[86]	2.28	3.89	16	2.36	3.95	17	6.7%	−0.02 (−0.70 to 0.66)
Lima 2002[107]	2334	2616	28	2837	2052	28	9.5%	−0.21 (−0.74 to 0.31)
Ott 2009[108]	−0.28	11.55	123	−0.92	2.47	60	16.0%	0.07 (−0.24 to 0.38)
Skoner 2010[196]	0.0003	1.64	33	0.63	1.06	36	10.7%	−0.46 (−0.93 to 0.02)
Valovirta 2006[90]	2.9	3.4	27	3.9	4.6	29	9.5%	−0.24 (−0.77 to 0.28)
Vervloet 2006[117]	3.39	3.94	19	4.71	5	19	7.4%	−0.29 (−0.93 to 0.35)
Vourdas 1998[89]	1.39	3.41	34	1.77	3.85	32	10.6%	−0.10 (−0.59 to 0.38)
Total (95% CI)			383			325	100.0%	−0.26 (−0.47 to −0.06)

Heterogeneity: $\tau^2=0.04$; $\chi^2=15.51$, df=9 ($p=0.08$); $I^2=42\%$
Test for overall effect: $z=2.50$ ($p=0.01$)

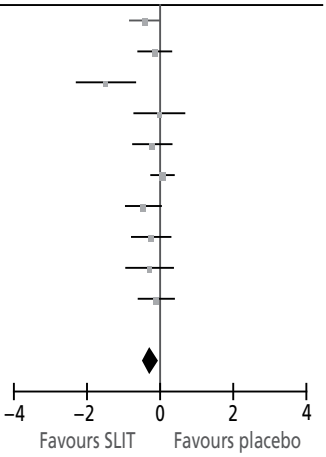

FIGURE 81 Sublingual immunotherapy vs placebo, major allergen content, >20μg, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	3.83	4.9	19	3.71	2.7	17	1.5%	0.03 (−0.63 to 0.68)
Blaiss 2011[189]	3.71	4.88	149	4.91	5.03	158	6.3%	−0.24 (−0.47 to −0.02)
Bufe 2004[84]	1.54	0.77	68	1.59	0.96	64	4.1%	−0.06 (−0.40 to 0.28)
Bufe 2009[85]	2.67	2.38	117	3.17	2.14	121	5.6%	−0.22 (−0.48 to 0.03)
Dahl 2006[93]	2.1	1.7	61	3.3	2.2	32	2.9%	−0.63 (−1.07 to −0.19)
de Blay 2003[101]	20.55	15.88	33	23.49	18.76	42	2.7%	−0.17 (−0.62 to 0.29)
Didier 2007[24]	3.58	2.976	136	4.93	3.229	148	6.0%	−0.43 (−0.67 to −0.20)
Didier 2011[25]	2.67	3.63	149	4.03	3.71	165	6.3%	−0.37 (−0.59 to −0.15)
Drachenberg 2001[91]	25.2	19.9	19	37.4	37	7	0.9%	−0.47 (−1.34 to 0.41)
Durham 2006[104]	2.48	2.1	131	2.96	2.09	129	5.9%	−0.23 (−0.47 to 0.02)
Durham 2010[200]	2.7	2.1	142	3.7	2.1	115	5.7%	−0.47 (−0.72 to −0.23)
Feliziani 1995[105]	109.7	92.46	18	215.8	114.2	16	1.3%	−1.00 (−1.72 to −0.28)
Hordijk 1998[106]	3.21	3.05	35	5.13	3.6	36	2.6%	−0.57 (−1.04 to −0.09)
Lima 2002[107]	2494	2326	28	2465	1537	28	2.2%	0.01 (−0.51 to 0.54)
Nelson 2011[192]	3.83	4.07	184	4.69	4.32	207	6.9%	−0.20 (−0.40 to −0.01)
Ott 2009[108]	−1.02	4.54	123	1.32	4.54	60	4.5%	−0.51 (−0.83 to −0.20)
Palma-Carlos 2006[109]	31.15	32.61	17	55.86	50.48	16	1.4%	−0.57 (−1.27 to 0.13)
Panzner 2008[110]	111.35	114.91	20	321.6	211.22	15	1.2%	−1.26 (−2.00 to −0.52)
Peter 2009[112]	0.732	0.483	176	0.78	0.544	189	6.7%	−0.09 (−0.30 to 0.11)
Pfaar 2008[113]	146.2	123	42	236.2	133.6	48	3.0%	−0.69 (−1.12 to −0.27)
Pradalier 1999[114]	2.33	1.6	63	2.65	2	63	4.0%	−0.18 (−0.53 to 0.17)
Roder 2007[87]	2.45	1.48	91	2.74	1.66	77	4.7%	−0.18 (−0.49 to 0.12)
Rolinck-Werninghaus 2004[88]	13.71	23.12	39	12.66	21.65	38	2.8%	0.05 (−0.40 to 0.49)
Smith 2004[115]	2.58	2.48	45	2.32	1.67	51	3.3%	0.12 (−0.28 to 0.52)
Wahn 2009[26]	3.25	2.86	131	4.51	2.931	135	5.9%	−0.43 (−0.68 to −0.19)
Wessner 2001[118]	0.32	0.26	14	0.51	0.38	18	1.3%	−0.56 (−1.27 to 0.16)
Total (95% CI)			2050			1995	100.0%	−0.31 (−0.39 to −0.22)

Heterogeneity: $\tau^2=0.02$; $\chi^2=42.46$, df=25 ($p=0.02$); $I^2=41\%$
Test for overall effect: $z=6.81$ ($p<0.00001$)

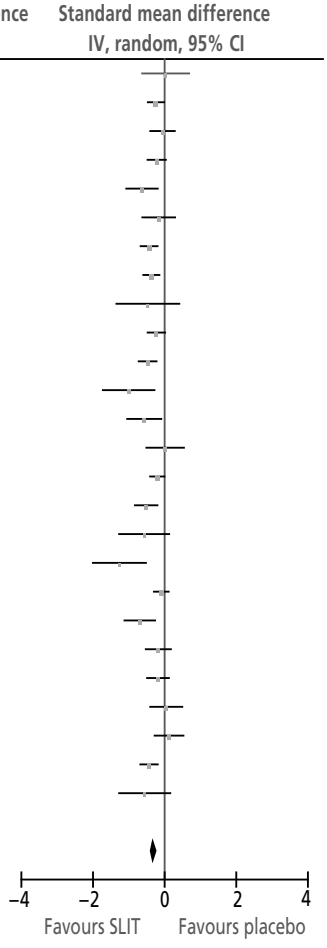

FIGURE 82 Sublingual immunotherapy vs placebo, grass pollen, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Amar 2009[94]	0.44	1.2	19	0.14	0.24	17	2.4%	0.33 (–0.33 to 0.99)
Blaiss 2011[189]	0.91	3.66	149	1.33	2.51	158	7.9%	–0.13 (–0.36 to 0.09)
Bufe 2004[84]	0.24	0.19	68	0.18	0.019	64	5.6%	0.44 (0.09 to 0.78)
Bufe 2009[85]	2.13	3.48	117	2.53	3.03	121	7.3%	–0.12 (–0.38 to 0.13)
Dahl 2006[93]	2.4	3.9	61	4.2	4.1	32	4.4%	–0.45 (–0.88 to –0.02)
de Blay 2003[101]	3.48	5.37	33	7.57	8.23	42	4.0%	–0.57 (–1.03 to –0.10)
Didier 2011[25]	0.31	3.63	149	0.47	3.71	165	8.0%	–0.04 (–0.26 to 0.18)
Drachenberg 2001[91]	9.6	19.9	19	24.3	31.4	7	1.5%	–0.61 (–1.50 to 0.27)
Durham 2006[104]	1.4	2.13	131	2.03	2.39	129	7.5%	–0.28 (–0.52 to –0.03)
Durham 2010[200]	1.82	3.01	160	3.04	3.01	127	7.7%	–0.40 (–0.64 to –0.17)
Feliziani 1995[105]	24.06	25.72	18	75.9	50.3	16	2.0%	–1.29 (–2.04 to –0.54)
Hordijk 1998[106]	0.16	0.37	35	0.31	0.45	36	4.0%	–0.36 (–0.83 to 0.11)
Lima 2002[107]	2334	2616	28	2837	2052	28	3.4%	–0.21 (–0.74 to 0.31)
Nelson 2011[192]	1.25	2.71	184	1.7	2.88	207	8.4%	–0.16 (–0.36 to 0.04)
Ott 2009[108]	–0.28	11.55	123	–0.92	2.47	60	6.3%	0.07 (–0.24 to 0.38)
Palma-Carlos 2006[109]	15.38	32.98	17	44.57	65.05	16	2.2%	–0.56 (–1.26 to 0.14)
Pradalier 1999[114]	1.77	2.3	63	2.13	2.7	63	5.6%	–0.14 (–0.49 to 0.21)
Rolinck-Werninghaus 2004[88]	2.54	3.58	39	2.85	3.87	38	4.2%	–0.08 (–0.53 to 0.36)
Wahn 2009[26]	0.6	0.611	131	0.79	0.647	135	7.5%	–0.30 (–0.54 to –0.06)
Total (95% CI)			1544			1461	100.0%	–0.20 (–0.31 to –0.08)

Heterogeneity: τ^2=0.03; χ^2=39.32, df=18 (p=0.003); I^2=54%
Test for overall effect: z=3.31 (p=0.0009)

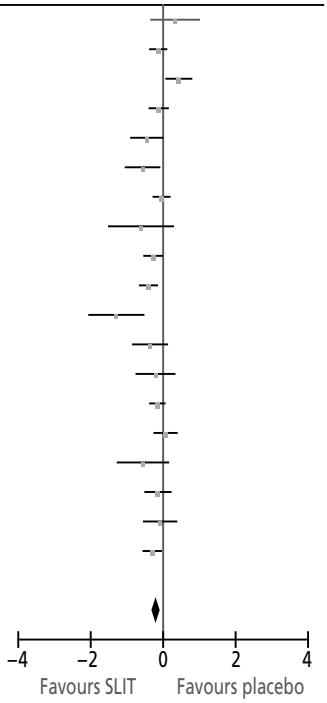

FIGURE 83 Sublingual immunotherapy vs placebo, grass pollen, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	4.62	6.1	149	6.25	6.3	158	24.2%	–0.26 (–0.49 to –0.04)
Didier 2011[25]	3.46	3.625	149	5.28	3.942	165	24.2%	–0.48 (–0.70 to –0.25)
Durham 2010[200]	0.17	0.19	160	0.26	0.19	127	22.3%	–0.47 (–0.71 to –0.24)
Nelson 2011[192]	5.08	5.4	184	6.39	4.8	207	29.3%	–0.26 (–0.46 to –0.06)
Total (95% CI)			642			657	100.0%	–0.36 (–0.48 to –0.24)

Heterogeneity: τ^2=0.00; χ^2=3.69, df=3 (p=0.30); I^2=19%
Test for overall effect: z=5.77 (p<0.00001)

FIGURE 84 Sublingual immunotherapy vs placebo, grass pollen, SMSs.

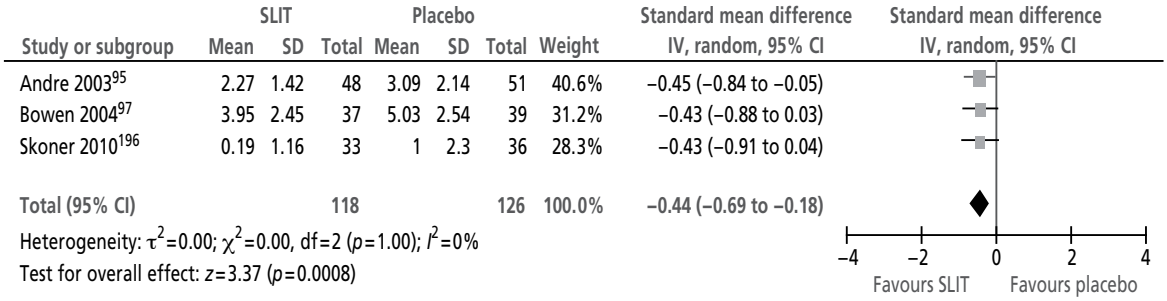

FIGURE 85 Sublingual immunotherapy vs placebo, ragweed, SSs.

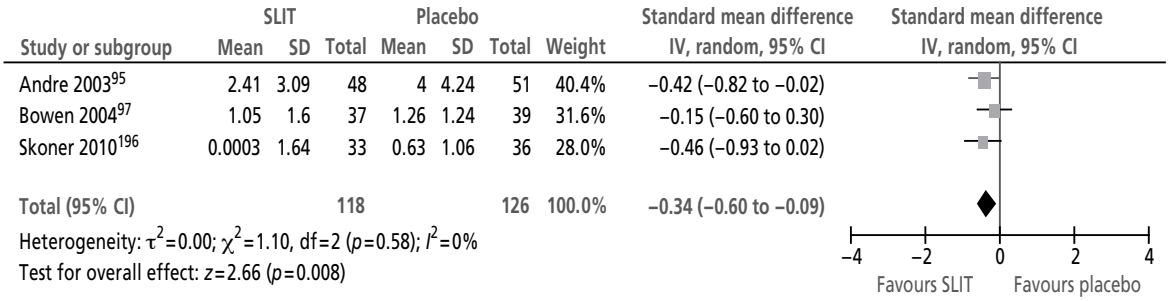

FIGURE 86 Sublingual immunotherapy vs placebo, ragweed, MSs.

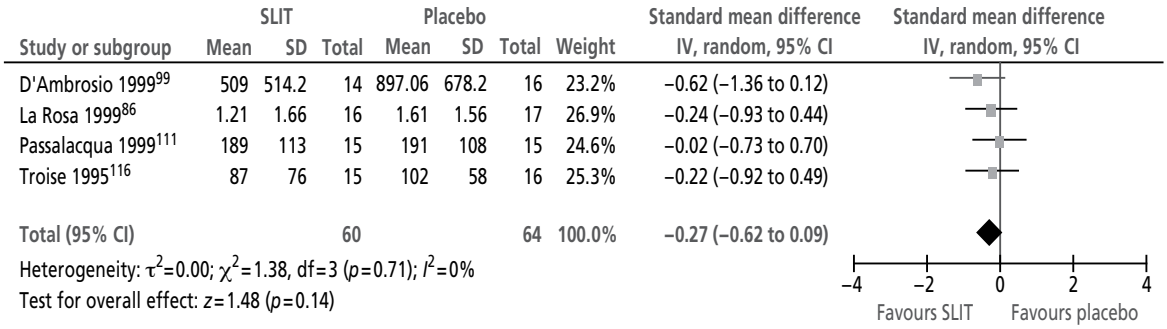

FIGURE 87 Sublingual immunotherapy vs placebo, *Parietaria*, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
D'Ambrosio 1999[99]	48.1	46.6	14	124.37	121	16	23.2%	−0.79 (−1.54 to −0.04)
La Rosa 1999[86]	2.28	3.89	16	2.36	3.95	17	27.9%	−0.02 (−0.70 to 0.66)
Passalacqua 1999[111]	42	49.5	15	83	65	15	23.8%	−0.69 (−1.43 to 0.05)
Troise 1995[116]	17	21	15	33	33	16	25.1%	−0.56 (−1.28 to 0.16)
Total (95% CI)			60			64	100.0%	−0.49 (−0.85 to −0.13)

Heterogeneity: $\tau^2=0.00$; $\chi^2=2.75$, df=3 ($p=0.43$); $I^2=0\%$
Test for overall effect: $z=2.68$ ($p=0.007$)

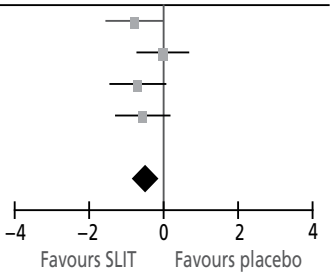

FIGURE 88 Sublingual immunotherapy vs placebo, *Parietaria*, MSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Ariano 2001[96]	1.8	1.75	10	5.38	1.57	10	6.7%	−2.06 (−3.19 to −0.93)
Casanovas 1994[98]	5.46	3.56	9	10.98	7.1	6	6.8%	−1.00 (−2.11 to 0.12)
Di Rienzo 2006[102]	0.4	0.3	18	0.8	0.5	14	10.7%	−0.98 (−1.72 to −0.23)
Drachenberg 2001[91]	34	27.8	18	35	21.9	5	7.9%	−0.04 (−1.03 to 0.95)
Dubakiene 2003[103]	0.48	0.3	47	0.64	0.43	53	16.1%	−0.42 (−0.82 to −0.03)
Valovirta 2006[90]	1.5	1.4	27	2.2	1.4	29	13.9%	−0.49 (−1.03 to 0.04)
Vervloet 2006[117]	2.68	1.64	19	2.44	2.06	19	12.3%	0.13 (−0.51 to 0.76)
Voltolini 2001[197]	130	154	15	83	79	15	11.0%	0.37 (−0.35 to 1.10)
Vourdas 1998[89]	1.07	1.63	34	1.38	2.01	32	14.7%	−0.17 (−0.65 to 0.32)
Total (95% CI)			197			183	100.0%	−0.42 (−0.77 to −0.06)

Heterogeneity: $\tau^2=0.17$; $\chi^2=20.17$, df=8 ($p=0.010$); $I^2=60\%$
Test for overall effect: $z=2.29$ ($p=0.02$)

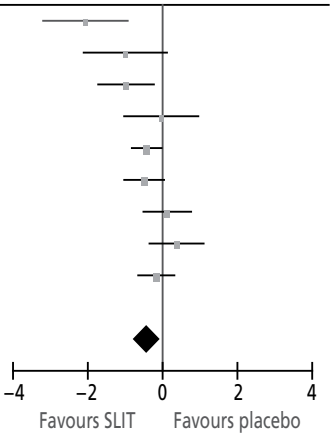

FIGURE 89 Sublingual immunotherapy vs placebo, tree, SSs.

Study or subgroup	SLIT Mean	SD	Total	Placebo Mean	SD	Total	Weight	Standard mean difference IV, random, 95% CI
Ariano 2001[96]	2.5	2.1	10	5.3	4.9	10	6.3%	−0.71 (−1.62 to 0.20)
Casanovas 1994[98]	1.69	2.46	9	2.13	2.22	6	5.0%	−0.17 (−1.21 to 0.86)
Di Rienzo 2006[102]	3.2	0.7	18	4.9	1.5	14	7.9%	−1.48 (−2.28 to −0.68)
Drachenberg 2001[91]	15.6	17.4	18	23.2	20.7	5	5.4%	−0.41 (−1.40 to 0.59)
Dubakiene 2003[103]	0.13	0.17	47	0.17	0.19	53	22.2%	−0.22 (−0.61 to 0.17)
Valovirta 2006[90]	2.9	3.4	27	3.9	4.6	29	15.3%	−0.24 (−0.77 to 0.28)
Vervloet 2006[117]	3.39	3.94	19	4.71	5	19	11.4%	−0.29 (−0.93 to 0.35)
Voltolini 2001[197]	22	30	15	39	34	15	9.3%	−0.52 (−1.25 to 0.21)
Vourdas 1998[89]	1.39	3.41	34	1.77	3.85	32	17.2%	−0.10 (−0.59 to 0.38)
Total (95% CI)			197			183	100.0%	−0.38 (−0.62 to −0.13)

Heterogeneity: $\tau^2=0.03$; $\chi^2=10.24$, df=8 ($p=0.25$); $I^2=22\%$
Test for overall effect: $z=3.02$ ($p=0.002$)

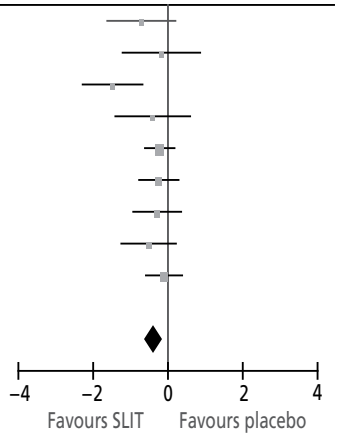

FIGURE 90 Sublingual immunotherapy vs placebo, tree, MSs.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Di Rienzo 2006[102]	0.5	1.52	18	1.83	1.14	14	4.6%	−0.95 (−1.69 to −0.21)
Didier 2011[25]	−0.43	1.02	149	0	1.02	165	18.9%	−0.42 (−0.64 to −0.20)
Durham 2010[200]	0.78	0.71	160	1.01	0.71	127	18.4%	−0.32 (−0.56 to −0.09)
Horak 2009[202]	−0.3	0.44	143	0	0.44	148	18.3%	−0.68 (−0.92 to −0.44)
Nelson 2011[192]	1.3	1.31	172	1.57	1.4	197	19.9%	−0.20 (−0.40 to 0.01)
Peter 2009[112]	−1.127	1.531	176	−0.81	1.601	189	19.9%	−0.20 (−0.41 to 0.00)
Total (95% CI)			818			840	100.0%	−0.39 (−0.56 to −0.21)

Heterogeneity: $\tau^2=0.03$; $\chi^2=14.48$, df=5 ($p=0.01$); $I^2=65\%$
Test for overall effect: $z=4.33$ ($p<0.0001$)

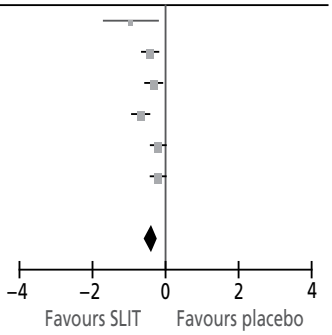

FIGURE 91 Sublingual immunotherapy vs placebo, QoL, adults.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Blaiss 2011[189]	1.45	1.04	109	1.77	1.05	111	28.3%	−0.31 (−0.57 to −0.04)
Di Rienzo 2006[102]	0.5	1.52	18	1.83	1.14	14	10.7%	−0.95 (−1.69 to −0.21)
Horak 2009[202]	−0.3	0.44	143	0	0.44	148	29.8%	−0.68 (−0.92 to −0.44)
Peter 2009[112]	−1.127	1.531	176	−0.81	1.601	189	31.3%	−0.20 (−0.41 to 0.00)
Total (95% CI)			446			462	100.0%	−0.45 (−0.74 to −0.17)

Heterogeneity: $\tau^2=0.06$; $\chi^2=11.54$, df=3 ($p=0.009$); $I^2=74\%$
Test for overall effect: $z=3.09$ ($p=0.002$)

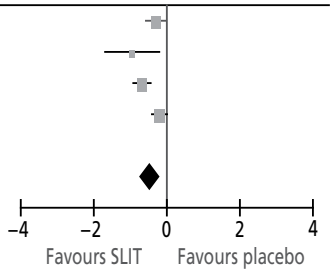

FIGURE 92 Sublingual immunotherapy vs placebo, QoL, <6 months.

Study or subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standard mean difference IV, random, 95% CI
Didier 2011[25]	−0.43	1.02	149	0	1.02	165	52.3%	−0.42 (−0.64 to −0.20)
Durham 2010[200]	0.78	0.71	160	1.01	0.71	127	47.7%	−0.32 (−0.56 to −0.09)
Total (95% CI)			309			292	100.0%	−0.37 (−0.54 to −0.21)

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.35$, df=1 ($p=0.56$); $I^2=0\%$
Test for overall effect: $z=4.53$ ($p<0.00001$)

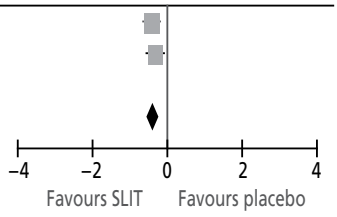

FIGURE 93 Sublingual immunotherapy vs placebo, QoL, >12 months.

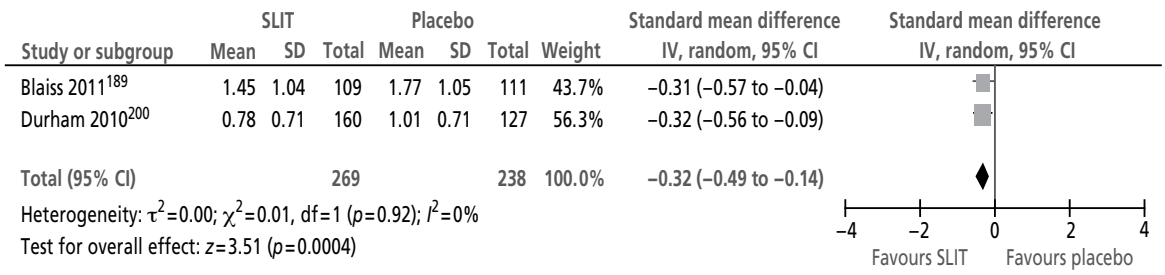

FIGURE 94 Sublingual immunotherapy vs placebo, QoL, major allergen content, 5–20 μg.

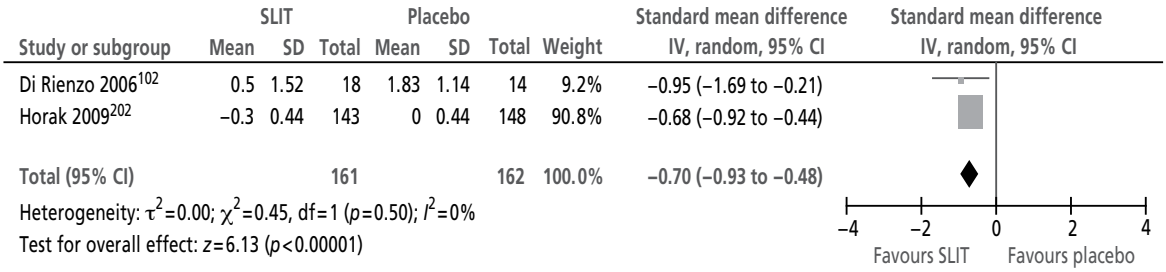

FIGURE 95 Sublingual immunotherapy vs placebo, QoL, major allergen content, >20 μg.

Appendix 8 Symptom scores across studies

Study ID	Nasal symptoms							Ocular symptoms						Respiratory symptoms							Mouth and throat		Others				No. symptoms measured (nose/ eyes/ bronchial/ other)	Total no. symptoms measured
	Sneezing	Runny nose	Nasal obstruction (blocked nose)	Itchy nose	Itching and sneezing	Postnasal drip	Nasal symptoms (general)	Gritty/itchy eyes	Red eyes	Watery eyes	Swollen eyes	Foreign body sensation	Ocular symptoms (general)	Cough	Wheeze	Chest tightness/shortness of breath	Mucus	Asthma	Exercise-induced symptoms	Respiratory symptoms (general)	Itching	Dryness	Ear itch	Headache	Tiredness	Hyperaemia		
SCIT																												
Ortolani 1984[174]	✗	✗	✗					✗		✗				✗	✗			✗			✗		✗	✗	✗		3/2/3/4	12
Varney 1991[172]	✗	✗	✗					✗	✗	✗	✗			✗	✗	✗					✗	✗					3/4/3/2	12
Kuna 2011[152]	✗	✗	✗					✗	✗	✗				✗	✗	✗											3/3/3	9
Corrigan 2005[164]	✗	✗	✗					✗	✗	✗				✗	✗	✗											3/3/3	9
Jutel 2005[166]	✗	✗	✗					✗	✗	✗				✗	✗	✗											3/3/3	9
Walker 2001[173]	✗	✗	✗					✗	✗	✗	✗										✗	✗					3/4/2	9
Pauli 2008[154]	✗	✗	✗	✗				✗	✗	✗		✗															4/4/0	8
Bousquet 1990[170]	✗	✗	✗					✗	✗	✗					✗	✗											3/3/2	8
Ferrer 2005[165]	✗	✗	✗	✗									✗	✗	✗	✗											4/1/3	8
Ortolani 1994[167]	✗	✗	✗					✗	✗	✗				✗		✗											3/3/2	8

Study ID	Nasal symptoms						Ocular symptoms						Respiratory symptoms								Mouth and throat		Others			No. symptoms measured (nose/ eyes/ bronchial/ other)	Total no. symptoms measured
	Sneezing	Runny nose	Nasal obstruction (blocked nose)	Itchy nose	Itching and sneezing	Postnasal drip	Nasal symptoms (general)	Gritty/itchy eyes	Red eyes	Watery eyes	Swollen eyes	Foreign body sensation	Ocular symptoms (general)	Cough	Wheeze	Chest tightness/shortness of breath	Mucus	Asthma	Exercise-induced symptoms	Respiratory symptoms (general)	Itching	Dryness	Ear itch	Headache	Tiredness	Hyperaemia		
Charpin 2007[142]	x	x	x	x				x	x	x																	4/3/0	7
Balda 1998[163]							x	x					x							x							1/1/1	3
Bodtger 2002[169]							x	x					x							x							1/1/1	3
Zenner 1997[168]							x	x					x							x							1/1/1	3
SLIT																												
Lima 2002[107]	x	x	x					x	x	x	x			x	x	x					x	x					3/4/3/2	12
Panzner 2008[110]	x	x	x	x				x	x	x	x			x	x	x	x										4/4/4	12
Bufe 2004[84]	x	x	x	x				x	x	x	x			x	x	xx											4/4/4	12
Rolinck-Werninghaus 2004[88]	x	x	x	x				x	x	x				x	x	xx											4/3/4	11
Blaiss 2011[189]	x	x	x	x				x		x				x	x	x			x								4/2/4	10

Study ID	Nasal symptoms							Ocular symptoms						Respiratory symptoms							Mouth and throat		Others				No. symptoms measured (nose/ eyes/ bronchial/ other)	Total no. symptoms measured
	Sneezing	Runny nose	Nasal obstruction (blocked nose)	Itchy nose	Itching and sneezing	Postnasal drip	Nasal symptoms (general)	Gritty/itchy eyes	Red eyes	Watery eyes	Swollen eyes	Foreign body sensation	Ocular symptoms (general)	Cough	Wheeze	Chest tightness/shortness of breath	Mucus	Asthma	Exercise-induced symptoms	Respiratory symptoms (general)	Itching	Dryness	Ear itch	Headache	Tiredness	Hyperaemia		
Nelson 2011[192]	✗	✗	✗	✗				✗		✗				✗	✗	✗			✗								4/2/4	10
Bufe 2009[85]	✗	✗	✗	✗				✗		✗				✗	✗	✗			✗								4/2/4	10
Dahl 2006[100]	✗	✗	✗	✗				✗		✗				✗	✗	✗			✗								4/2/4	10
Durham 2006[104]	✗	✗	✗	✗				✗		✗				✗	✗	✗			✗								4/2/4	10
Pfaar 2008[155]	✗	✗	✗	✗				✗	✗	✗				✗	✗	✗											4/3/3	10
Cortellini 2010[190]	✗	✗	✗	✗				✗	✗					✗	✗	✗											4/2/4	10
Valovirta 2006[90]	✗	✗	✗					✗	✗	✗				✗	✗	✗✗											3/3/4	10
Smith 2004[115]	✗	✗	✗					✗		✗	✗			✗		✗✗					✗						3/3/3/1	10
D'Ambrosio 1999[99]	✗	✗	✗	✗				✗	✗					✗	✗	✗											4/2/3	9
Feliziani 1995[105]	✗	✗	✗	✗				✗	✗					✗	✗	✗											4/2/3	9

Study ID	Nasal symptoms							Ocular symptoms						Respiratory symptoms								Mouth and throat		Others			No. symptoms measured (nose/eyes/bronchial/other)	Total no. symptoms measured
	Sneezing	Runny nose	Nasal obstruction (blocked nose)	Itchy nose	Itching and sneezing	Postnasal drip	Nasal symptoms (general)	Gritty/itchy eyes	Red eyes	Watery eyes	Swollen eyes	Foreign body sensation	Ocular symptoms (general)	Cough	Wheeze	Chest tightness/shortness of breath	Mucus	Asthma	Exercise-induced symptoms	Respiratory symptoms (general)	Itching	Dryness	Ear itch	Headache	Tiredness	Hyperaemia		
La Rosa 1999[86]	x	x	x					x	x	x				x	x	x											3/3/3	9
Ott 2009[108]	x	x	x					x	x	x				x	x	x											3/3/3	9
Passalacqua 1999[111]	x	x	x	x				x			x			x				x								x	4/2/2/1	9
Vourdas 1998[89]	x	x	x					x	x	x				x	x	x											3/3/3	9
Amar 2009[94]	x	x	x	x				x	x	x											x						4/3/0/1	8
Andre 2003[95]	x	x	x	x				x	x	x																	4/3/0	7
Bowen 2004[97]	x	x	x	x				x	x	x																	4/3/0	7
Pradalier 1999[114]	x	x	x	x				x	x	x																	4/3/0	7
Vervloet 2007[117]	x	x	x	x				x	x	x																	4/3/0	7
Didier 2007[24]	x	x	x	x				x		x																	4/2/0	6
Didier 2011[25]	x	x	x	x				x		x																	4/2/0	6

Study ID	Nasal symptoms							Ocular symptoms						Respiratory symptoms							Mouth and throat		Others				No. symptoms measured (nose/ eyes/ bronchial/ other)	Total no. symptoms measured
	Sneezing	Runny nose	Nasal obstruction (blocked nose)	Itchy nose	Itching and sneezing	Postnasal drip	Nasal symptoms (general)	Gritty/itchy eyes	Red eyes	Watery eyes	Swollen eyes	Foreign body sensation	Ocular symptoms (general)	Cough	Wheeze	Chest tightness/shortness of breath	Mucus	Asthma	Exercise-induced symptoms	Respiratory symptoms (general)	Itching	Dryness	Ear itch	Headache	Tiredness	Hyperaemia		
Wahn 2009[26]	✗	✗	✗	✗				✗		✗																	4/2/0	6
Durham 2010[200]	✗	✗	✗	✗				✗																			4/1/0	5
Casanovas 1994[98]	✗	✗	✗	✗				✗																			4/1/0	5
Roder 2007[87]	✗	✗	✗	✗				✗																			4/1/0	5
Di Rienzo 2006[102]	✗	✗	✗										✗														4/1/0	5
Hordijk 1998	✗	✗		✗				✗																			3/1/0	4
Troise 1995[116]	✗	✗	✗	✗																							4/0/0	4
Palma-Carlos 2006[109]	✗	✗											✗														2/1/0	3

Not stated: Ariano 2001,[96] Brewczynski 1999,[171] Drachenberg 2001 (SLIT),[95] Frew 2006,[161] Skoner 2010[196] and Wessner 2001.[118]

Full text of paper not available: de Blay 2003,[101] Drachenberg 2001 (SCIT),[91] Dubakiene 2003,[103] Peter 2009[112] and Voltolini 2001.[119]

Appendix 9 Characteristics of ongoing trials

Source: ClinicalTrials.gov and UK Clinical Research Network Portfolio Database and metaRegister (controlled-trials.com) searched August 2011.

Trial ID	Sponsor/institution	Population	Intervention/comparators	Outcomes	Status
SLIT trials					
NCT01061203	ALK-Abelló	1000 children (5–12 years)	Grazax tablet vs placebo	Evaluation of allergy and asthma symptoms (5 years) QoL AEs	Active, not recruiting *Start date*: January 2010 *Expected completion*: September 2015
NCT00623701	Allergopharma Joachim Ganzer KG	226 adults	High-dose (40μg) Allerslit forte vs placebo	SMS	Active, not recruiting *Start date*: March 2008 *Expected completion*: February 2012
NCT00264459	Allergopharma Joachim Ganzer KG	483 adults	Grass pollen mixture vs placebo	Not stated	Active, not recruiting *Start date*: February 2003 *Expected completion*: September 2012
NCT00841256	Allergopharma Joachim Ganzer KG	Children (number enrolled not stated)	Grass pollen allergen extract vs standard symptomatic treatment plus placebo	Change of SMS AEs	Active, not recruiting *Start date*: April 2009 *Expected completion*: not stated
NCT00812799	Artu Biologicals	374 adults	Sublingual oralgen vs placebo	Combined SMS SS	Active, not recruiting *Start date*: December 2008 *Expected completion*: December 2011
NCT00824447	Artu Biologicals	356 adults	Oralgen vs placebo (dose comparison study)	Rhinoconjunctivitis Rescue medication usage RQLQ Proportion symptom-free days Global evaluation Tolerability and AEs	Completed
NCT00537342	Laboratorios LETI, SL	83 Adults	Modified extract *Olea europaea* vs placebo	SS MS RQLQ Analogue visual scale AEs	Completed

Trial ID	Sponsor/institution	Population	Intervention/comparators	Outcomes	Status
NCT01012882	Roxall Medizin	120 adults	Allergen extract vs placebo	SMS AEs, RQLQ Clinical global improvement	Not yet open for recruitment *Start date*: November 2011 *Estimated completion*: February 2013
NCT00550550	Schering-Plough	450 children	SCH697243 (*P. pratense* extract) vs placebo	Combined rhinoconjunctivitis daily SS and daily MS	Completed
NCT00562159	Schering-Plough	450 adults	SCH697243 (*P. pratense* extract) vs placebo	Combined daily SS and daily MS Average daily SS Average daily MS Average weekly rhinoconjunctivitis QoL score	Completed
NCT00803244	Stallergènes	420 adults and adolescents (12–65 years)	Grass pollen tablet vs placebo	Average adjusted SS SSs MSs Global patient evaluation Safety	Completed
NCT00955825	Stallergènes	473 adults	Grass pollen allergen extract vs placebo	Average combined SSs and MSs Average rhinoconjunctivitis TSS Average rescue MS Proportion of symptom-controlled days Average adjusted SS	Completed
SCIT trials					
NCT00263601	Allergopharma Joachim Ganzer KG	150 adults	Grass pollen allergoid vs placebo	SMS	Active, not recruiting *Start date*: November 2001 *Expected completion*: August 2013
NCT01353755	Allergopharma Joachim Ganzer KG	195 adults and adolescents (12–65 years)	Recombinant *Phleum* allergens vs placebo (dose comparison study; 2 years´ treatment, 1-year follow-up)	Rhinoconjunctivitis SMS AEs	Active, not recruiting *Start date*: October 2009 *Expected completion*: August 2016
NCT00263627	Allergopharma Joachim Ganzer KG	Adults (no. enrolled not stated)	Birch pollen allergoid vs placebo	Not stated	Completed

Trial ID	Sponsor/institution	Population	Intervention/comparators	Outcomes	Status
NCT00671268	Allergopharma Joachim Ganzer KG	498 adults	AL0704rP (recombinant major allergens of timothy grass pollens) vs placebo	Change of symptom and MS	Active, not recruiting *Start date*: March 2008 *Expected completion*: October 2013
NCT00309036	Allergopharma Joachim Ganzer KG	Adults (no. enrolled not stated)	Recombinant grass pollen vs placebo	Not stated	Active, not recruiting *Start date*: January 2004 *Expected completion*: December 2009
NCT00309062	Allergopharma Joachim Ganzer KG	Adults (no. enrolled not stated)	Recombinant birch pollen vs placebo	Not stated	Active, not recruiting *Start date*: January 2004 *Expected completion*: October 2009
NCT00916760	Laboratorios Leti, SL	150 adults	Monthly depigoid vs placebo	SS QoL questionnaire Visual scales Asthma SSs MSs AEs and severity Unplanned health-care resource utilisation	Active, not recruiting *Start date*: February 2008 *Expected completion*: January 2013
NCT00916422	Laboratorios Leti, SL	150 adults	*P. pratense* extract vs placebo	Symptoms and medications score RQLQ Visual scales Asthma SSs MSs AEs Severity of AEs Unplanned health-care resource utilisation	Active, not recruiting *Start date*: January 2008 *Expected completion*: December 2012

Trial ID	Sponsor/institution	Population	Intervention/comparators	Outcomes	Status
NCT00831025	Laboratorios Leti, SL	150 adults	Modified extract of *Olea europaea* pollen vs placebo	MS RQLQ VASs	Active, not recruiting *Start date*: January 2008 *Expected completion*: December 2012
NCT01012752	Roxall Medizin	150 adults	Modified allergen extract vs placebo	SMS Safety of treatment, AEs RQLQ Clinical global improvement	Not yet recruiting *Start date*: November 2012 *Expected completion*: January 2014
SLIT vs SCIT trials					
NCT01335139	University of California, San Francisco, CA	90 adults	Three-year study of Grazax + SCIT placebo vs Alutard SQ + SLIT placebo vs SCIT placebo + SLIT placebo	Use of rescue medications Hay fever severity score QoL Weekly visual analogue SS	Recruiting *Start date*: March 2011 *Estimated completion*: September 2014

TSS, total symptom score.

Appendix 10 Reasons for exclusion: cost-effectiveness studies and reviews

Reference	Reason for exclusion
Allison C, Fraser J. Grazax: an oral vaccine for the treatment of grass pollen allergy (hay fever). *Issues Emerg Health Tech* 2007;**107**:1–4	Not EE, does not report relevant information
Alvarez-Cuesta E, Gonzelez-Mancebo E. Immunotherapy in bronchial asthma. *Curr Opin Pulm Med* 2000;**6**:50–4	Not EE, does not report relevant information
Bachert CJ, Jorissen M, Bertrand B, Khattaev N, Bousquet J. Allergic Rhinitis and its Impact on Asthma update (ARIA 2008). The Belgian perspective', *B-ENT* 2008;**4**:253–7	No relevant information reported
Baiardini I, Braido F, Tarantini F, Porcu A, Bonini S, Bousquet PJ, *et al*., GA2LEN. ARIA-suggested drugs for allergic rhinitis: what impact on quality of life? A GA2LEN review. *Allergy* 2008;**63**:660–9	No relevant information reported
Barnes PJ. Is immunotherapy for asthma worthwhile? *N Engl J Med* 1996;**334**:531–2	Editorial, No relevant information reported
Belliveau PP. Omalizumab: A monoclonal anti-IgE antibody. *Medsc Gen Med* 2005;**7**:27	No relevant information reported
Bergmann KC, Wolf H, Schnitker J, *et al*. Quality of life and compliance of patients treated with specific immunotherapy using grass and rye allergens (LQC study). *Allergo J* 2000;**9**:480–8	No relevant information reported
Bernstein JA. Cost-benefit analysis for allergen immunotherapy. *Immunol Allergy Clin* 2000;**20**:593–608	No relevant information reported
Bernstein JA. Pharmacoeconomic considerations for allergen immunotherapy. *Clin Allergy Immunol* 2004;**8**:151–64	Not EE, does not report relevant information
Berto P, Frati F, Incorvaia C, Cadario G, Contiguglia R, Di Gioacchino M, *et al*. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin* 2008;**24**:261–6	Not EE, does not report relevant information
Büchner KS. An economic evaluation of a specific immunotherapeutic drug. Summary of results from an Infratest Suisse study, conducted for the Federal Republic of Germany (West). *Allergo J* 1995;**4**:156–63	No relevant information reported
Canonica GW, Passalacqua G. Sublingual immunotherapy in the treatment of adult allergic rhinitis patients. *Allergy* 2006;**61**:20–3	Not a review of EEs
Canonica GW, Passalacqua P. Disease-modifying effect and economic implications of sublingual immunotherapy. *J Allergy Clin Immunol* 2011;**127**:44–5	Commentary, does not report relevant information
Carr,WW, Nelson MR, Hadley JA. Managing rhinitis: Strategies for improved patient outcomes. *Allergy Asthma Proc* 2008;**29**:349–57	No relevant information reported
Compalati E, Penagos E. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol* 2009;**102**:22–8.	No relevant information reported
Cox L. Sublingual immunotherapy and allergic rhinitis. *Current Allergy Asthma Rep* 2008;**8**:102–10	Not a review of EEs.
del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, *et al*. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients: The ADRIAL cohort study. *Rhinology* 2010;**48**:201–5	No relevant information reported
Douglass JA, Thien FC, O'Hehir RE. Immunotherapy in asthma. *Thorax* 1997;**52**:S22–9	No relevant information reported
Fell WR, Mabry RL, Mabry C. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. *Ear Nose Throat J* 1997;**76**:528–32	No relevant information reported

Reference	Reason for exclusion
Goksel O, Sin B, Aydy'n O, Mungan D, Demirel Y, Pinar M, *et al*. Grass pollen preseasonal immunotherapy: the effect on direct medical cost and quality of life. *Allergy* 2009;**64**:458 (poster 1200)	Conference poster, no relevant information reported
Goldman M. Sublingual immunotherapy: The quest for innovative adjuvants. *Clin Exp Allergy* 2008;**38**:1705–6	Editorial, no relevant information reported
Goldschmidt O. Treatment of allergic rhinoconjunctivitis seen from health economical point of view. *Allergologie* 1998;**21**:S68–72	No relevant information reported
Greiner AN. Allergic rhinitis: impact of the disease and considerations for management. *Med Clin North Am* 2006;**90**:17–38	No relevant information reported
Hadley JA. Overview of otolaryngic allergy management: An eclectic and cost- effective approach. *Otolaryngol Clin North Am* 1998;**31**:69–82	Not immunotherapy
Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G, *et al*. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 2008;**121**:227–32	Not EE, does not report relevant information
Hankin CS, Cox L, Leatherman B, Lang D, Gross G, Fass P, *et al*. Allergy immunotherapy confers significant health care cost savings within 3 months of initiation: a matched retrospective cohort study of Medicaid-enrolled children newly diagnosed with allergic rhinitis. *Value Health* 2009;**12**:A122	Conference proceeding, does not report any relevant information
Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B, *et al*. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol* 2010;**104**:79–85	Not EE, does not report relevant information
Hankin CS, Cox L, Lang D, Bronston A, Fass P, Leatherman B, *et al*. 2011, Does allergen-specific immunotherapy reduce the risk, reverse, and/or mitigate asthma in children with allergic rhinitis? The pediatric improved access to allergen-specific immunotherapy - asthma incidence rates among Medicaid enrollees (pediatric-IMAGINE-AIRE) study, funded by the Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2011;**127**:AB73	Conference proceeding, does not report any relevant information
Incorvaia C, Agostinis F, Amoroso S, Ariano R, Barbato A, Bassi M, *et al*. Pharmacoeconomics of subcutaneous allergen immunotherapy. *Eur Ann Allergy Clin Immunol* 2007;**39**:17–20	Not EE, does not report relevant information
Kay AB, Lessof MH. Allergy: Conventional and alternative concepts. A report of the Royal College of Physicians Committee on Clinical Immunology and Allergy. *Clin Exp Allergy* 1992;**22**:1–44.	No relevant information reported
Kozma CM, Sadik MK, Watrous ML. Economic outcomes for the treatment of allergic rhinitis. *Pharmacoeconomics* 1996;**10**:4–13	No relevant information reported
Lockey RF, Hankin CS. Health economics of allergen-specific immunotherapy in the United States. *J Allergy Clin Immunol* 2011;**127**:39–43	Editorial, no relevant information reported
McCrory DC, Williams JW, Dolor RJ, Gray RN, Kolimaga JT, Reed S, *et al*. Management of allergic rhinitis in the working-age population. *Evidence Report: Technology Assessment (Summary)* 2003;**67**:1–4	No relevant information reported
McEwen LM. Immunotherapy and hayfever. *BMJ* 1991;**302**:530–1	Correspondence, no relevant information reported
Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988;**43**:523–9	No relevant information reported
Nalebuff, D. J. PRIST, RAST, and beyond. Diagnosis and therapy. *Otolaryngol Clin North Am* 1985;**18**:725–44	Not immunotherapy
Nash DB, Sullivan SD, Mackowiak J. Optimizing quality of care and cost effectiveness in treating allergic rhinitis in a managed care setting. *Am J Manag Care* 2000;**6**:S3–15	No relevant information reported
Passalacqua G, Guerra L, Fumagalli F, Compalati E, Canonica GW. An update on sublingual immunotherapy. *Allergy and Clinical Immunology International* 2005;**17**:181–5	No relevant information reported

Reference	Reason for exclusion
Passalacqua G, Guerra L, Pasquali M, Canonica GW. Non-injection routes for allergen immunotherapy: Focus on sublingual immunotherapy. *Inflamm Allergy Drug Targets* 2006;**5**:43–51	No relevant information reported
Poulsen PB, Pedersen KM, Christensen J, Vestenbaek U. Economic evaluation of a tablet-based vaccination against hay fever in Denmark. *Ugeskrift Laeger* 2008;**170**:138–42	Data reported in Bachert 2007 (included in review)
Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004;**22**:345–61	No relevant information reported
Sanico AM. Latest developments in the management of allergic rhinitis. *Clin Rev Allergy Immunol* 2004;**27**:181–9	No relevant information reported
Schafer T, Riehle A, Wichmann HE, Ring J. Alternative medicine in allergies: prevalence, patterns of use, and costs. *Allergy* 2002;**57**:694–700	Not immunotherapy
Tamayama K, Hoshi SL, Kondo M, Okubo I. Cost-effectiveness analysis of pre-seasonal medication for cedar pollinosis in Japan. *Yakugaku Zasshi* 2010;**130**:1725–36	Not immunotherapy
Thomas, M. Allergic rhinitis: evidence for impact on asthma. *BMC Pulm Med* 2006;**6**:S4	Not a review of EEs
Tripathi A, Patterson R. Impact of allergic rhinitis treatment on quality of life. *Pharmacoeconomics* 2001;**19**:891–9	No relevant information reported
Wang ZH, Hankin CS, Cox L, Bronstone A. Allergen immunotherapy significantly reduces healthcare costs among US adults with allergic rhinitis: a retrospective matched cohort study Jointly Funded by the AAAAI and ACAAI. *J Allergy Clin Immunol* 2011;**127**:AB150	Conference proceeding, does not report any relevant information
Weiner JM. Allergen injection immunotherapy. *Med J Aust* 2006;**185**:234	No relevant information reported
Weiss KB, Haus M, Ikura Y. The costs of allergy and asthma and the potential benefit of prevention strategies. *Allergy* 2000;**55**:1083–4	No relevant information reported
Whitehead S, Taylor MJ, Christensen J. An economic evaluation of Grazax for the treatment of grass pollen induced rhinoconjunctivitis in children. *Value Health* 2009;**12**:A125 (PRS 26)	Conference proceeding, does not report any relevant information
Yilmaz M, Bingol G, Altintas D, Kendirli SG. Effect of SIT on quality of life. *Allergy* 2000;**55**:302	No relevant information reported
Yuta A, Miyamoto Y, Hattori R, Ogihara H, Takeuchi K, Majima Y. The influence of medical economy from the aspect of medical direct costs by a difference of the number of the pollen scattering on an allergen-specific immunotherapy for Japanese cedar pollinosis. *Jpn J Allergol* 2007;**56**:1366–71	Not EE, does not report relevant information

Full text not obtainable (British Library unable to supply at the time of ordering)

Blaiss MS. Cost-effectiveness of H1-antihistamines. *Clin Allergy Immunol* 2002;**17**:319–36

Grevers G. Rising prevalence, high costs. Hay fever remains a challenge. *MMW Fortsch Med* 2008;**150**:28

Pedersen KM. Economic evaluation of new medicines: when safety and efficacy are not enough. *Drugs Today* 2008;**44**:69–71

Pruzinec P. Economical evaluation of the allergen vaccination profit comparing to the symptomatic therapy of allergic diseases. *Klin Imunol Alergol* 2003;**13**:25–7

Scadding GK. Hay fever and asthma: are we failing our patients? *Drugs Today* 2008;**44**:19–24

Solari JE, Loo J, Felices A, Casas J. Immunotherapy for patients with persistent allergic rhinitis unsatisfied with free chronic pharmacotherapy. *Allergol Immunopathol* 2006;**34**:102–6

Warner-Klein MK. Sublingual immunotherapy of allergic diseases. *Expert Opin Drug Deliv* 2006;**3**:599–612

Identified after report completed

Hagen A, Gorenoi V, Schönermark MP. *Spezifische Immuntherapie (SIT) zur Behandlung der allergischen Rhinitis*. Köln, Germany: Deutsche Agentur für HTA des Deutschen Instituts für Medizinische Dokumentation und Information; 2010

Appendix 11 Characteristics of included economic studies

Economic evaluations

Title: Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma

Ariano 2006[222]

Journal

Allergy and Asthma Proceedings

Type of economic analysis	Study population	Perspective
Cost–consequence analysis	Patients with seasonal *Parietaria* pollen-induced AR and asthma	Societal, national health-care system and patient

Research question

Evaluation of the economic advantage of subcutaneous allergen immunotherapy plus standard antiallergic drugs compared with standard antiallergic drugs alone

Intervention (comparator)	Country	Time horizon
Subcutaneous allergen immunotherapy + standard antiallergic drugs (standard antiallergic drugs only)	Italy	6 years

Effectiveness data	Sample size	Discount rate	Cost year (currency)
SSs	30	Not reported	Not reported (US$)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs – GP or specialist visits, drugs, specialist examinations

Results

- Immunotherapy + drug treatment was associated with better SSs compared with drug treatment only over 6 years
- Immunotherapy + drug treatment was associated with better patient satisfaction scores compared with drug treatment only over 6 years
- Net savings associated with immunotherapy plus drug treatment were €623 (US$830) per year at year 6 (net savings start 3 years after treatment)

Sensitivity analysis: None

Assumption tested: N/A

Result: N/A

Author's conclusion

Subcutaneous immunotherapy is associated with significant economic advantages over antiallergic drug treatment in the long term

General comments

- Small patient numbers ($n = 30$) and loss to follow-up up to year 6 not stated
- SSs were evaluated at baseline and annually for 6 years. No utility-based outcome measure was used
- As is the case with CCA, no single measure of economic benefit was derived making it difficult to conclusively comment on whether the interventions were value for money
- No discounting is applied to costs and therefore cost estimates may not be appropriate
- As the price year is not reported, future reflation exercises based on results from this study will be hindered
- The authors also classified side effects as 0 = absent, 1 = local reactions such as itching and oedema around the site of the injection, 2 = slight systemic reaction, such as rhinitis or conjunctivitis, and 3 = moderate/severe systemic reactions, such as asthma, urticaria, angioedema and/or anaphylactic shock. However, there are no details on differences between groups and it is unclear if costs for side effects were included in the EE
- Data used were from a prospective randomised long-term study

N/A, not applicable.

Title: Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis – a Northern European perspective

Bachert 2007[228]

Journal
Clinical and Experimental Allergy

Type of economic analysis	Study population	Perspective
Cost–utility analysis	Patients with grass pollen-induced rhinoconjunctivitis	Societal

Research question

Assessment of cost-effectiveness of Grazax (grass allergen tablet) compared with symptomatic treatment in seven northern European countries

Intervention (comparator)	Country	Time horizon
Sublingual Grazax (symptomatic treatment)	UK, Germany, Netherlands, Sweden, Denmark, Norway and Finland	Nine years (3 years with Grazax treatment and 6 years post Grazax discontinuation)

Effectiveness data	Sample size	Discount rate	Cost year (currency)
QALYs – based on EQ-5D	493	3–5% (depending on country)	2005 (euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: visits to physician, acute ward visits, use of symptomatic rescue medication for AR and asthma and hospitalisation

Indirect costs: productivity losses (hours missed from work owing to AR)

Results

- Grazax associated with more QALY gains compared with symptomatic treatment (0.0287 additional QALYs per season and 0.222 QALYs gained over 9 years discounted at 4%)
- At an annual cost of <€2200 for the societal perspective, and based on a threshold of €29,000 (£20,000) per QALY, Grazax is cost-effective compared with standard (symptomatic) treatment in northern Europe

Sensitivity analysis

Univariate deterministic

Assumption tested	Result
• Including direct costs only	• Annual cost of Grazax should be below €2200 to be cost-effective at €29,000 threshold
• Using the upper threshold of €43,800 (£30,000) for cost-effectiveness (societal perspective)	• Annual cost of Grazax should be below €3400 to be cost-effective

Author's conclusion

For a tablet below €6, Grazax is a cost-effective intervention for the prevention of grass pollen-induced rhinoconjunctivitis

General comments

- Data used in the cost–utility analysis were collected prospectively alongside a randomised parallel group, DBPC trial conducted during the 2005 pollen season
- Although not many sensitivity analyses has been explicitly reported, it is important to note that wide ranges of values were used in the CUA, which increases the rigour of the results, for example discount rates (1.5–5%), annual costs for Grazax (€1200–4400), EQ-5D (country-specific versions of EQ-5D)
- No information has been given about private patient costs (other than indirect costs attributed to hours missed from work)
- Country-specific resource use and unit cost data were used
- Neither actual EQ-5D inputs (based on country specific valuations) nor QALY estimates for each arm are presented in the paper, which makes it impossible to apply effectiveness measures from this study in other studies
- The burden of AR was assumed to be uniform across all northern European countries
- This analysis was undertaken alongside a multinational clinical trial
- The study was funded by a manufacturer of SIT products

N/A, not applicable.

Title : Influence of time horizon and treatment patterns on cost-effectiveness measures: the case of allergen-specific immunotherapy with Grazax

Beriot-Mathiot 2007[232]

Journal

Journal of Medical Economics

Type of economic analysis	Study population	Perspective
Cost–utility analysis	Patients with grass pollen-induced rhinoconjunctivitis	Societal

Research question

Estimation of cost-effectiveness of two treatment patterns for Grazax (seasonal and WHO-recommended pattern) relative to standard care, as well as the effect that time horizon has on this estimation. The seasonal scenario involves administering Grazax 16 weeks prior to, and during, the pollen season, whereas the WHO-recommended scenario involves daily intake of Grazax for 3 years

Intervention (comparator)	Country	Time horizon
Seasonal or WHO-recommended sublingual Grazax (symptomatic treatment)	UK, Netherlands, Denmark and Sweden	15 years (3 years with GRAZAX treatment and 12 years post GRAZAX discontinuation)

Effectiveness data	Sample size	Discount rate	Cost year (currency)
QALYs – based on EQ-5D	493	3%	2004/5 (euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: visits to physician, acute ward visits, use of symptomatic rescue medication for AR and asthma and hospitalisation

Indirect costs: productivity losses (hours missed from work owing to AR)

Results

- In the seasonal scenario, Grazax is more cost-effective than standard care with an ICER of €21,829. This ICER is independent of the time horizon considered
- In the WHO-recommended SIT scenario, Grazax is more cost-effective than standard care (at a threshold of €29,200) if the sustained effect of treatment is 2 years. The ICER decreases from €47,844 at the 1-year time horizon to €7894 at the 9-year time horizon
- The WHO-recommended SIT scenario is the most cost-effective when the time horizon is 6.3 years or more

Sensitivity analysis

Univariate deterministic

Assumption tested	Result
• Changing the time point when seasonal treatment commences from 16 weeks to 8 weeks before the pollen season	• Grazax was still more cost-effective than standard care with an even lower ICER of €13,797

Author's conclusion

Grazax is cost-effective both for the WHO-recommended SIT and the seasonal treatment

General comments

- Data used in the cost–utility analysis were collected prospectively alongside a randomised parallel group, DBPC trial conducted during the 2005 pollen season
- The only sensitivity analysis carried out was changing the time point at which seasonal treatment commences
- No information has been given about private patient costs (other than indirect costs attributed to hours missed from work)
- Country-specific resource use and unit cost data were used
- Some actual EQ-5D inputs were provided, but not disaggregated for the SIT or standard treatment group. In the same vein, QALY estimates for each arm were also not presented in the paper which makes it impossible to apply effectiveness measures from this study in other studies
- This analysis was undertaken alongside a multinational clinical trial
- It is not clear what the treatment used in the no-SLIT control group is, but it seems to be standard treatment

N/A, not applicable; WHO, World Health Organization.

Title: Cost-effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma

Berto 2005[223]

Journal

European Annals of Allergy and Clinical Immunology

Type of economic analysis	Study population	Perspective
Cost–consequence analysis	Children with either seasonal or perennial AR and asthma	Societal

Research question

Assessment of the cost of treating children with AR using sublingual immunotherapy (SLIT)

Intervention (comparator)	Country	Time horizon
SLIT (no SLIT control – for second analysis)	Italy	Four years (1 year pre-SLIT and 3 years on SLIT)

Effectiveness data	Sample size	Discount rate	Cost year (currency)
No. of asthma and rhinitis exacerbations, visits, absence from nursery or school	135	Not reported	Not reported (euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: concomitant pharmacological treatment for allergic disease, specialist visits, SLIT

Indirect costs: productivity losses (nursery/school days lost – proxy for working days lost by parents)

Results

- Compared with the pre-SLIT period and with no-SLIT control groups, SLIT was associated with substantial reductions in the no. of exacerbations, no. of school/nursery days lost and number of medical visits
- Mean direct and indirect costs per year during the SLIT period (again compared with pre-SLIT and no-SLIT groups) were also lower

Sensitivity analysis

None

Assumption tested: N/A

Result: N/A

Author's conclusion

High-dose SLIT may be effective in reducing the cost of AR and asthma

General comments

- Data were based on a sample from only one allergy centre in northern Milan but sample characteristics are not given making it difficult to know how generalisable the results are
- The interventions are not very well or clearly described
- As is the case with CCA, no single measure of economic benefit was derived, making it difficult to conclusively comment on whether the interventions were value for money
- No discounting is applied to costs and therefore cost estimates may not be appropriate
- It is not clear what the treatment is used in the no-SLIT control group, but it seems to be standard treatment

N/A, not applicable.

Title: Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study

Berto 2006[226]

Journal

Annals of Allergy, Asthma and Immunology

Type of economic analysis	Study population	Perspective
Cost-effectiveness analysis	Young adults with seasonal pollen-induced AR with or without asthma	National health-care system (NHS) and societal

Research question

Assessment of cost and consequences of SLIT added to pharmacotherapy in comparison to pharmacotherapy alone

Intervention (comparator)	Country	Time horizon
SLIT + pharmacotherapy (pharmacotherapy only)	Italy	6 years

Effectiveness data	Sample size	Discount rate	Cost year (currency)
No. of patients improved; number of asthma cases avoided	2230	3%	2002 (euros and US $)

Structure of model	Assumptions of model
Decision-tree model	Same rate of hospitalisation attributed to both the SLIT and no-SLIT groups

Resource and cost data

NHS perspective: direct medical costs (visits, diagnostic procedures, drugs, SLIT and hospitalisations)

Societal perspective: direct (as above), indirect (working days lost) and patient out-of-pocket costs

Results

From both the NHS and societal perspectives and for both outcomes (cost per additional improved patient and cost per additional asthma case avoided), SLIT dominates no-SLIT (i.e. it is cheaper and more effective)

Sensitivity analysis

Univariate deterministic

Assumption tested	Result
• Changing perspective from NHS to societal	• SLIT still dominates no-SLIT
• Varying distribution of disease and severity level	• SLIT still dominates no-SLIT
• Varying the cost of hospitalisations (from €1491.11 to €864.00)	• SLIT still dominates no-SLIT

Author's conclusion

SLIT is less expensive and more effective that pharmacotherapy alone from both perspectives and for both effectiveness outcomes

General comments

- It is not clear whether the two arms are comparable in terms of baseline characteristics
- The lack of details on the study sample characteristics makes it difficult to ascertain how generalisable the results of the study are to a wider population
- Effectiveness estimates were based on a retrospective cohort study in which clinicians enrolled in the study reported the outcomes for 100 of their patients. It is not clear whether this introduced any selection bias and, if it did, what effect it had on the results
- The data used to populate the model was not clearly presented making it problematic to replicate the decision tree model-based analysis
- The study was funded by a manufacturer of SIT products

Title: Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma

Brüggenjürgen 2008[229]

Journal
Annals of Allergy, Asthma and Immunology

Type of economic analysis
Cost–utility analysis

Study population
Patients with either seasonal or perennial AR and allergic asthma

Perspective
Societal and third-party payer

Research question
Assessment of cost-effectiveness of SCIT in addition to ST compared with ST alone

Intervention (comparator)
SCIT + ST (ST alone)

Country
Germany

Time horizon
15 years

Effectiveness data
Utilities

Sample size
2000

Discount rate
3%

Cost year (currency)
Not reported (euros)

Structure of model
Markov model

Assumptions of model
Markov cycle length = 1 year

Six disease/health states: mild AR; moderate to severe AR; moderate to severe AR and mild allergic asthma; moderate to severe AR and severe allergic asthma; no symptoms; and dead

Resource and cost data
Annual costs from Schramm *et al.*[271]

Direct costs associated with disability, early retirement and loss of work

Other data
Transition probabilities from published literature sources

Results

- From a societal point of view at 15 years, SCIT + ST dominates ST only (ICER of €–19,787 per QALY) (break-even point is reached after 10 years)
- From a third-party payer's perspective, SCIT + ST is associated with an ICER of €8308 per QALY

Sensitivity analysis: Univariate deterministic

Assumption tested	Result
Shortening SCIT treatment length from 3 to 2 years	SCIT + ST still dominates but is associated with even greater cost savings
Varying price of SCIT	Reducing cost of SCIT resulted in even greater savings – SCIT + ST still dominates
Varying the discount rate between 0% and 10%	SCIT + ST still dominates ST alone
Using third-party payers' perspective	SCIT + ST was associated with an ICER of €8308 per QALY
Extending SCIT to all patients	SCIT + ST was associated with an ICER of €3713 per QALY

Author's conclusion
Subcutaneous immunotherapy + ST was associated with cost savings and improved medical outcomes

General comments

- No probabilistic sensitivity analysis carried out
- It is not clear what instrument was used to derive the 'utilities' – reference cited is a report on acupuncture
- Assumptions that could not be validated by any literature sources were based on the consensus of a board of experts in paediatrics, dermatology, allergy, pneumonia and otolaryngology
- The interventions were not presented clearly in the article
- The resource use and cost data details were not reported in sufficient details to allow for replication
- Further, future reflation exercises will be hindered as the price year was not reported
- Because of the foregoing (i.e. lack of detail), it is hard to assess the rigour of the results obtained
- Study was funded by a manufacturer of SIT products

Title: Cost-effectiveness of GRAZAX for the prevention of grass pollen induced rhinoconjunctivitis in Southern Europe

Canonica 2007[230]

Journal
Respiratory Medicine

Type of economic analysis
Cost–utility analyses

Study population
Patients with seasonal grass pollen-induced rhinoconjunctivitis

Perspective
Societal

Research question
Assessment of cost-effectiveness of Grazax (grass allergen tablet) compared with symptomatic treatment in four southern European countries

Intervention (comparator)
Sublingual Grazax (symptomatic treatment)

Countries
Spain, France, Italy and Austria

Time horizon
Nine years (3 years with GRAZAX treatment and 6 years post GRAZAX discontinuation)

Effectiveness data
QALYs – based on EQ-5D

Sample size
634

Discount rate
3–6% (depending on country)

Cost year (currency)
2004/5 (Euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data
Directs costs: visits to physician and acute wards, symptomatic medication, asthma medication, eventual hospitalisation

Indirect costs: productivity losses (hours missed from work due to AR)

Other data
Risk of developing asthma

Results

- Grazax associated with more QALY gains compared with symptomatic treatment (0.0167 additional QALYs per season and 0.134 discounted QALYs gained over 9 years)
- At an annual cost of between €1500 and €1900, and based on a threshold of €29,000 (£20,000) per QALY, Grazax is cost-effective compared with standard (symptomatic) treatment

Sensitivity analysis
Univariate deterministic

Assumption tested	Result
• Impact of allergic asthma (including future costs related to asthma)	• ICERs associated with Grazax become even more favourable
• Excluding patients from Spain from the analysis (due to low pollen counts in Spain in 2005 which had impact on QoL)	• Mean QALY in Grazax group increased from 0.9492 to 0.9686
• Using the upper threshold of €43,800 (£30,000) for cost-effectiveness (societal perspective)	• Annual cost of Grazax should be <€2550 to be cost-effective

Author's conclusion
Grazax is cost-effective compared with standard (symptomatic) treatment in southern Europe

General comments

- Data used in the cost–utility analysis were collected prospectively alongside a randomised parallel group, DBPC trial conducted during the 2005 pollen season
- Even although not many sensitivity analyses has been explicitly reported, it is important to note that ranges of values were used in the CUA, for example discount rates (3–6%), annual costs for Grazax (€900–2900), EQ-5D (country-specific versions of EQ-5D)
- No information has been given about private patient costs (other than indirect costs attributed to hours missed from work)
- Neither actual EQ-5D inputs (based on country-specific valuations) nor QALY estimates for each arm are presented in the paper, which makes it impossible to apply effectiveness measures from this study in other studies
- This analysis was undertaken alongside a multinational clinical trial

N/A, not applicable.

Title: Health economic model of allergen–specific immunotherapy in seasonal allergic rhinitis from a health care payer's perspective

Claes 2009[224]

Journal

Allergo Journal

Type of economic analysis

Cost analysis

Study population

Paediatric and adult patients with SAR

Perspective

Health insurers

Research question

Comparative assessment of costs of five forms of immunotherapy:

- Long-term subcutaneous immunotherapy (LT SCIT)
- sublingual immunotherapy (SLIT)
- short-term subcutaneous immunotherapy with maintenance injections (ST SCIT + injections)
- short-term subcutaneous immunotherapy without maintenance injections (ST SCIT)
- short-term subcutaneous immunotherapy with an adjuvant-supported allergoid (allergoid + MPL) (ST SCIT MPL)

Intervention (comparator)

LT SCIT (SLIT; ST SCIT; ST SCIT + injections; ST SCIT MPL)

Country

Germany

Time horizon

Three years

Other scenarios look at 15-year time period

Effectiveness data

For base case assume 100% effectiveness for all different treatment strategies

Sample size

Not stated. Hypothetical paediatric and adult cohorts

Discount rate

5%

Cost year (currency)

Not reported (euros)

Structure of model

Markov model

Assumptions of model

Markov cycle length = 1 week

Base case: 100% effectiveness for all treatments being compared, no discontinuations and 100% compliance

Resource and cost data

Costs of diagnosis, clinician time, services, supplies (e.g. injections), SAR medication, hospital visits, costs of treating asthma

Other data

Transition probabilities (children) given for development over time of SAR (from non-SAR population), lower airway symptoms or asthma. Data mainly from PAT study[272]

Results

- Three-year average direct costs for the five forms of immunotherapy were: €2584 (LT SCIT), €4269 (SLIT), €1533 (ST SCIT), €2523 (ST SCIT + injections) and €2080 (ST SCIT MPL)
- Direct costs of the ST SCIT MPL arm, compared with those of other forms SCIT and SLIT, are higher at the beginning of therapy
- Other scenarios show that, compared with other forms of immunotherapy, ST SCIT and ST SCIT MPL have favourable sustainability and adherence-related outcomes

Sensitivity analysis

Univariate deterministic

Assumption tested

- Variation in discontinuation rates, discount rates, time horizon (5, 12 and 15 years), some costs and effectiveness (source for effectiveness data not clear)

Result

- Sensitivity analyses have an influence on costs, but overall no effect on the relative cost differences between different treatment strategies

Author's conclusion

Short-term SCIT and allergoid + MPL seem to be associated with fewer costs compared with other forms of immunotherapy. After 3 years giving no SIT is still the cheapest option, whereas after 15 years it becomes the most expensive option

General comments

- The authors assume 100% effectiveness, 0% discontinuation rates and 100% compliance for all therapies (base case), which seems infeasible
- Some of these assumptions are varied in sensitivity analyses but at least for effectiveness do not seem to be based on any clinical data
- Only total direct costs considered, no utilities estimated (not a CBA)

Title: A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries

Keiding and Jørgensen 2007[233]

Journal

Current Medical Research and Opinion

Type of economic analysis

Cost-effectiveness analysis and cost–utility analyses

Study population

Patients with seasonal (grass-induced) allergic rhinoconjunctivitis

Perspective

Not stated

Research question

Assessment of cost-effectiveness of Alutard SQ (ASQ) compared with emergency/standard treatment in six European countries

Intervention (comparator)

Subcutaneous ASQ (emergency/standard treatment)

Countries

Austria, Denmark, Finland, Germany, Netherlands and Sweden

Time horizon

Nine years (updosing and maintenance in year 1, follow-up in years 2 and 3, and emergency treatment for rest of time)

Effectiveness data

Symptom free and well-days (based on RQLQ), MSs, VAS, QALYs – based on mapping from RQLQ to EQ-5D

Sample size

Not reported

Discount rate

3%

Cost year (currency)

2005 (euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: updosing visits, maintenance visits, cost of ASQ, cost of specific immunotherapy, rescue medication, other direct costs

Indirect costs: productivity gain (through reduced number of working days lost)

Results

- ICERs associated with ASQ are between €9716 and €25,863 per QALY without accounting for indirect costs. When indirect costs are included, ASQ dominates emergency treatment in all countries except two, in which it is associated with low ICERs (€6458 per QALY for The Netherlands and €5024 per QALY for Sweden)
- ASQ was more favourable when outcomes were expressed as cost per symptom-free day and cost per well-day

Sensitivity analysis

None reported

Assumption tested: N/A

Result: N/A

Author's conclusion

ASQ is cost-effective compared with emergency treatment regardless of whether indirect costs are included or not

General comments

- Indirect costs relating to loss of working days were not considered, as data were not available in all of the six countries; instead those relating to productivity gain through reduced number of working days lost were used
- Difficult to assess the robustness of the results as sensitivity analyses were not conducted or reported
- The sample size should have also been given to give an idea of the how robust the analyses were
- The 'other direct costs' could have been enumerated to enable testing of the costing procedure. In addition, the cost perspective should have also been specified
- Data for the study came from the UK Immunotherapy Study Group (UKIS) trial
- A 10-cm VAS was used to measure allergic symptoms with '0' representing 'no symptoms' and '10' representing 'severe symptoms'

N/A, not applicable.

Title: Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma

Nasser 2008[231]

Journal

Allergy

Type of economic analysis	Study population	Perspective
Cost–utility analysis	Patients with grass pollen-induced rhinoconjunctivitis including those with co-existing asthma	Societal

Research question

Assessment of cost-effectiveness of Grazax (tablet-base allergen-SIT) plus ST compared with ST only

Intervention (comparator)	Countries	Time horizon
Sublingual Grazax + ST (ST only)	United Kingdom, Germany, Netherlands, Denmark, Sweden, Spain, Austria and Italy	Nine years (3 years of GRAZAX treatment and 6 years of sustained effect)

Effectiveness data	Sample size	Discount rate	Cost year (currency)
QALYs – based on EQ-5D	151	3.5%	2005 (UK £)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: emergency physician visits, acute ward visits, acute ward visits, hospitalisations

Indirect costs: hours missed from work, reduced productivity

Results

- Grazax was associated with more QALY gains than symptomatic treatment (0.0250 additional QALYs per season and 0.197 QALYs gained over 9 years discounted at 3.5%)
- Grazax was associated with a cost per QALY gained of £4319

Sensitivity analysis

Univariate deterministic

Assumptions tested	Results
Excluding influence of reduced productivity at work	Grazax was associated with an ICER of £8816 per QALY gained
Varying time horizon to 7 years but including influence of reduced productivity at work	Grazax was associated with an ICER of £7272 per QALY gained
Varying time horizon to 7 years but excluding influence of reduced productivity at work)	Grazax was associated with an ICER of £11,769 per QALY gained
Varying annual costs of Grazax from £1000 to £3000	Grazax remains cost-effective up to an annual cost of £1850 (£5.07 per tablet). Base-case price was £2.25 per tablet

Author's conclusion

SIT with Grazax is cost-effective compared with standard (symptomatic) treatment

General comments

- Data used in the cost–utility analysis were collected prospectively alongside a randomised parallel group, DBPC trial conducted during the 2005 pollen season
- No information has been given about private patient costs (other than indirect costs attributed to hours missed from work)
- Actual EQ-5D inputs (based on country-specific valuations) are not presented in the paper
- No EQ-5D values or QALY estimates for each arm are presented in the paper, which makes it impossible to apply effectiveness measures from this study in other studies
- This analysis was undertaken alongside a multinational clinical trial

N/A, not applicable.

Title: Pharmacoeconomic assessment of specific immunotherapy vs current symptomatic treatment for allergic rhinitis and asthma in France

Author
Omnes 2007[227]

Journal
European Annals of Allergy and Clinical Immunology

Type of economic analysis
Cost-effectiveness analysis

Study population
Adults and children suffering from either seasonal or perennial AR (with or without asthma)

Perspective
Health insurers

Research question
Assessment of comparative cost-effectiveness of three strategies: (i) symptomatic treatment (CST) alone; (ii) injectable specific immunotherapy (SCIT) plus CST (SCIT + CST); and (iii) sublingual immunotherapy (SLIT) plus CST (SLIT + CST)

Intervention (comparator)
SCIT + CST (SLIT + CST; CST only)

Country
France

Time horizon
Six years (adult population) and 7 years (juvenile population)

Effectiveness data
Proportions of individuals with rhinitis or allergic asthma in the four models (juvenile, adult, dust mite allergy and pollen allergy), distribution of severity levels, and treatment efficacy (the numbers of improved patients and asthma cases)

Sample size
1000

Discount rate
3%

Cost year (currency)
2003 (euros)

Structure of model
Decision-tree model

Resource and cost data
Direct costs: costs associated with drugs, visits and diagnostic tests. Expert opinion (Delphi panel) and recommendations from both French and international guidelines used to determine resource quantities

Indirect costs: no. of work-days lost

Results

Adults (6 years)

When compared with CST only:

- The incremental costs per asthma case avoided with SCIT + CST were €393 and €1327 for dust mite and pollen allergy, respectively
- The incremental costs per asthma case avoided with SLIT + CST were €3158 and €1708 for dust mite and pollen allergy, respectively

Children (over 7 years)

When compared with CST only:

- The incremental costs per asthma case avoided with SCIT + CST were €583 and €597 for dust mite and pollen allergy, respectively
- The incremental costs per asthma case avoided with SLIT + CST were €3938 and €824 for dust mite and pollen allergy, respectively

Sensitivity analysis: Univariate deterministic

Assumptions tested	Results
• Use of the official GP's tariff for SCIT from the nomenclature générale des actes professionnels (NGAP) nomenclature instead of the GP's tariff in adult model	• SCIT became the dominant strategy compared with CST in dust mite and pollen allergy • Results were unchanged
• Alternative distributions of severity levels were derived from two published studies in adult model	• Results were unchanged
• Ranges of values defined by the Delphi panel were also used for other clinical data in child model	

Author's conclusion

Injectable specific immunotherapy (SCIT) is a more cost-effective treatment in children with pollen allergy and in adults with dust mite allergy in comparison with both CST and sublingual SIT. Sublingual SIT was more cost-effective than CST in pollen-induced rhinitis, especially in children

General comments

- Most (all) of the epidemiological data for the adult (child) model were based on expert opinion, i.e. a Delphi panel of 11 members (10 allergologists and one epidemiologist); although this was justified (due to heterogeneity in published estimates), this was one weakness of the study
- Another limitation of the analysis was the lack of more rigorous assessment of uncertainty, for example using probabilistic sensitivity analysis
- Other aspects of the study were adequately addressed
- Although no head-to-head comparisons were made between SCIT + CST and SLIT + CST, SCIT + CST was associated with better outcome, i.e. lower ICERs, when both were compared with CST only

Title: Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy

Petersen 2005[234]

Journal

Allergol et Immunopathol

Type of economic analysis	Study population	Perspective
CBA and CEA	Patients with grass pollen or mite allergy (seasonal or perennial allergy)	Societal

Research question

Assessment of the health and monetary consequences of treating allergy with SIT compared with standard (symptomatic) treatment

Intervention (comparator)	Country	Time horizon
SCIT (standard/symptomatic treatment)	Denmark	Eight years (3 years treatment with SIT and 5 years' extrapolation)

Effectiveness data	Sample size	Discount rate	Cost year (currency)
Monetary benefits and measure of psychological well-being	204	5%	2002 (Danish krone, DKK)

Structure of model: N/A – retrospective observational study

Assumptions of model: N/A

Resource and cost data

Direct costs: medicine use; visits to medical doctors; visits to emergency rooms; visits to doctors on emergency duty; hospital stays pre-, per- and post-SIT

Patient costs: transportation; time costs

Indirect costs: work-related sick days; leisure activity sick days

Results

Subcutaneous immunotherapy is associated with an ICER of DKK 2.784 per patient/year of improved well-being. From a CBA perspective, SCIT was shown to be net beneficial

Sensitivity analysis: Univariate deterministic

Assumption tested	Result
Varying the time horizon considered after the start of SIT from 4 to 9 years	Cost per patient year of improved well-being lies in the range DKK 16,408 to DKK 2784

Author's conclusion

SIT is associated with increases in societal welfare

General comments

- The methodology for determining outcomes in the CBA is also not very clear (it seems only indirect costs associated with sick days were included in estimation)
- The results of the CEA (based on cost per year improvement in psychological well-being) are difficult to generalise
- It is also not clear what technique was used to value the monetary benefits used in the CBA

N/A, not applicable.

Title: Economic evaluation of sublingual vs subcutaneous allergen immunotherapy

Pokladnikova 2007[225]

Journal

Annals of Allergy, Asthma and Immunology

Type of economic analysis

CCA

Study population

Patients with seasonal allergic rhinoconjunctivitis

Perspective

Third-party payer, patient and societal

Research question

Evaluation of the cost and cost-effectiveness of SLIT compared with SCIT and standard ST

Intervention (comparator)

SLIT (SCIT; ST)

Country

Czech Republic

Time horizon

15 years

Effectiveness data

RQLQ score; VAS score; symptomatic medication reduction; health-care utilisation

Sample size

64 (19 = SLIT, 23 = SCIT and 22 = ST)

Discount rate

0%

Cost year (currency)

2002 (euros)

Structure of model: N/A – within-trial-based analysis

Assumptions of model: N/A

Resource and cost data

- Direct medical costs: costs of treatment and health-care services. Health-care services include specialist visits (consultations, laboratory tests, diagnostic tests, nurse services)
- Costs associated with adverse effects of treatment (medication, emergency department visits and hospitalisations)
- Patient costs: medication co-payment, over-the-counter drugs, travel costs, loss of income due to allergy symptoms, treatment and productivity costs (using human capital approach)

Results

- Clinical benefits for SLIT were comparable to those for SCIT but SCIT patients showed a slightly better improvement especially in VAS and symptomatic MSs
- Compared with SCIT, SLIT was associated with lower costs (from all perspectives)

Sensitivity analysis

Univariate deterministic

Assumption tested

- Varying costs of interventions by ± 50% for the third-party payer perspective

Result

- SLIT associated with lower costs compared with SCIT

Author's conclusion

Compared with SCIT, SLIT is a less expensive alternative from all perspectives except for patients who do not experience loss of income and travel costs associated with treatment (from the patients' perspective)

General comments

- SA conducted for only third-party payer perspective, making it difficult to ascertain the rigour of all the results
- The sample also seems to be fairly small, implying that one needs to interpret the results obtained with caution
- As is the case with CCA, no single measure of economic benefit was derived, making it difficult to conclusively comment on whether the interventions were value for money
- Data used in this study was derived from an open-label randomised clinical trial

N/A, not applicable.

Title: Economic evaluation of specific immunotherapy (SIT) vs symptomatic treatment of allergic rhinitis in Germany

Schädlich and Brecht 2000[235]

Journal

Pharmacoeconomics

Type of economic analysis

CEA, CCA

Study population

Patients with either pollen or mite allergy (seasonal or perennial allergy)

Perspective

Societal, national health-care system and SHI provider

Research question

Evaluation of the economic consequences of SIT lasting 3 years in comparison to those of continuous symptomatic treatment

Intervention (comparator)

Specific subcutaneous immunotherapy (continuous symptomatic treatment)

Country

Germany

Time horizon

10 years

Effectiveness data

No. of additional patients free from asthma symptoms; break-even points of costs/expenses per patient and difference in costs/expenses per patient after 10 years

Sample size

Cohort of 2000 patients

Discount rate

5%

Cost year (currency)

1997 (Deutschmarks, DM)

Structure of model

Decision-tree model

Assumptions of model

Base-case results based on average values of clinical effectiveness parameters and average case-related treatment costs and statutory health insurer (SHI) expenses

Resource and cost data

Directs costs: drugs (injections), medical services, diagnoses, adverse effects, SHI costs, rehabilitation

Indirect cost: loss of productivity caused by absence from work, premature retirement and premature death

Results

- Break-even point reached between 6 and 8 years after commencement of therapy
- Net savings associated with therapy were between DM650 and DM1190 per patient after 10 years
- SIT associated with ICERs of between DM3640 and DM7410 per additional patient free from asthmatic symptoms

Sensitivity analysis

Univariate deterministic

Assumption tested

- Use of best-/worst-case scenarios for SIT
- Impact of exogenous parameters on target variables

Results

- Best-case scenario – SIT was superior; worst-case scenario – symptomatic treatment superior
- Direct medical cost for symptomatic treatment has greatest impact on the target variable followed by average increase of asthma prevalence with symptomatic treatment

Author's conclusion

SIT results in net savings after 10 years from societal, health-care and SHI perspectives

General comments

- Target variables used in CCA not very clearly described, i.e. break-even points of costs/expenses per patient and difference in costs/expenses
- Difficult to ascertain the internal validity of the estimate of benefit as there is limited reporting of the literature review from where these estimates are sourced
- The results provided have, however, been subjected to some rigorous sensitivity analysis

SHI, statutory health insurance.

Reviews

Title: Economic studies of immunotherapy: a review

Berto 2008[247]

Journal

Current Opinion in Allergy and Clinical Immunology

Type of economic analysis

Review of cost analyses (cost and cost–cost analyses) and EEs

Study population

Patients with seasonal and PAR and asthma

Perspective

Societal, national health-care system and patient

Research question

Assessment of evidence on the economic advantages offered by immunotherapy

Intervention (comparator)

Immunotherapy (standard pharmaceutical treatment – for cost–cost analyses and EEs)

Countries

USA, UK, Spain, Italy, Germany, France, northern EU, southern EU, Austria, Denmark, Finland, Netherlands and Sweden

Time horizon

10 years

Effectiveness data

QALYs and other (unreported) physical/natural outcomes

Sample size

14 papers

Discount rate: N/A

Cost year (currency)

Not reported (euros)

Structure of model: N/A

Assumptions of model: N/A

Resource and cost data

Directs costs: outpatient and inpatient visits, specialist visits, immunotherapy, symptomatic medication, asthma medication, eventual hospitalisation

Indirect costs: productivity losses (working days lost by patients and nursery/school days lost – proxy for working days lost by parents)

Results

- Cost analyses: costs per patient/year varied from €96 to €348.50
- Cost–cost analyses: average costs/patient for immunotherapy ranged from €288 to €1182, whereas those for pre-immunotherapy/controls ranged from €116 to €2672
- EEs: immunotherapy is more cost-effective than standard treatment

Sensitivity analysis: None

Assumption tested: N/A

Result: N/A

Author's conclusion

Immunotherapy can be cheaper and also more cost-effective than standard therapy alone

General comments

- The results of the review are not reported in enough detail, for example the outcomes used in the cost-effectiveness analyses were not presented
- The results of head-to-head comparisons between SCIT and SLIT are not reported in sufficient detail

N/A, not applicable.

Title: The Health Economics of Allergen Immunotherapy

Hankin 2011[237]

Journal

Immunology and Allergy Clinics of North America

Type of economic analysis

Review of cost analyses (cost and cost-to-cost analyses) and EEs

Study population

Patients with seasonal or PAR and/or asthma

Perspective

Health-care system, societal and patient

Research question

Evaluation of the economic benefit of allergen-specific immunotherapy (SIT) compared

Intervention (comparator)

SIT [standard drug treatment (SDT) in certain instances]

Countries

USA, Germany, France, Italy, Denmark and northern Europe

Time horizon

From 1995 to 2011

Effectiveness data

QALYs, net benefits and other physical/natural outcomes

Sample size

15 studies

Discount rate

N/A

Cost year (currency)

2010 (US$)

Structure of model: N/A – systematic review

Assumptions of model: N/A

Resource and cost data

- Direct costs: encounters (visits), tests, allergic reactions, procedures, drugs, hospital services, SIT
- Indirect costs: productivity losses (days lost from work, disability and premature death)

Results

SIT provides cost benefits ranging from $96 to $5465. Average annual costs for SIT per patient ranged from US$247 to US$10,200; average annual costs for STD per patient ranged from US$1,335 to US$24,243; mean cost of allergy medications per patient year varied from US$23 to $37 and costs per QALY gained ranged from US$14,536 to US$38,695

Sensitivity analysis: N/A

Assumption tested: N/A

Result: N/A

Author's conclusion

SIT has cost benefits over SDT and therefore introduction of new SDTs must be carefully assessed in terms of clinical effectiveness and cost-effectiveness

General comments

- The details of the studies included in the review are presented with adequate details making a distinction between cost analyses and EEs

N/A, not applicable.

Appendix 12 Quality assessment of economic evaluations

Philips criteria: model-based economic evaluations

		Berto 2006[226]	Brüggenjürgen 2008[229]	Omnes 2007[227]	Schädlich and Brecht 2000[235]	Claes 2009[224]
Structure						
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y
3.	Is the primary decision-maker specified?	Y	Y	Y	Y	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y	Y
6.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	N	N	Y	Y	Y
7.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	N	Y
8.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	UC	Y	UC	UC	UC
9.	Is there a clear definition of the options under evaluation?	Y	N	Y	N	Y
10.	Have all feasible and practical options been evaluated?	N	N	Y	N	Y
11.	Is there justification for the exclusion of feasible options?	Y	N	N/A	N	N/A
12.	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y
13.	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	Y	Y	Y	N
14.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	Y	Y
15.	Is the cycle length defined and justified in terms of the natural history of disease?	N/A	Y	N/A	N/A	Y

Philips criteria: model-based economic evaluations

		Berto 2006[226]	Brüggenjürgen 2008[229]	Omnes 2007[227]	Schädlich and Brecht 2000[235]	Claes 2009[224]
Data						
16.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	N	N	N	N
17.	Where choices have been made between data sources, are these justified appropriately?	UC	N	N	N	N
18.	Where expert opinion has been used are the methods described and justified?	N/A	N/A	Y	UC	N/A
19.	Is the choice of baseline data described and justified?	N	N/A	N	N	N/A
20.	Are transition probabilities calculated appropriately?	UC	UC	Y	Y	UC
21.	Has a half-cycle correction been applied to both costs and outcomes?	N	N	UC	N	N
22.	If not, has the omission been justified?	N	N	UC	N	UC
23.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	N	N	N	N	N
24.	Are the costs incorporated into the model justified?	Y	N	Y	Y	Y
25.	Has the source for all costs been described?	N	N	N	N	N
26.	Have discount rates been described and justified given the target decision-maker?	Y	Y	Y	Y	Y
27.	Are the utilities incorporated into the model appropriate?	N/A	UC	N/A	N/A	N/A
28.	Is the source of utility weights referenced?	N/A	N	N/A	N/A	N/A
29.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	N/A	N/A	N/A	N/A	N/A
30.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	N	N	Y	N
31.	Has heterogeneity been dealt with by running the model separately for different subgroups?	N	N	Y	N	N
32.	Have the results been compared with those of previous models and any differences in results explained?	Y	N	N	Y	Y

N, no; N/A, not applicable; UC, unclear; Y, yes.

Evers checklist: non-model-based economic evaluations

		Ariano 2006[222]	Bachert 2007[228]	Beriot-Mathiot 2007[232]	Berto 2005[223]	Canonica 2007[230]	Keiding & Jørgensen 2008[233]	Nasser 2008[231]	Petersen 2005[234]	Pokladnikova 2007[225]
1.	Is the study population clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.	Are competing alternatives clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3.	Is a well-defined research question posed in answerable form?	Y	Y	Y	Y	Y	Y	Y	Y	Y
4.	Is the economic study design appropriate to the stated objective?	Y	Y	Y	Y	Y	Y	Y	Y	Y
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	Y	N	Y	Y	N	N	N	Y	N
6.	Is the actual perspective chosen appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y
7.	Are all important and relevant costs for each alternative identified?	N	N	N	N	Y	Y	Y	Y	Y
8.	Are all costs measured appropriately in physical units?	Y	Y	Y	Y	Y	Y	Y	Y	Y
9.	Are costs valued appropriately?	N	N	N	N	Y	Y	Y	Y	Y
10.	Are all important and relevant outcomes for each alternative identified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
11.	Are all outcomes measured appropriately?	Y	Y	Y	Y	Y	Y	Y	Y	Y

		Ariano 2006[222]	Bachert 2007[228]	Beriot-Mathiot 2007[232]	Berto 2005[223]	Canonica 2007[230]	Keiding & Jørgensen 2008[233]	Nasser 2008[231]	Petersen 2005[234]	Pokladnikova 2007[225]
12.	Are outcomes valued appropriately?	Y	Y	Y	Y	Y	Y	Y	Y	Y
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	Y	Y	Y	Y	Y	Y	Y	Y	Y
14.	Are all future costs and outcomes discounted appropriately?	N	Y	Y	N	Y	Y	Y	Y	Y
15.	Are all-important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N	Y	N	N	Y	N	Y	Y	Y
16.	Do the conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y
17.	Does the study discuss the generalisability of the results to other settings and patient/client groups?	Y	Y	N	N	Y	N	Y	N	Y
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	N	N	N	N	N	N	N	N	N
19.	Are ethical and distributional issues discussed appropriately?	N	N	N	N	N	N	N	N	N

N, no; Y, yes.

Appendix 13 Transition probabilities

Adult Markov model transition probabilities

Subcutaneous immunotherapy arm

Start immunotherapy

- Given that an adult with hay fever first started on SCIT treatment, what is the probability that they:
  - continue with SCIT without adding any symptomatic treatment?
  - then add on treatments to control all of their symptoms?
  - then add on treatments to control some of their symptoms (symptoms partly controlled)?
- Given that an adult with hay fever is on SCIT only (without any symptomatic treatment), what is the probability that they:
  - will survive within 1 year?
  - will quit SCIT within 1 year?
- Given that an adult with hay fever is on SCIT and treatments to control all of their symptoms, what is the probability that they:
  - will survive within 1 year?
  - will quit SCIT within 1 year?
- Given that an adult with hay fever is on SCIT and treatments to control only some of their symptoms, what is the probability that they:
  - will survive within 1 year?
  - will quit SCIT within 1 year?

On immunotherapy, no symptomatic treatment

- Given that an adult with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment), what is the probability that they:
  - continue with this treatment from the second year onwards?
  - will add on treatments to control all of their symptoms from the second year onwards?
  - will add on treatments to control only some of their symptoms from the second year onwards?
- Given that an adult with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment):
  - and then continued with this treatment from the second year onwards, what is the probability that they will quit SCIT treatment?
  - and then added treatments to control all of their symptoms from the second year onwards, what is the probability that they will quit SCIT treatment?
  - and then added treatments to control only some of their symptoms from the second year onwards, what is the probability that they will quit SCIT treatment?

On immunotherapy, symptoms controlled

- Given that an adult with hay fever has carried on from the previous year on SCIT and treatments to control all of their symptoms, what is the probability that they:
  - continue only with SCIT from the second year onwards?
  - continue with this treatment from the second year onwards?
  - will continue with SCIT but switch to treatments that control only some of their symptoms at some point within the second year?
- Given that an adult with hay fever has carried on from the previous year on SCIT and treatments to control all of their symptoms:
  - but then continued with only SCIT treatment at some point within the second year, what is the probability that they will quit SCIT treatment?

  - and then continued with this treatment from the second year onwards, what is the probability that they will quit SCIT treatment?
  - and then switched to treatments that control all of their symptoms at some point within the second year, what is the probability that they will quit SCIT treatment?

On immunotherapy, symptoms part controlled

- Given that an adult with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms, what is the probability that they:
  - will continue only with SCIT from the second year onwards?
  - will continue with SCIT but switch to treatments that control all of their symptoms at some point within the second year?
  - will continue with this treatment from the second year onwards?
- Given that an adult with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms:
  - but then continued with only SCIT treatment at some point within the second year, what is the probability that they will quit SCIT treatment?
  - and then continued with SCIT and switched to treatments that control all of their symptoms at some point within the second year, what is the probability that they will quit SCIT treatment?
- Given that an adult with hay fever has carried on from the previous year on SCIT and treatments to control all of their symptoms and then continued with this treatment from the second year onwards, what is the probability that they will quit SCIT treatment?

Completed immunotherapy, no symptomatic treatment

- Given that an adult with hay fever completed treatment with SCIT in the first year and is not on any other treatment, what is the probability that they:
  - continue this way from the second year onwards?
  - will add treatments to control all of their symptoms at some point within the second year?
  - will add treatments to control some of their symptoms at some point within the second year?

Completed immunotherapy, symptoms controlled

- Given that an adult with hay fever completed treatment with SCIT in the first year and is on treatment to control all of their symptoms, what is the probability that they:
  - will not have any symptomatic treatment from the second year onwards?
  - will continue with this treatment from the second year onwards?
  - will switch to treatments that control only some of their symptoms at some point within the second year?

Completed immunotherapy, symptoms part controlled

- Given that an adult with hay fever completed treatment with SCIT in the first year and is on treatment to control only some of their symptoms, what is the probability that they:
  - will not have any symptomatic treatment from the second year onwards?
  - will switch to treatments to control all of their symptoms at some point within the second year?
  - will continue with the same treatment from the second year onwards?

Early quit immunotherapy, no symptomatic treatment

- Given that an adult with hay fever quit treatment with SCIT early in the first year and is not on any other treatment, what is the probability that they:
  - continue this way from the second year onwards?
  - will add treatments to control all of their symptoms at some point in the second year?
  - will add treatments to control some of their symptoms at some point in the second year?

Early quit immunotherapy, symptoms controlled

- Given that an adult with hay fever quit treatment with SCIT early in the first year and is on treatment to control all of their symptoms, what is the probability that they:
  - will not have any symptomatic treatment from the second year onwards?
  - will continue with this treatment from the second year onwards?
  - will switch to treatments that control only some of their symptoms at some point within the second year?

Early quit immunotherapy, symptoms part controlled

- Given that an adult with hay fever quit treatment with SCIT early in the first year and is on treatment to control only some of their symptoms, what is the probability that they:
  - will not have any symptomatic treatment from the second year onwards?
  - will switch to treatments that control all of their symptoms at some point within the second year?
  - will continue with the same treatment from the second year onwards?

Sublingual immunotherapy arm

Same as for SCIT arm: replace 'SCIT' with 'SLIT'.

Symptomatic treatment-only arm

- Given that an adult with hay fever first started on symptomatic treatment only, what is the probability that they:
  - will continue without any symptomatic treatment?
  - will continue with treatments to control all of their symptoms?
  - will continue with treatments to control some of their symptoms?

No symptomatic treatment

- Given that an adult with hay fever has carried on from the previous year on no symptomatic treatment, what is the probability that they:
  - will continue without any symptomatic treatment from the second year onwards?
  - will add treatments to control all of their symptoms at some point within the second year?
  - will add treatments to control only some of their symptoms at some point within the second year?

Symptoms controlled

- Given that an adult with hay fever has carried on from the previous year on treatments that control all of their symptoms, what is the probability that they:
  - will continue without any symptomatic treatment from the second year onwards?
  - will continue with this treatment from the second year onwards?
  - switch to treatments that control only some of their symptoms at some point within the second year?

Symptoms part controlled

- Given that an adult with hay fever has carried on from the previous year on treatments that control only some of their symptoms, what is the probability that they:
  - will continue without any symptomatic treatment from the second year onwards?
  - switch to treatments that control all of their symptoms at some point within the second year?
  - will continue with this treatment from the second year onwards?

Child Markov model transition probabilities

Subcutaneous immunotherapy arm

Start immunotherapy

- Given that a child with hay fever first started on SCIT treatment, what is the probability that in the first hay fever season:
  - the patient does not require symptomatic treatment?
  - they then add on treatments to control all of their symptoms?
  - they then add on treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a child with hay fever is on SCIT only (without any symptomatic treatment), what is the probability that they will also have asthma after 1 year?
- Given that a child with hay fever is on SCIT and treatments to control all of their symptoms, what is the probability that they will also have asthma after 1 year?
- Given that a child with hay fever is on SCIT and treatments to control only some of their symptoms, what is the probability that they will also have asthma after 1 year?
- Given that a child with hay fever is on SCIT only (without any symptomatic treatment), what is the probability that they will quit SCIT after 1 year if they do not have asthma?
- Given that a child with hay fever is on SCIT and treatments to control all of their symptoms, what is the probability that they will quit SCIT after 1 year if they do not have asthma?
- Given that a child with hay fever is on SCIT and treatments to control only some of their symptoms, what is the probability that they will quit SCIT within 1 year if they do not have asthma?
- Given that a child with hay fever is on SCIT only (without any symptomatic treatment), what is the probability that they will quit SCIT after 1 year if they have asthma?
- Given that a child with hay fever is on SCIT and treatments to control all of their symptoms, what is the probability that they will quit SCIT after 1 year if they have asthma?
- Given that a child with hay fever is on SCIT and treatments to control only some of their symptoms, what is the probability that they will quit SCIT within 1 year if they have asthma?

On immunotherapy, no symptomatic treatment without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment); what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add on treatments to control all of their symptoms?
  - they then add on treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment):
  - and then continued with this treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then added treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then added treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then added treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then added treatments to control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?

- and then added treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?
- and then added treatments to control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?

On immunotherapy, no symptomatic treatment with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment), what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add on treatments to control all of their symptoms?
  - they then add on treatments to control some of their symptoms (symptoms partly controlled)?
- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT only (without any symptomatic treatment):
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
  - and then added treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
  - and then added treatments to control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?

On immunotherapy, symptoms controlled without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year SCIT and treatments to control all of their symptoms:
  - but then continued with only SCIT treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with this treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments that control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then switched to treatments that control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?
  - and then switched to treatments that control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?

On immunotherapy, symptoms controlled with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control some of their symptoms (symptoms partly controlled)?
- Given that an asthmatic child with hay fever has carried on from the previous year SCIT and treatments to control all of their symptoms:
  - but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
  - and then switched to treatments that control only some of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?

On immunotherapy, symptoms part controlled without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms:
  - but then continued with only SCIT treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - but then switched to treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with this treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - but then switched to treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they did not develop asthma?
  - but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?
  - but then switched to treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?
  - and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year if they developed asthma?

On immunotherapy symptoms part controlled with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?

- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms but then continued with only SCIT treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms but then switched to treatments to control all of their symptoms during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?
- Given that an asthmatic child with hay fever has carried on from the previous year on SCIT and treatments to control only some of their symptoms and then continued with this treatment during the second year, what is the probability that they will quit SCIT treatment before the start of the third year?

Completed immunotherapy no symptomatic treatment without asthma

- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT and did not require symptomatic treatment in the previous year, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT only (without any symptomatic treatment):
  - and then continued with no symptomatic treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then added treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then added treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Completed immunotherapy, no symptomatic treatment with asthma

- Given that an asthmatic child with hay fever has completed 3 years' treatment with SCIT and did not require symptomatic treatment in the previous year, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?

Completed immunotherapy, symptoms controlled without asthma

- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control all of their symptoms in the previous year, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms?
- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control all of their symptoms in the previous year:
  - but continued without any SCIT or treatments to control their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Completed immunotherapy symptoms controlled with asthma

- Given that an asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control all of their symptoms in the previous year, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms?

Completed immunotherapy symptoms part controlled without asthma

- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control only some of their symptoms in the previous year, what is the probability that in the current year;
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms?
- Given that a non-asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control only some of their symptoms in the previous year
  - but continued without any SCIT or treatments to control their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Completed immunotherapy symptoms part controlled with asthma

- Given that an asthmatic child with hay fever completed 3 years' treatment with SCIT and was on treatment to control only some of their symptoms in the previous year, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms?

Early quit immunotherapy, no symptomatic treatment without asthma

- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is not on any other treatment, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and was not on any other treatment
  - and continued without any treatment during the second year, what is the probability that they develop asthma by the end of the third year?
  - but then added treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - but then added treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Early quit immunotherapy, no symptomatic treatment with asthma

- Given that an asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is not on any other treatment, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?

Early quit immunotherapy, symptoms controlled without asthma

- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is on treatment to control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms?
- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and was on treatment to control all of their symptoms
  - and then continued without any treatments to control their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Early quit immunotherapy, symptoms controlled with asthma

- Given that an asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is on treatment to control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms?

Early quit immunotherapy, symptoms part controlled without asthma

- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is on treatment to control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is on treatment to control only some of their symptoms
  - and then continued without any treatments to control their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control all of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with treatments to control only some of their symptoms during the second year, what is the probability that they develop asthma by the end of the third year?

Early quit immunotherapy, symptoms part controlled with asthma

- Given that an asthmatic child with hay fever quit treatment with SCIT before the start of the third year and is on treatment to control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?

Sublingual immunotherapy arm

Same as for SCIT arm: replace 'SCIT' with 'SLIT'.

Symptomatic treatment-only arm

No symptomatic treatment without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on no symptomatic treatment, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year on no symptomatic treatment:
  - and then continued without symptomatic treatment during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control all of their symptoms during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control only some of their symptoms during the subsequent year, what is the probability that they develop asthma by the end of the third year?

No symptomatic treatment with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on no symptomatic treatment, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they then add treatments to control all of their symptoms?
  - they then add treatments to control some of their symptoms (symptoms partly controlled)?

Symptoms controlled without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on treatments that control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year on treatments that control all of their symptoms
  - and then continued without symptomatic treatment during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with this treatment during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control only some of their symptoms during the subsequent year, what is the probability that they develop asthma by the end of the third year?

Symptoms controlled with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on treatments that control all of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they continue with treatments to control all of their symptoms?
  - they switch to treatments to control only some of their symptoms (symptoms partly controlled)?

Symptoms part controlled without asthma

- Given that a non-asthmatic child with hay fever has carried on from the previous year on treatments that control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?

  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?
- Given that a non-asthmatic child with hay fever has carried on from the previous year on treatments that control only some of their symptoms
  - and then continued without symptomatic treatment during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then switched to treatments to control all of their symptoms during the subsequent year, what is the probability that they develop asthma by the end of the third year?
  - and then continued with this treatment during the subsequent year, what is the probability that they develop asthma by the end of the third year?

Symptoms part controlled with asthma

- Given that an asthmatic child with hay fever has carried on from the previous year on treatments that control only some of their symptoms, what is the probability that in the current year:
  - the child does not require symptomatic treatment?
  - they switch to treatments to control all of their symptoms?
  - they continue with treatments to control only some of their symptoms (symptoms partly controlled)?

Appendix 14 Cost-effectiveness analysis based on six-weekly injections

The resource use and unit costs for SCIT and ST are the same as in the main analysis. The only difference is in the number of injections/clinic visits. The total number of clinic visits over a 3-year period was assumed to be 36, i.e. 19 in year 1 (including updosing), eight in year 2 and nine in year 3.

Shown below are the costs and ICERs when the 6-week maintenance schedule is used. The effectiveness estimates based on change in RQLQ were assumed to remain the same.

TABLE 67 Costs: SCIT (6-weekly maintenance schedule)

	Year 1	Year 2[a]	Year 3[a]
Staff during clinic visits			
Consultant	£702.81	£285.91	£310.78
Band 8 nurse	£208.74	£84.92	£92.30
Supplies/consumables[b]			
	£3.80	£1.55	£1.68
SCIT medication			
Allergy medicine			
Alutard	£1051.82	£725.18	£788.24
Symptomatic medicine			
Desloratadine	£24.15	£23.33	£22.54
Budesonide	£41.86	£40.45	£39.08
Productivity loss			
Hours missed from work	£49.74	£48.05	£46.43
Hours at work with reduced productivity	£95.14	£91.92	£88.82
Total annual costs	**£2178.06**	**£1301.32**	**£1389.86**
Total cumulative costs	**£2178.06**	**£3479.38**	**£4869.24**

a Costs discounted at 3.5%.
b Supplies are made of swabs, syringes, hypodermic needles and gloves.

TABLE 68 Subcutaneous immunotherapy costs for years 4–10 (6-weekly maintenance schedule)

	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Staff during clinic visits							
Consultant	–	–	–	–	–	–	–
Band 8 nurse	–	–	–	–	–	–	–
SCIT medication							
Alutard	–	–	–	–	–	–	–
Symptomatic medicine							
Desloratadine	£21.78	£21.05	£20.33	£19.65	£18.98	£18.34	£17.72
Budesonide	£37.76	£36.48	£35.25	£34.06	32.90	31.79	£30.72
Productivity loss							
Hours missed from work	£44.86	£43.34	£41.88	£40.46	£39.09	£37.77	£36.49
Hours at work with reduced productivity	£85.81	£82.91	£80.11	£77.40	£74.78	£72.25	£69.81
Total annual costs	**£190.21**	**£183.78**	**£177.56**	**£171.56**	**£165.76**	**£160.15**	**£154.74**
Total cumulative costs[a,b]	**£5059.45**	**£5243.23**	**£5420.79**	**£5592.35**	**£5758.11**	**£5918.27**	**£6073.00**

a Costs discounted at 3.5%.

b Includes cumulative cost of SCIT incurred in years 1–3.

TABLE 69 Economic evaluation results: SCIT vs ST (based on direct comparisons, 6-weekly maintenance schedule)

Cost difference (£) at	
3 years	4085
4 years	4032
5 years	3980
6 years	3930
7 years	3882
8 years	3835
9 years	3790
10 years	3746
RQLQ difference	0.740 (95% CI 0.560 to 0.920)
ICER (£): costs/unit improvement in RQLQ	5521 (95% CI 4441 to 7295)
Total QALY gain in 3 years	0.0957 (95% CI 0.0724 to 0.1189)
ICER (£): costs per QALY	42,705 (95% CI 34,349 to 56,431)
Total QALY gain in 4 years	0.1254 (95% CI 0.0949 to 0.1559)
ICER (£): costs per QALY	32,145 (95% CI 25,856 to 42,478)
Total QALY gain in 5 years	0.1542 (95% CI 0.1167 to 0.1917)
ICER (£): costs per QALY	25,815 (95% CI 20,764 to 34,113)
Total QALY gain in 6 years	0.1820 (95% CI 0.1377 to 0.2262)
ICER (£): costs per QALY	21,599 (95% CI 17,373 to 28,541)
Total QALY gain in 7 years	0.2088 (95% CI 0.1580 to 0.2596)
ICER (£): costs per QALY	18,591 (95% CI 14,953 to 24,566)
Total QALY gain in 8 years	0.2347 (95% CI 0.1776 to 0.2918)
ICER (£): costs per QALY	16,338 (95% CI 13,141 to 21,589)
Total QALY gain in 9 years	0.2598 (95% CI 0.1966 to 0.3230)
ICER (£): costs per QALY	14,588 (95% CI 11,734 to 19,278)
Total QALY gain in 10 years	0.2840 (95% CI 0.2149 to 0.3531)
ICER (£): costs per QALY	13,191 (95% CI 10,610 to 17,431)

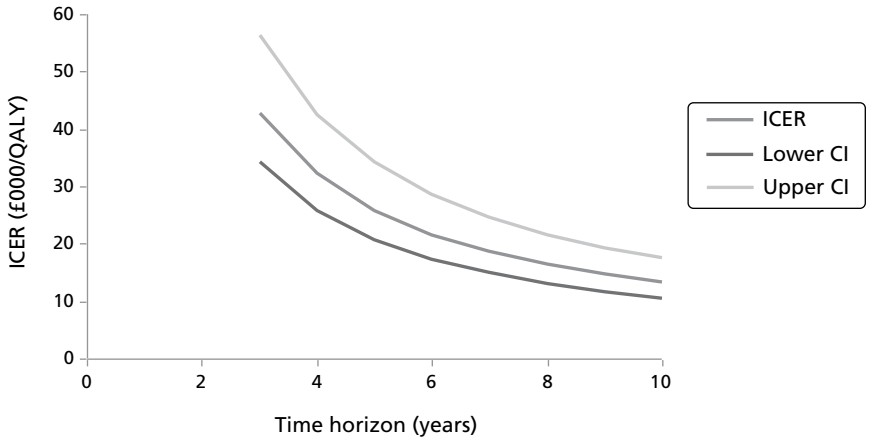

FIGURE 96 Cost-effectiveness of SCIT vs ST (direct comparison, 6-weekly maintenance schedule).

TABLE 70 Economic evaluation results: SCIT vs ST (based on indirect comparisons, 6-weekly maintenance schedule)

Cost difference (£) at	
3 years	4085
4 years	4032
5 years	3980
6 years	3930
7 years	3882
8 years	3835
9 years	3790
10 years	3746
RQLQ difference	0.764 (95% CI 0.425 to 1.116)
ICER (£): costs/unit improvement in RQLQ	5347 (95% CI 3661 to 9613)
Total QALY gain in 3 years	0.0988 (95% CI 0.0549 to 0.1443)
ICER (£): costs per QALY	41,363 (95% CI 28,317 to 74,356)
Total QALY gain in 4 years	0.1295 (95% CI 0.0720 to 0.1892)
ICER (£): costs per QALY	31,136 (95% CI 21,315 to 55,971)
Total QALY gain in 5 years	0.1592 (95% CI 0.0885 to 0.2325)
ICER (£): costs per QALY	25,004 (95% CI 17,117 to 44,948)
Total QALY gain in 6 years	0.1879 (95% CI 0.1045 to 0.2744)
ICER (£): costs per QALY	20,920 (95% CI 14,322 to 37,607)
Total QALY gain in 7 years	0.2156 (95% CI 0.1199 to 0.3149)
ICER (£): costs per QALY	18,007 (95% CI 12,327 to 32,370)
Total QALY gain in 8 years	0.2423 (95% CI 0.1348 to 0.3540)
ICER (£): costs per QALY	15,825 (95% CI 10,833 to 28,447)
Total QALY gain in 9 years	0.2682 (95% CI 0.1492 to 0.3918)
ICER (£): costs per QALY	14,130 (95% CI 9673 to 25,401)
Total QALY gain in 10 years	0.2932 (95% CI 0.1631 to 0.4283)
ICER (£): costs per QALY	12,777 (95% CI 8747 to 22,968)

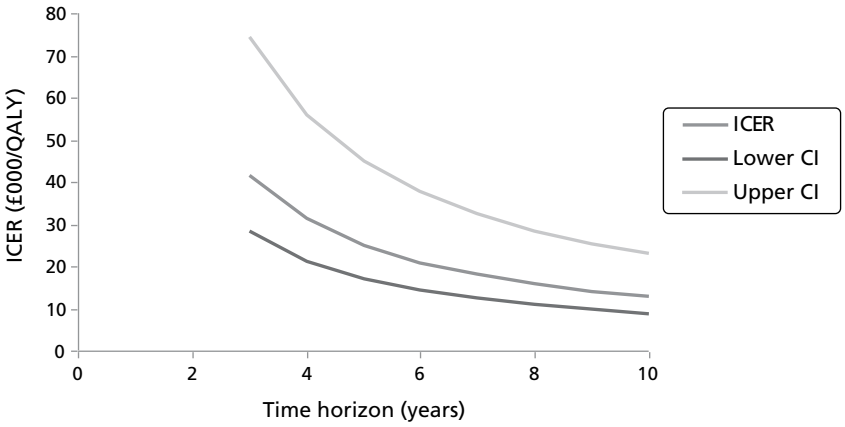

FIGURE 97 Cost-effectiveness of SCIT vs ST (indirect comparison, 6-weekly maintenance schedule).

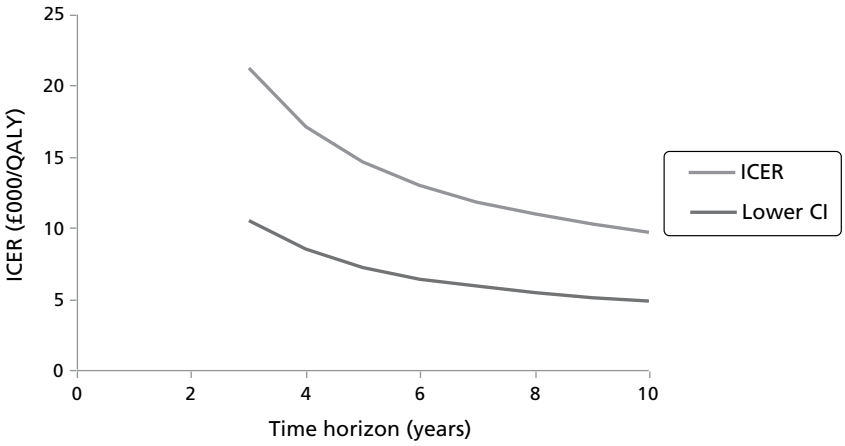

FIGURE 98 Cost-effectiveness of SCIT vs SLIT (6-weekly maintenance schedule).

TABLE 71 Economic evaluation results: SCIT vs SLIT (based on indirect comparisons 6-weekly maintenance schedule)

Cost difference (£) at	
3 years	1417
4 years	1498
5 years	1575
6 years	1650
7 years	1723
8 years	1793
9 years	1860
10 years	1926
RQLQ difference	0.517 (95% CI –0.0710 to 1.045)
ICER (£): costs/unit improvement in RQLQ	2741 (1356 to SLIT dominates)
Total QALY gain in 3 years	0.0668 (95% CI –0.0092 to 0.1351)
ICER (£): costs per QALY	21,203 (95% CI 10,490 to SLIT dominates)
Total QALY gain in 4 years	0.0876 (–0.0120 to 0.1771)
ICER (£): costs per QALY	17,090 (95% CI 8455 to SLIT dominates)
Total QALY gain in 5 years	0.1077 (–0.0148 to 0.2177)
ICER (£): costs per QALY	14,624 (95% CI 7235 to SLIT dominates)
Total QALY gain in 6 years	0.1271 (–0.0175 to 0.2569)
ICER (£): costs per QALY	12,982 (95% CI 6423 to SLIT dominates)
Total QALY gain in 7 years	0.1459 (–0.0200 to 0.2948)
ICER (£): costs per QALY	11,810 (95% CI 5843 to SLIT dominates)
Total QALY gain in 8 years	0.1640 (–0.0225 to 0.3315)
ICER (£): costs per QALY	10,932 (95% CI 5409 to SLIT dominates)
Total QALY gain in 9 years	0.1815 (–0.0249 to 0.3668)
ICER (£): costs per QALY	10,251 (95% CI 5072 to SLIT dominates)
Total QALY gain in 10 years	0.1984 (–0.0272 to 0.4010)
ICER (£): costs per QALY	9707 (95% CI 4802 to SLIT dominates)

'ST dominates' means that ST is more effective and also cheaper.

Appendix 15 Funnel plots

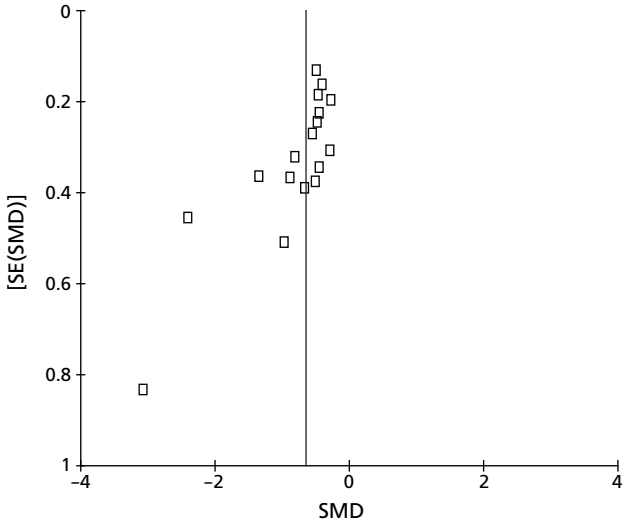

FIGURE 99 Funnel plot: SCIT vs placebo, SSs. SE, standard error.

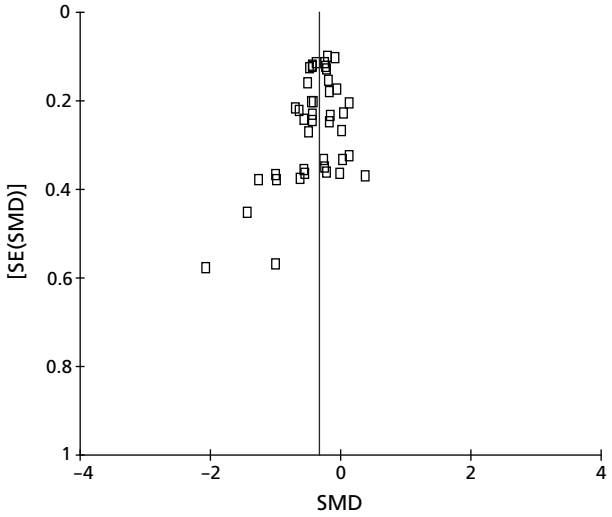

FIGURE 100 Funnel plot: SLIT vs placebo, SSs. SE, standard error.

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