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Health Economic Analysis of Allergen Immunotherapy (AIT) for the Management of Allergic Rhinitis, Asthma, Food Allergy and Venom Allergy: A Systematic Overview

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Abstract

Background: The European Academy of Allergy and Clinical Immunology (EAACI) is developing guidelines for allergen immunotherapy (AIT) for the management of allergic rhinitis, allergic asthma, IgE-mediated food allergy and venom allergy. To inform the development of clinical recommendations, we undertook systematic reviews to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT for these conditions. This paper focusses on synthesizing data and gaps in the evidence on the cost-effectiveness of AIT for these conditions.

Methods: We produced summaries of evidence in each domain and then synthesized findings on health economic data identified from four recent systematic reviews on allergic rhinitis, asthma, food allergy and venom allergy, respectively. The quality of these studies were independently assessed using the Critical Appraisal Skills Programme (CASP) tool for health economic evaluations.

Results: 23 studies satisfied our inclusion criteria. Of these, 19 studies investigated the cost-effectiveness of AIT in allergic rhinitis, of which seven were based on data from randomized controlled trials with economic evaluations conducted from a health system perspective. This body of evidence suggested that sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) would be considered cost-effective using the (English) National Institute for Health and Clinical Excellence (NICE) cost-effectiveness threshold of £20,000/quality adjusted life year (QALY). However, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data should be taken into account when interpreting these results. For asthma, there were three eligible studies, all of which had significant methodological limitations; these suggested that SLIT, when used in patients with both asthma and allergic rhinitis, may be cost-effective with an incremental cost-effectiveness ratio (ICER) of £10,726 per QALY. We found one economic modelling study for venom allergy which, despite being based largely on expert opinion and plausible assumptions, suggested that AIT for bee and wasp venom allergy is only likely to be cost-effective for very high risk groups who may be exposed to multiple exposures to venom/year (e.g., bee keepers). We found no eligible studies investigating the cost-effectiveness of AIT for food allergy.

Conclusions: Overall the evidence to support the cost-effectiveness of AIT is limited and of low methodological quality, but suggests that AIT may be cost-effective for people with allergic rhinitis with or without asthma and in high risk subgroups for venom allergy. We were unable to draw any conclusions on the cost-effectiveness of AIT for food allergy.

Keywords: allergy; cost-effectiveness; immunotherapy; payer; quality adjusted life year

Background

Allergen immunotherapy (AIT) is a potential treatment option in those with severe and/or potentially life-threatening allergic disorders who are inadequately managed with pharmacotherapy. AIT is most relevant n relation to the management of allergic rhinitis, asthma, food allergy and venom allergy and it is for this reason that the European Academy of Allergy and Clinical Immunology (EAACI) is in the process of producing clinical practice guidelines for these conditions.

We have recently completed systematic reviews investigating the role of AIT in the management of allergic rhinitis, asthma, food allergy and venom allergy focusing on the effectiveness, safety and cost-effectiveness of AIT.[1 2 3 4] During the course of undertaking these reviews, we identified a number of health economic evaluations, which we considered it prudent to synthesize with a view to drawing overarching insights into the state of this evidence-base and in order to guide future evaluations.

Our specific aims were to:

- Synthesize data on the cost-effectiveness of AIT for the clinical management of allergic rhinitis, allergic asthma, IgE-mediated food allergy and venom allergy from the perspective of health payers; and
- Identify research gaps in relation to the cost-effectiveness of AIT for these conditions.

METHODS

A detailed outline of the methods have previously been published in the protocols and papers of each individual review.[i ii iii iv v vi vii viii] We therefore confine ourselves to a synopsis of the methods employed.

Search strategies

Highly sensitive search strategies were developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic rhinitis, asthma, food allergy and venom allergy from electronic bibliographic databases. The search strategies were developed on OVID MEDLINE and then adapted for the other databases.[1-4] In all cases, the databases were searched from inception to October 31, 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field. There were no language restrictions employed.

Study selection

All references were uploaded into the systematic review software DistillerSR and duplicate records were removed. Studies were independently checked by two reviewers (SD, MA, AaS) against the inclusion criteria detailed in the reviews.[1-4] Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

Quality assessment

Quality assessments were independently carried out on each study by two reviewers (MA and SD). The Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies was used for this purpose.[ix] Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

Data extraction, analysis and synthesis

A data extraction sheet was developed to capture the pertinent features of the cost-effectiveness analysis based on the Drummond checklist and the National Institute for Health and Clinical Excellence (NICE) reference case for economic evaluations.[x xi] Data were independently extracted onto a customized data

extraction sheet developed for the purposes of these reviews by two reviewers (MA, AaS or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). Where studies reported results from multiple perspectives, results from the health systems perspective were presented and where there were multiple outcome measures including quality adjusted life years (QALYs) the focus of the review was to present results in terms of QALYs. Costs were translated to 2014/15 GBP prices using National Health Service Personal Social Services Research Unit (NHS PSSRU) inflation indices[xii] and standard exchange rates to aid the comparability of the studies.

A detailed descriptive report was produced on each study to summarize the literature. This data extraction process was used to assess the methodological features of the applied economic evaluations and highlight key methodological gaps in the studies from a health economics perspective. The summary tables are reproduced in the results section of this article, with full data extraction forms available in Appendix 1.

Registration and reporting

The underpinning reviews have been registered with the International Prospective Register of Systematic Reviews (PROSPERO): Allergic Rhinitis: CRD42016035373; Allergic Asthma: CRD42016035372; Venom: CRD42016035374; Food Allergy: CRD42016039384. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (Appendix 2).

RESULTS

Overall description

Our searches yielded 21 studies assessing the cost-effectiveness of allergic rhinitis, asthma and venom allergy that met our inclusion criteria (see Table 1 and Appendix 1). Two of these studies are included separately in both the asthma and rhinitis analyses. Nineteen studies focussed on allergic rhinitis,[xiii,xiv,xv,xvi,xvii,xviii,xix,xx,xxi,xxii,xxiii, xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx,xxxi] three on asthma[13,14,xxxii] and one on venom allergy.[xxxiii] No studies were identified investigating the cost-effectiveness of food allergy. We identified

studies looking at both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT), and which included both children and adults.

Quality assessment

The overall quality of the studies was low. Of the 19 allergic rhinitis studies, nine were assessed to be of low quality,[13,16-19,22,24,28,29] six medium[15,20,21,23,25,30] and four high quality.[14,26,27,30] Of the three asthma studies, two were of a low quality[13,32] and one high quality.[14] The one included venom allergy study was assessed to be of medium quality.[33] The quality of the studies is summarized in Table 2a-e.

Summary of evidence

We begin by briefly summarizing the data in relation to each condition, and then synthesize findings across this body of evidence in order to highlight gaps and provide insights to inform the planning of future studies.

Allergic rhinitis

Of the 19 allergic rhinitis studies, two focussed on patients who all had both allergic rhinitis and allergic asthma [13,14] and the remaining 17 focussed on patients who had allergic rhinitis (some of whom also had asthma, but it was difficult to know how many because of lack of clarity in the descriptions of studies). Three of these studies reported results from a societal perspective[18,21,23] with the remaining 16 reporting information from a health systems perspective.

Studies were based in a range of countries: Germany (N=7), Denmark (N=4), Italy (N=4), UK (N=4), Austria (N=2), Finland (N=2), France (N=2), Sweden (N=2), the Netherlands (N=2), Canada (N=1), Czech Republic (N=1), Norway (N=1) and Spain (N=1). Three studies reported including participants from more than one country.[15,18,20]

Seven of the studies reported results against disease specific outcome measures whilst the remaining twelve reported results based on QALYs. A detailed summary of each study can be found in Table 1 and Appendix 1.

Thirteen of the studies[13-15,18-21,24-27,30,31] were based on randomized controlled trial (RCT) data or meta-analyses of RCT data including two model-based evaluations.[26,30] The remaining studies were based on a mixture of questionnaires, observational data and expert opinion. None of the studies based on non-random data attempted to control for selection bias. None of the RCT-based studies described the amount of missing data in the study or explained how if at all any missing data was imputed for in the analyses.

Study time horizons ranged between 1-15 years with the longer time horizon studies typically based on much shorter follow-up trial data (typically 1 year) and assuming constant continued treatment effects after AIT was discontinued.

Nine of the studies[13-16,18,25,26,28] compared SLIT with standard care; three studies[17,20,26] compared SCIT with standard care; two studies[23,29] compared AIT (undefined) versus standard care; seven studies [19,21,22,24,26,30,31] compared SCIT versus SLIT, and two of these studies also compared different SLIT preparations.[19,31]

There were seven studies based on RCT data conducted from a health system perspective and using QALYs as their outcome measure. Two high quality studies were based in the UK. The first found that in patients with both rhinitis and asthma the incremental cost-effectiveness ratio (ICER) for SLIT versus standard care was £8,816 per QALY at 2005 prices inflated using NHS inflation indices (PSSRU) to £10,726 per QALY at 2014/15 prices.[14] The second study found that in 5-16 year olds with rhinoconjuctivitis with or without asthma in the UK the ICER for SLIT versus standard care was £12,168 per QALY at 2008 prices. Updating to 2014/15 prices this translated to an ICER of £13,357 per QALY.[27]

Three studies were conducted in Germany in patients with rhinoconjunctivitis without asthma. The first medium quality study found the ICER for SLIT (Oralair) versus standard care was €14,728 per QALY at 2011 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £11,460 per QALY.[31] The remaining two studies were both of high quality. The second found the ICER for SLIT (Oralair) versus SCIT to be €12,593 per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £9,627 per QALY.[30] The third German study found SCIT (Allergovit) to be cheaper and more effective than SLIT (Oralair). The ICER for SCIT (Allergovit) standard care was estimated to be €11,000 per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro translated this to an ICER of £8,334 per QALY.[26]

A medium quality study from Denmark looked at adult patients with rhinoconjuctivitis and found the ICER for SLIT versus standard care to be 134,105 DKK per QALY (no price year was given so we assumed the study was undertaken in the publication year i.e. 2008) updating to current prices and GBP at 0.1 GBP per DKK translated this to an ICER of £15,294 per QALY at 2014/15 prices.[25] Finally a further medium quality study conducted in adult patients with rhinoconjuctivitis performed in the UK in which ICERs for SCIT were calculated using healthcare data from Austria, Denmark, Finland, Germany, Sweden and the Netherlands. The ICERs of SCIT compared to standard care in 2005 Euro per QALY were 9716, 2586, 13683, 10300, 24519 and 22675, respectively. Updating to current prices and at 0.75 GBP per Euro gave ICERs of £8,866, £2,360, £12,486, £9,399, £22,374 and £20,691 per QALY respectively at 2014/15 prices.[20]

It was unclear how comparable the patient populations were between the studies. A particularly important factor that impacted on the costs and quality of life observed was the proportion of patients who also had asthma, but these proportions were not reported in many of the studies. The other interesting observation to be made is that the ICERs for AIT seemed to vary substantially between different health systems as demonstrated in Keiding et al 2007[20] where ICERs ranges from £2,360 per QALY in Denmark to £22,374 per QALY in the Netherlands suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.

In general, the studies find that AIT and where defined both SLIT and SCIT were more effective than standard care, but also more expensive. The studies that compared SLIT with SCIT gave mixed results not allowing us to conclude that either treatment is necessarily more effective or more costly than the other from a health system perspective. The studies comparing SLIT (Grazax) and SLIT (Oralair) suggested SLIT (Oralair) is both more effective and cheaper than SLIT (Grazax).[19,31]

The seven RCT studies compared, disregarding the caveats about generalizability, suggested that SLIT and SCIT treatment would be considered cost-effective in this patient population in England at the standard NICE cost-effectiveness threshold of £20,000 per QALY. However, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data should be taken into account when interpreting these results.

Asthma

Three studies were deemed suitable for use in the review of AIT to treat patients with allergic asthma. Data extraction of these studies is summarized in Table 1.

Of the three health economic studies included, only one low quality study focussed on patients with allergic asthma without reported rhinitis.[32] This was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease specific outcome measure (mean morning peak flow) with no attempt to convert it to a general quality of life measure such as QALYs making it impossible to assess the cost-effectiveness of the treatment. The study found that over the three years SCIT was more expensive than standard care and performed better than standard care on the disease specific outcome measure.

The remaining two studies looked at people with both allergic rhinitis and asthma. The first of these compared SLIT with standard care in a RCT (N=151) conducted in the UK, Germany, Holland, Denmark, Sweden, Spain, Austria and Italy with results evaluated from an English NHS perspective.[14] This trial, which was already discussed in the rhinitis section above, used one year of treatment data and assumed a constant treatment effect over the three-year treatment period and the six years following the

end of the treatment, thereby extrapolating the treatment effect over years 2-9. EQ5D was used to evaluate the treatment outcome and the ICER of SLIT as compared to standard care at 2005 prices was calculated as £8,816 per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using NHS PSSRU inflation indices translated this to an ICER of £10,726 per QALY.

The final study, also in patients with rhinitis and asthma, based on a RCT (N=70) with five years of follow-up conducted in Italy compared SLIT with standard care and found that patients on SLIT cost less and suffered less symptoms than those on standard care.[13] Methods of the study were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score reported in the study to a general quality of life scale making it impossible to undertake a formal assessment of cost-effectiveness.

From the very limited set of studies found, all of which had significant methodological limitations, we can conclude that there is a suggestion that SLIT when used in patients with both allergic asthma and allergic rhinitis may be cost-effective from an English NHS perspective with an ICER of £10,726 per QALY, well below the stated NICE threshold on £20,000 per QALY.

Venom allergy

Only one study of moderate quality was found that looked at the economic evaluation of AIT for venom.[33] This was a modelling study looking at the cost-effectiveness of AIT for the treatment of bee and wasp venom allergy (Table 1). The study assessed Pharmalgen venom immunotherapy (PhVIT) + high-dose anti-histamines (HDA) + adrenaline auto-injector (AAI) versus HDA + AAI and avoidance advice only. It found that AIT was not cost-effective in the general population (ICERs of £18 million and £7.6 million per QALY against HDA + AAI and avoidance advice only, respectively), but more effective than other treatment options with the potential for cost saving in patients likely to be stung more than five times a year (e.g., bee keepers).

This study, despite the fact that it was based largely on expert opinion and plausible assumptions, suggested that AIT for bee and wasp venom allergy was only likely to be cost-effective from an English NHS perspective for very high risk groups likely to be exposed to multiple exposures to venom per year. The modelling study suggested plausible ranges of exposure to such events to qualify a patient as a member of a high risk group and explored a wide range of sensitivity and scenario analyses to demonstrate the robustness of its findings.

Food allergy

We found no studies that met our inclusion criteria that looked at the cost-effectiveness of AIT for food allergy. Studies are needed in this area in order to provide information on this rapidly expanding treatment area.

Gaps in the literature

There is significant scope for future well designed studies looking at the cost-effectiveness of AIT for the treatment of patients with allergic rhinitis, allergic asthma and IgE-mediated food allergy. However, there seems little scope for further research regarding the use of AIT in patients with venom allergy. Key areas that future studies should address include: (1) effectiveness in different populations e.g. children versus adults, patients with only allergic rhinitis vs patients with allergic rhinitis and asthma; (2) well conducted RCTs with reasonable sample sizes and enough follow-up data to capture treatment effects during and after treatment; (3) directly collecting health related quality of life outcomes in the trial using instruments such as EQ5D; (4) comparison of the full range of treatment options (i.e. standard care, SCIT and SLIT) from a health system perspective; (5) using methodologically sound analyses to handle missing data and selection bias where observational data are used; and (6) fully characterizing the decision uncertainty through the use of sensitivity analyses exploring both parameter uncertainty as well as key model assumptions such as the duration of treatment effect.

DISCUSSION

Statement of principal finding

This review has found a limited amount of evidence in relation to the cost-effectiveness of AIT from a health system perspective in allergic rhinitis, allergic asthma and venom allergy and no evidence with regards to IgE-mediated food allergy. The limited studies identified looking at AIT for the treatment of allergic rhinitis suggest that SLIT and SCIT treatment would be considered cost-effective for these conditions in England at the standard NICE cost-effectiveness threshold of £20,000 per QALY. However, the quality of the studies and the general lack of attention to characterising uncertainty and handling missing data should be taken into account when interpreting these results.

Strengths and limitations

Our search strategies were robust and comprehensive filtering the vast literature pertaining to the subject. Furthermore, we actively sought expert opinions to add to the literature in case we had missed studies. There is however, always the possibility as with all such overviews, that some studies may not have been identified or have slipped through our search processes.

Studies were conducted in varied patient populations and health care settings, and used a variety of outcome measures to assess cost-effectiveness making pooling of results challenging. Where possible however, we have used QALYs from an English NHS perspective and converted costs to 2014/15 prices in GBP to compare cost-effectiveness results across the studies.

Interpretation in the light of the previous literature

This is, as far as we are aware, the first economic overview of AIT that has been conducted in relation to the conditions under study.

Implications for policy, practice and research

The findings from this overview will be considered together with the related evidence on the effectiveness and safety of AIT in drawing up guidelines and developing recommendations for practice. The findings from this analysis will be particularly helpful in relation to countries such as the UK and the Netherlands that have an explicit focus on health economic evaluations when deciding whether to promote use of interventions throughout their health systems. That said, with increasing pressure on health budgets globally the findings from this study are also likely to be of wider interest.

This work has also highlighted the need for investigators routinely to consider including formal cost-effectiveness analyses in their research plans and ensuring that these studies are undertaken to international standards. Consideration also needs to be given to undertaking health economic analyses from societal/patient perspectives as the condition can result in a significant personal societal/economic burden.

Conclusions

Overall the evidence to support the cost-effectiveness of AIT is limited and of a low methodological quality but appears to suggest that from an English NHS perspective AIT is cost-effective for allergic rhinitis, asthma and venom allergy in very high risk subgroups. No studies were identified assessing the cost-effectiveness of AIT for treating people with food allergy. There is much scope for further high quality studies addressing the methodological gaps identified in this review assessing the cost-effectiveness of AIT against various allergic conditions.

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Conflicts of interest: M Asaria**:** reports grants from EAACI to carry out the review, during the conduct of the study; S Dhami: reports grants from EAACI to carry out the review, during the conduct of the study; R van Ree: reports personal fees from HAL Allergy BV, personal fees from Citeq BV, outside the submitted work; R. Gerth van Wijk reports personal fees from ALK-Abello, Circassia, and Allergopharma, during the conduct of the study; A. Muraro reports personal fees from Novartis, Meda, and Mylan, outside the submitted work; G Roberts reports that his university has received payments for work undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck; A. Sheikh reports grants from the EAACI during the conduct of the study.

Figure 1: Conceptualization of cost-effectiveness of allergen immunotherapy for allergic rhinoconjunctivitis, allergic asthma, food allergy and venom allergy- a systematic overview

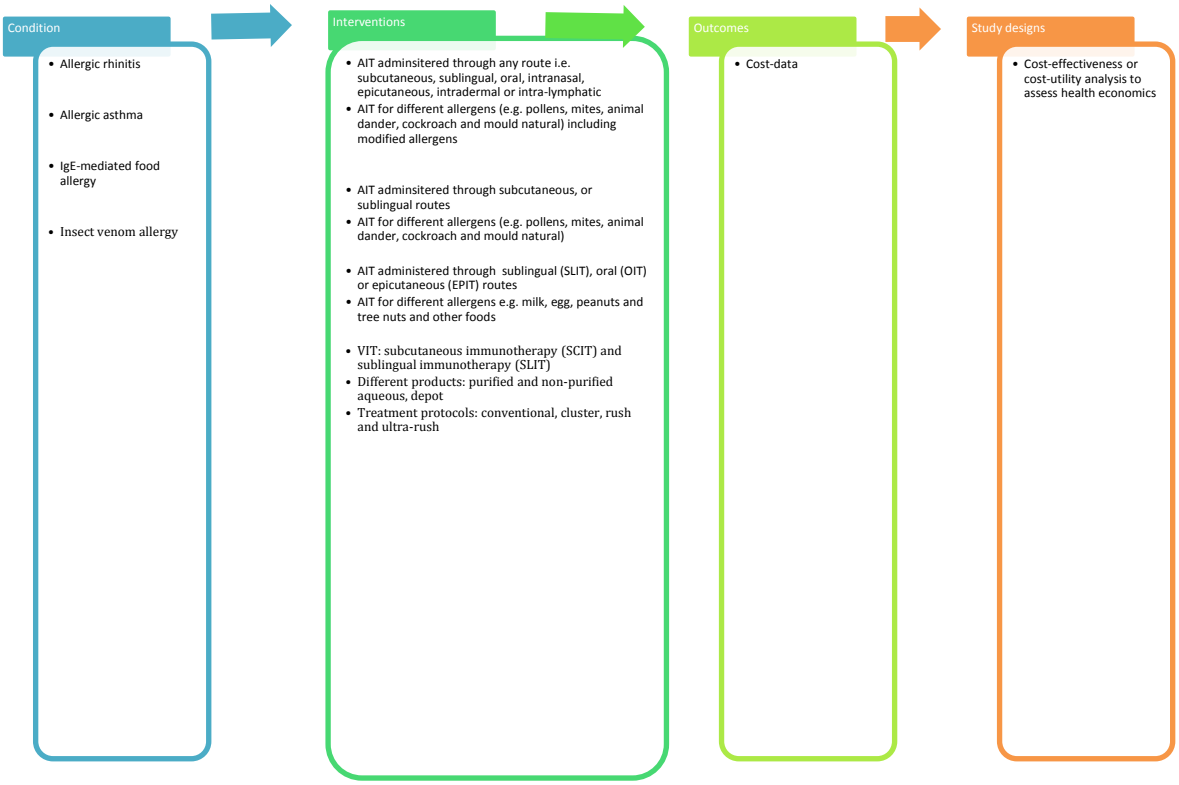

Table 1: Data extraction

Author, Year & Country	Type of Economic Analysis	Perspective	Study Population	Intervention/ Comparator	Time Horizion	Effectiveness Data	Sample Size	Outcome Measure	Outcome Discount Rate	Cost Data	Cost year / currency	Cost Discount Rate	Results	Sensitivity Analysis	General Comments
Rhinitis and asthma studies															
Ariano, 2009, Italy[13]	CEA	Health system	Patients with dust mite induced allergic asthma and rhinitis	SLIT / Standard Care	5 years	RCT 5 year follow up	70	VAS symptom score	0%	RCT patient diary and unit costs	?/Euros	0%	Overall costs lower in SLIT patients and lower symptom score	NA	Very little detail provided of the analysis performed no real economic analysis or interpretation of the results provided
Nasser, 2008, UK[14]	CUA	Health system	Patients suffering from grass pollen induced RC co-existing with asthma	SLIT(Grazax)/ Standard care	9 years	RCT 1 year follow-up	151	EQ5D - QALYs	3.50%	RCT patient diary linked to unit costs	2005/GBP	3.50%	ICER £8816 per QALY	One way sensitivity analysis to explore impact of changing time horizon	Results based on patients in UK, Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy· Treatment effect assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
Rhinitis with or without asthma															

Bachert, 2007, UK, Germany, Netherlands, Sweden, Denmark, Norway, Finland[15]	CUA	Health system	Patients with grass pollen induced rhinoconjunctivitis	SLIT / Standard care	9 years	RCT 1 year follow up	493	EQ5D - QALYs	3 – 5% depending on country	RCT patient diary mapped to country specific unit costs	2005 / Euro	3 – 5% depending on country	Cost per year of treatment must be below 2200 euros for SLIT to be cost effective at NICE threshold of £20000 per QALY	N/A	Price of SLIT not given so ICERs not calculated, rather max price for SLIT to be cost effective calculated Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
Berto,2006, Italy[16]	CEA	Health system	Young adults with pollen induced rhinitis with or without allergic asthma	SLIT / Standard care	6 years	Retrospective non-random subset selected from clinical study	2000	Number of patients improved	0%	Clinical records linked to unit costs	2002 / Euro	3%	SLIT is cost saving and more effective than standard care	Deterministic one way exploration of hospital costs	Potential for selection bias as physicians asked to pick subsets of patients from clinical study for economic evaluation
Bruggenjurgen, 2008, Germany[17]	CUA	Health system	Patients with pollen or mite induced allergic rhinitis with or without asthma	SCIT / Standard care	15 years	Published study	N/A	QALYs	3%	Published study	? / Euro	3%	ICER SCIT vs standard care 8308 euros per QALY	One way deterministic exploration od alternative treatment durations and discount rates	Difficult to assess the validity of cost or utility data as very little detail of studies that this analysis is based on given in the paper

Canonica,2007, Spain, Italy, France, Austria[18]	CUA	Societal	Patients with a 2 year history of grass pollen induced allergic rhinoconjunctivitis with or without asthma	SLIT / Standard care	9 years	RCT 1 year follow up	Unclear subset of 634	EQ5D - QALYs	3 – 5 % depending on country	RCT patient diary linked to unit costs	2004 / Euro	3 – 5 % depending on country	0.134 incremental QALYs in SLIT patients. 29000 euro per QALY in all four countriesif SLIT costs 1400 euro per year then ICER would be less than	Repeated analysis excluding Spanish patients	Results calculated for France even though trial did not cover France.. Unclear exactly what data from the multi country trial was used to calculatethese results. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation.

Dranitsaris, 2014, Canada[19]	CEA	Health system	Patients with grass induced allergic rhinitis with or without asthma	SCIT / SLIT (GRX) / SLIT (OA) / Standard care	1 year	Meta-analysis of 20 RCTs	N/A	Symptom control	0%	Expert opinion	2012 / CAD	0%%	SCIT, SLIT(GRX) and SLIT (OA) had similar efficacy in terms of symptom control. Cost of SCIT = 946 CAD; Cost of SLIT (GRX) =2122 CAD; Cost of SLIT (OA) = 844 SLIT (OA) is as effective as SLIT (GRX) and SCIT but cheaper over 1 year	N/A	Unclear what the allergic rhinitis symptom score represents and if it was comparable between studies Unclear about how much of the cost data was expert opinion as opposed to data from the meta analysis

Keiding ,2007, UK[20]	CUA	Health system	Adults with clinical history of grass pollen induced seasonal allergic rhinoconjunctivitis	SCIT / Standard treatment	9 years	RCT 1 year follow up	306	RQLQ mapped to EQ5D - QALYs	0%	Resource use collected in trial with national unit costs applied	2005 / Euro	3%%	ICER in Euro per QALY Austria 9716; Denmark 2586; Finland 13683; Germany 10300; Netherlands 24519; Sweden 22675	one way deterministic analysis on costs described but results not reported	Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation. Mapping from RQLQ to EQ5D applied to calculate QALYs not standard or validated
Meadows,2013, England[21]	CUA	Societal	Patients with pollen induced allergic rhinitis with or without allergic asthma	SLIT / SCIT / Standard care	6 years	Meta-analysis of RCTs	N/A	RQLQ mapped to EQ5D - QALYs	3.5%%	Resource use from expert opinion with unit costs applied	2011 / GBP	3.50%	ICER SLIT vs standard care £37537 per QALY ICER SCIT vs standard care £29579 per QALY ICER SCIT vs SLIT £24404 per QALY	N/A	Mapping between RQLQ and EQ5D to calculate QALYs not validated

Omnes,2007, France[22]	CEA	Health system	Children over 5 and adults over 16 with dust mite or pollen induced allergic rhinitis	SLIT / SCIT/ Standard care	7 years children ; 6 years adults	Expert opinion	N/A	Asthma cases avoided	0%%	Expert opinion	? / Euro	0%%	ICER vs standard care children dust mite SLIT: 3938; SCIT: 583 ICER vs standard care children dust pollen SLIT: 824; SCIT: 597 ICER vs standard care adults dust mite SLIT: 3158; SCIT: 393 ICER vs standard care adults dust pollen SLIT: 1708; SCIT: 1327 All in Euros per asthma case avo	N/A	Entire study seems to be based on expert opinion Does not compare treatment with SLIT against SCIT incrementally

Petersen, 2005, Denmark[23]	CEA	Societal	Patients with grass pollen or mite allergy	SIT / Standard care	5 years	Retrospective questionnaire following trial	253	Patient year of improved well being	5%	Administrative data	2002 / DKK	5%	ICER 2784 DKK per patient year of improved well being	N/A	Selection bias due to partial response rate to questionnaire not controlled for. Recall bias not controlled for. Outcome measure is not validated and does not capture degree of improvement.
Pokladnikova, 2008, Czech Republic[24]	CEA	Health system	Adults with at least 2 years of seasonal allergic rhinoconjuctivitis with or without allergic asthma	SLIT / SCIT / Standard Care	3 years	RCT 5 years follow up	19 SLIT, 23 SCIT, 22 Standard Care	RQLQ	0%	Administrative data linked to unit costs	2002 / Euro	3%	SLIT and SCIT both performed better on RQLQ than standard care	One way deterministic sensitivity analysis performed on costs and discount rates	No incremental cost effectiveness results were provided
Poulsen , 2008, Denmark[25]	CUA	Health system	Adults with grass pollen induced rhinotconjuctivitis	SLIT / Standard care	9 years	RCT one year follow up	493	EQ5D / QALYs	3%%	Unclear	? / DKK	3%%	ICER: 134105 DKK per QALY	N/A	Based on patients in Denmark, Sweden, England, Germany, Holland with Danish QALY weights and unit costs applied to EQ5D and resource use data. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation

Reinhold, 2016, Germany[26]	CEA	Health system	29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma	SLIT (OA) vs SCIT (Allergovit) vs symptomatic treatment	9 years	RCT	?	Utility mapped to QALY	3%	Administrative data	2013/euro	3%	SCIT dominates SLIT and has an ICER of 11000 euros per QALY against symptomatic treatment	Probabilistic and deterministic sensitivity analysis conducted	This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years
Ronaldson, 2014, UK[27]	CUA	Health system	5-16 year olds with grass pollen induced rhinoconjunctivitis with or without asthma	SLIT / Standard care	9 years	RCT 1 year follow up	253	Symptom scores mapped to QALYs	3.5%%	RCT Patient diaries mapped to unit costs	2008 / GBP	4%	ICER £12168 per QALY	PSA showed 90% probability of SLIT being cost effective at £30000 per QALY threshold and 60% probability cost effective at £20000 per QALY threshold	Mapping from symptom scores to QALYs not validated. Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation

Ruggeri, 2013, Italy[28]	CUA	Health system	Patients with grass pollen induced allergic rhinitis	SLIT / Standard care	4 years	Posthoc analysis of 2 RCTs	?	AAdSS mapped to QALYs	3%	SIMAP study updated to 2011	2011 / Euro	3%%	At low AAdSS SLIT is dominated by standard care At medium AAdSS ICER 1024 euros per QALY At high AAdSS ICER 1035 euros per QALY	PSA showed 99% probability ICER less that 30000 euros per QALY for medium and high AAdSS	Not clear how AAdSS is converted to QALYs. Cost and effectiveness estimates taken from different studies
Schadlich, 2000, Germany[29]	CEA	Health system	Patients with seasonal (pollen) and perennial (mite) allergy with or without asthma	SIT / Standard Care	10 years	Unclear	UC	Patients who do not develop asthma	0%	Resource use surveys	1990 / DM	0%	SLIT performed better than SCIT and was cheaper from a health system perspective	N/A	It was very unclear what data sources were used to populate the model in this study

Verheggen, 2015, Germany[30]	CEA	Payers perspective	29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma	SLIT vs blended mix of current SCIT treatments	9 years	RCT	?	QALYs mapped from Rhinitis Symptom Utility Index (RSUI)	3%	Administrative data	2013/euros	3%	ICER of SLIT vs SCIT is 12,593 euro per QALY with a probability of being cost effective at 20,000 euro per QALY of 76%	Probabilistic and deterministic sensitivity analysis as well as scenario analysis performed	This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis Comparator is a mix of SCIT treatments rather than one specific treatment Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years
Westerhout, 2012, Germany[31]	CUA	Health system	Patients with grass pollen induced rhinoconjunctivitis without asthma	SLIT (OA) / SLIT (GRZ) / SCIT (ALD) / Standard care	9 years	Meta-analysis	N/A	QALYs	3%	Survey data	2011 / Euro	3%	SLIT (OA) dominates SLIT (GRZ) and SCIT (ALD). ICER SLIT (OA) vs Standard care 14728 euros per QALY	PSA suggests 79% probability SLIT (OA) cost effective at a threshold of £20000 per QALY	Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation• Resource use taken from external survey rather than measured in the underlying studies in meta-analysis
Asthma only studies															
Reinhold ,2013, Germany[26]	CEA	Health system	Children and adolescents with mite induced allergic asthma	SCIT / Standard Care	3 years	RCT 3 year mean follow up	65	Mean morning peak flow (l/min)	0%	RCT – patient diary	2009 / Euro	0%	ICER: 11 Euros per l/min mean morning peak flow	Bootstrapping performed but not used in cost effectiveness results	No hospital costs included 5 SCIT and 1 non-SCIT patients excluded because of "outlier" levels of costs
Venom studies															

Hockenhull, 2012,England	CUA	Health system	General population as well as high risk of sting subset of population	PhVIT + HAD + AAI / HAD + AAI / avoidance advice only	10 years	Subset of RCT and survey data	337	Systemic reaction or death following sting converted to QALYs	3.50%	Administrative data and reference costs	? / GBP	3.50%	PhVIT + HAD + AAI is cost saving and more effective when compared to either HAD + AAI or avoidance advice only for patients likely to be stung more than five times a year. In the general population the ICER for PhVIT + HAD + AAI against HAD + AAI is > £18 million per QALY and against avoidance advice only is > £ 7.6 million	Extensive sensitivity analysis on wide range of model parameters	Very little data available to base the model on. Extensive use of sensitivity and scenario analysis to explore all plausible assumption and demonstrate the robustness of the findings

Table 2: CASP Economic Evaluation Checklist – Quality

a) Asthma and rhinitis

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Nasser 2008	Y	Y	Y	Y	Y	Y	SLIT ICER £8816 (2005) per QALY	Y	N	Y	Y	H
Ariano 2009	Y	Y	N	N	N	N	Lower cost and symptom score with SLIT	N	N	N	N	L

b) Rhinitis with or without asthma

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Schadlich 2000	Y	Y	N	N	N	N	SIT is cost saving and reduces chances of developing asthma	N	N	N	N	L
Pokladnikova 2008	Y	Y	Y	Y	Y	Y	SLIT costs less that SCIT with similar effectiveness	N	N	N	Y	L
Peterson 2005	Y	Y	Y	N	Y	Y	SIT ICER 2784 DKK per patient year of improved well being	Y	N	N	Y	M
Poulson 2008	Y	Y	Y	Y	Y	Y	ICER SCIT 134105 KR per QALY	Y	N	Y	N	M

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Canonica 2007	Y	Y	N	N	N	Y	SLIT ICER < 29000 Euros per QALY when annual cost of treatment < 1400 euro	Y	N	N	N	L
Keiding 2007	Y	Y	Y	N	Y	N	SLIT ICER 9716 to 14519 euros (2005) per QALY	Y	N	Y	Y	M
Rugerri 2013	Y	Y	Y	N	N	Y	SLIT ICER 1035 euros per QALY	Y	Y	N	N	L
Ronaldson 2014	Y	Y	Y	Y	Y	Y	SCIT £12168 (2008) per QALY	Y	Y	Y	Y	H
Bachert 2007	Y	Y	Y	Y	N	Y	SLIT ICER less than £20000 per QALY if treatment cost < 2200 euro per year	Y	N	Y	Y	M
Westerhout 2012	Y	Y	Y	Y	N	Y	SLIT (OA) ICER 14728 euro per QALY	Y	Y	Y	N	M
Berto 2006	Y	Y	N	N	N	N	SLIT cost saving and more effective than standard care	Y	N	N	N	L
Meadows 2013	Y	Y	Y	N	N	Y	ICER SCIT vs ST £29579 per QALY SCIT vs SLIT £24404 per QALY	Y	N	Y	Y	M
Omnes 2007	Y	Y	N	N	N	N	ICERs euros per asthma cases avoided under 3983 for SLIT and under 1327 for SCIT in all subgroups	N	N	N	N	L

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Bruggenjurgen 2008	Y	Y	N	N	N	Y	ICER SCIT 8303 euro per QALY	Y	N	N	N	L
Dranitsaris 2014	Y	Y	Y	N	Y	N	SLIT (OA) cheaper than SLIT (GRX) and SCIT and similarly effective in terms of symptom control	N	N	N	Y	L
Reinhold 2016	Y	Y	Y	Y	Y	Y	SCIT (Allergovit) cheaper & more effective than SLIT (OA). ICER for SCIT against symptomatic treatment was 11000 euros per QALY	Y	Y	Y	N	H
Verheggen 2015	Y	Y	Y	Y	Y	Y	SLIT (OA) more costly & effective than SCIT. ICER of 12593 per QALY & 76% chance of being cost-effective at threshold of 20000 euro	Y	Y	N	N	H

c) Asthma only studies

Author /year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Reinhold 2013	Y	Y	Y	N	N	N	ICER 11 euro per l/min morning peak flow	Y	N	N	N	L

d) Asthma and rhinitis studies

Author /year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Nasser 2008	Y	Y	Y	Y	Y	Y	SLIT ICER £8816 (2005) per QALY	Y	N	Y	Y	H
Ariano 2009	Y	Y	N	N	N	N	Lower cost and symptom score with SLIT	N	N	N	N	L

e) Insect venom allergy

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
Hockenhull,2012[33]	Y	Y	Y	Y	Y	Y	PhVIT + HAD + AAI dominates other treatm	Y	Y	Y	Y	M good study but data that it is based on

Author/year	1. Well defined question posed	2. comprehensive description of competing alternatives	3. provides evidence of effectiveness	4. effects identified measured and valued appropriately	5. resource use identified measured and valued appropriately	6. discounting to adjust for timing of costs and consequences	7. what were the results	8. incremental analysis performed	9. sensitivity analysis performed	10. effectiveness generalisable	11. costs generalisable	Overall quality L/M/H
							ents in patients likely to be stung more than 5 times a year. However not close to being cost-effective in general population.					is very poor

Appendix 1: Data extraction forms

Rhinitis and asthma

Title: Cost effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma

Author / Year: Nasser / 2008[14]

Journal: Allergy

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	UK
Study population		
Patients suffering from grass pollen induced rhinoconjunctivitis co-existing with asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT (Grazax) / Standard Care	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
151	EQ5D - QALYs	3.5%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary linked to unit costs	2005 / GBP	3.5%
Results		**Sensitivity analysis**
ICER £8816 per QALY		One way sensitivity analysis to explore impact of changing time horizon
General comments		
• results based on patients in UK, Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy • treatment effect assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: Economic evaluation of sublingual immunotherapy vs symptomatic treatment in allergic asthma

Author / Year: Ariano / 2009[13]

Journal: Annals of Allergy, Asthma & Immunology

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Italy
Study population		
Patients with dust mite induced allergic asthma and rhinitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard Care	5 years	RCT 5 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
70	VAS symptom score	0%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary and unit costs	? / Euros	0%
Results		**Sensitivity analysis**
Overall costs lower in SLIT patients and lower symptom score		NA
General comments		
• very little detail provided of the analysis performed • no real economic analysis or interpretation of the results provided		

Data extraction of Rhinitis with or without Asthma studies

Title: Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany

Author / Year: Schadlich / 2000[29]

Journal: Pharmacoeconomics

Type of economic analysis	**Perspective**	**Countries**
CEA	Health System	Germany
Study population		
Patients with seasonal (pollen) and perennial (mite) allergy with or without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SIT / Standard Care	10 years	Unclear
Sample size	**Outcome measure**	**Outcome discount rate**
-	Patients who do not develop asthma	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Resource use surveys	1990 / DM	0%
Results		**Sensitivity analysis**
SIT was found to be cost saving as compared to standard care and reduced the chances of patients developing asthma		NA
General comments		
• It was very unclear what data sources were used to populate the model in this study		

Title: Economic evaluation of sublingual vs subcutaneous allergen immunotherapy

Author / Year: Pokladnikova / 2008[24]

Journal: Annals of Allergy, Asthma & Immunology

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Czech Republic
Study population		
Adults with at least 2 years of seasonal allergic rhinoconjuctivitis with or without allergic asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / SCIT / Standard Care	3 years	RCT 5 years follow up
Sample size	**Outcome measure**	**Outcome discount rate**
19 SLIT, 23 SCIT, 22 Standard Care	RQLQ	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Administrative data linked to unit costs	2002 / Euro	3%
Results		**Sensitivity analysis**
SLIT and SCIT both performed better on RQLQ than standard care SLIT performed better than SCIT and was cheaper from a health system perspective		One way deterministic sensitivity analysis performed on costs and discount rates
General comments		
• No incremental cost effectiveness results were provided		

Title: Health economic analysis of subcutaneous specific immunotherapy for grass pollen and mite allergy

Author / Year: Petersen / 2005[23]

Journal: Allergol et Immunopathol

Type of economic analysis	**Perspective**	**Countries**
CEA	Societal	Denmark
Study population		
Patients with grass pollen or mite allergy		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SIT / Standard care	5 years	Retrospective questionnaire following trial
Sample size	**Outcome measure**	**Outcome discount rate**
253	Patient year of improved well being	5%
Cost data	**Cost year / currency**	**Cost discount rate**
Administrative data	2002 / DKK	5%
Results		**Sensitivity analysis**
ICER 2784 DKK per patient year of improved well being		NA
General comments		
• Selection bias due to partial response rate to questionnaire not controlled for • Recall bias not controlled for • Outcome measure is not validated and does not capture degree of improvement		

Title: Economic evaluation of a tablet based vaccination against hay fever in Denmark

Author / Year: Poulsen / 2008[25]

Journal: Ugeskr Laeger

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	Denmark
Study population		
Adults with grass pollen induced rhinotconjuctivitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	9 years	RCT one year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
493	EQ5D / QALYs	3%
Cost data	**Cost year / currency**	**Cost discount rate**
Unclear	? / DKK	3%
Results		**Sensitivity analysis**
ICER: 134105 DKK per QALY		NA
General comments		
• Based on patients in Denmark, Sweden, England, Germany, Holland with Danish QALY weights and unit costs applied to EQ5D and resource use data • Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: Cost effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe

Author / Year: Canonica / 2007[18]

Journal: Respiratory Medicine

Type of economic analysis	**Perspective**	**Countries**
CUA	Societal	Spain, Italy, France, Austria
Study population		
Patients with a 2 year history of grass pollen induced allergic rhinoconjunctivitis with or without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
Unclear subset of 634	EQ5D - QALYs	3 – 5 % depending on country
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary linked to unit costs	2004 / Euro	3 – 5 % depending on country
Results		**Sensitivity analysis**
0.134 incremental QALYs in SLIT patients if SLIT costs 1400 euro per year then ICER would be less than 29000 euro per QALY in all four countries		Repeated analysis excluding Spanish patients
General comments		
• Results calculated for France even though trial did not cover France • Unclear exactly what data from the multi country trial was used to calculate these results • Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: A cost effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries

Author / Year: Keiding / 2007[20]

Journal: Current Medical Research and Opinions

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	Austria, Denmark, Finland, Germany, Netherlands, Sweden
Study population		
Adults with clinical history of grass pollen induced seasonal allergic rhinoconjunctivitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SCIT / Standard treatment	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
306	RQLQ mapped to EQ5D - QALYs	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Resource use collected in trial with national unit costs applied	2005 / Euro	3%
Results		**Sensitivity analysis**
ICER in Euro per QALY Austria 9716; Denmark 2586; Finland 13683; Germany 10300; Netherlands 24519; Sweden 22675		One way deterministic analysis on costs described but results not reported
General comments		
• Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation • Mapping from RQLQ to EQ5D applied to calculate QALYs not standard or validated		

Title: Economic evaluation of 5-grass pollen tablets versus placebo in the treatment of allergic rhinitis in adults

Author / Year: Ruggeri / 2013[28]

Journal: Clinical Drug Investigation

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	Italy
Study population		
Patients with grass pollen induced allergic rhinitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	4 years	Posthoc analysis of 2 RCTs
Sample size	**Outcome measure**	**Outcome discount rate**
?	AAdSS mapped to QALYs	3%
Cost data	**Cost year / currency**	**Cost discount rate**
SIMAP study updated to 2011	2011 / Euro	3%
Results		**Sensitivity analysis**
At low AAdSS SLIT is dominated by standard care At medium AAdSS ICER 1024 euros per QALY At high AAdSS ICER 1035 euros per QALY		PSA showed 99% probability ICER less that 30000 euros per QALY for medium and high AAdSS
General comments		
• Not clear how AAdSS is converted to QALYs • Cost and effectiveness estimates taken from different studies		

Title: Economic evaluation of SQ-standardized grass allergy immunotherapy tablet (GRAZAX) in children

Author / Year: Ronaldson / 2014[27]

Journal: ClinicoEconomics and Outcomes Research

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	UK
Study population		
5-16 year olds with grass pollen induced rhinoconjunctivitis with or without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
253	Symptom scores mapped to QALYs	3.5%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT Patient diaries mapped to unit costs	2008 / GBP	3.5%
Results		**Sensitivity analysis**
ICER £12168 per QALY		PSA showed 90% probability of SLIT being cost effective at £30000 per QALY threshold and 60% probability cost effective at £20000 per QALY threshold
General comments		
• Mapping from symptom scores to QALYs not validated • Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: Cost effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis – a Northern European perspective

Author / Year: Bachert / 2007[15]

Journal: Clinical and Experimental Allergy

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	UK, Germany, Netherlands, Sweden, Denmark, Norway, Finland
Study population		
Patients with grass pollen induced rhinoconjunctivitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
493	EQ5D - QALYs	3 – 5% depending on country
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary mapped to country specific unit costs	2005 / Euro	3 – 5% depending on country
Results		**Sensitivity analysis**
Cost per year of treatment must be below 2200 euros for SLIT to be cost effective at NICE threshold of £20000 per QALY		NA
General comments		
• Price of SLIT not given so ICERs not calculated, rather max price for SLIT to be cost effective calculated • Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjuntivitis in Germany

Author / Year: Westerhout / 2012[31]

Journal: Journal of Medical Economics

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	Germany
Study population		
Patients with grass pollen induced rhinoconjunctivitis without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT (OA) / SLIT (GRZ) / SCIT (ALD) / Standard care	9 years	Meta-analysis
Sample size	**Outcome measure**	**Outcome discount rate**
NA	QALYs	3%
Cost data	**Cost year / currency**	**Cost discount rate**
Survey data	2011 / Euro	3%
Results		**Sensitivity analysis**
SLIT (OA) dominates SLIT (GRZ) and SCIT (ALD) ICER SLIT (OA) vs Standard care 14728 euros per QALY		PSA suggests 79% probability SLIT (OA) cost effective at a threshold of £20000 per QALY
General comments		
• Treatment effect observed in 1 year RCT assumed to persist through 3 years of treatment and 6 years following treatment discontinuation • Resource use taken from external survey rather than measured in the underlying studies in meta analysis		

Title: Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen induced respiratory allergy: the sublingual immunotherapy pollen allergy Italy (SPAI) study

Author / Year: Berto / 2006[16]

Journal: Annals of Allergy, Asthma and Immunology

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Italy
Study population		
Young adults with pollen induced rhinitis with or without allergic asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard care	6 years	Retrospective non-random subset selected from clinical study
Sample size	**Outcome measure**	**Outcome discount rate**
2000	Number of patients improved	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Clinical records linked to unit costs	2002 / Euro	3%
Results		**Sensitivity analysis**
SLIT is cost saving and more effective than standard care		Deterministic one way exploration of hospital costs
General comments		
• Potential for selection bias as physicians asked to pick subsets of patients from clinical study for economic evaluation		

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

Author / Year: Meadows / 2013[21]

Journal: NIHR Health Technology Assessment

Type of economic analysis	**Perspective**	**Countries**
CUA	Societal	England
Study population		
Patients with pollen induced allergic rhinitis with or without allergic asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / SCIT / Standard care	6 years	Meta analysis of RCTs
Sample size	**Outcome measure**	**Outcome discount rate**
NA	RQLQ mapped to EQ5D - QALYs	3.5%
Cost data	**Cost year / currency**	**Cost discount rate**
Resource use from expert opinion with unit costs applied	2011 / GBP	3.5%
Results		**Sensitivity analysis**
ICER SLIT vs standard care £37537 per QALY ICER SCIT vs standard care £29579 per QALY ICER SCIT vs SLIT £24404 per QALY		NA
General comments		
• Mapping between RQLQ and EQ5D to calculate QALYs not validated		

Title: Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France

Author / Year: Omnes / 2007[22]

Journal: European Annals of Allergy and Clinical Immunology

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	France
Study population		
Children over 5 and adults over 16 with dust mite or pollen induced allergic rhinitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / SCIT/ Standard care	7 years children; 6 years adults	Expert opinion
Sample size	**Outcome measure**	**Outcome discount rate**
NA	Asthma cases avoided	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Expert opinion	? / Euro	0%
Results		**Sensitivity analysis**
ICER vs standard care children dust mite SLIT: 3938; SCIT: 583 ICER vs standard care children dust pollen SLIT: 824; SCIT: 597 ICER vs standard care adults dust mite SLIT: 3158; SCIT: 393 ICER vs standard care adults dust pollen SLIT: 1708; SCIT: 1327 All in Euros per asthma case avoided		NA
General comments		
• Entire study seems to be based on expert opinion • Does not compare treatment with SLIT against SCIT incrementally		

Title: Cost effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma

Author / Year: Bruggenjurgen / 2008[17]

Journal: Annals of Allergy, Asthma & Immunology

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	Germany
Study population		
Patients with pollen or mite induced allergic rhinitis with or without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SCIT / Standard care	15 years	Published study
Sample size	**Outcome measure**	**Outcome discount rate**
NA	QALYs	3%
Cost data	**Cost year / currency**	**Cost discount rate**
Published study	? / Euro	3%
Results		**Sensitivity analysis**
ICER SCIT vs standard care 8308 euros per QALY		One way deterministic exploration od alternative treatment durations and discount rates
General comments		
• Difficult to assess the validity of cost or utility data as very little detail of studies that this analysis is based on given in the paper		

Title: Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost

Author / Year: Dranitsaris / 2014[19]

Journal: Journal of Evaluation in Clinical Practice

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Canada
Study population		
Patients with grass induced allergic rhinitis with or without asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SCIT / SLIT (GRX) / SLIT (OA) / Standard care	1 year	Meta analysis of 20 RCTs
Sample size	**Outcome measure**	**Outcome discount rate**
NA	Symptom control	0%
Cost data	**Cost year / currency**	**Cost discount rate**
Expert opinion	2012 / CAD	0%
Results		**Sensitivity analysis**
SCIT, SLIT(GRX) and SLIT (OA) had similar efficacy in terms of symptom control. Cost of SCIT = 946 CAD; Cost of SLIT (GRX) = 2122 CAD; Cost of SLIT (OA) = 844 SLIT (OA) is as effective as SLIT (GRX) and SCIT but cheaper over 1 year		NA
General comments		
• Unclear what the allergic rhinitis symptom score represents and if it was comparable between studies • Unclear about how much of the cost data was expert opinion as opposed to data from the meta analysis		

Title: Cost-effectiveness of grass pollen SCIT compared with SLIT and symptomatic treatment

Author / Year: Reinhold / 2016[26]

Journal: Allergo Journal International

Type of economic analysis	**Perspective**	**Countries**
CEA	Health insurer	Germany
Study population		
29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT (OA) vs SCIT (Allergovit) vs symptomatic treatment	9 years	RCT
Sample size	**Outcome measure**	**Outcome discount rate**
?	Utility mapped to QALY	3%
Cost data	**Cost year / currency**	**Cost discount rate**
Administrative data	2013/euro	3%
Results		**Sensitivity analysis**
SCIT dominates SLIT and has an ICER of 11000 euros per QALY against symptomatic treatment		Probabilistic and deterministic sensitivity analysis conducted
General comments		
• This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis • Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years		

Title: Health economic comparison of SLIT allergen and SCIT allergoid immunotherapy in patients with seasonal grass-allergic rhinoconjunctivitis in Germany

Author / Year: Verheggen / 2015[30]

Journal: Clinical and Translational Allergy

Type of economic analysis	**Perspective**	**Countries**
CEA	Payer's perspective	Germany
Study population		
29 year old patients with seasonal grass-allergic rhinoconjunctivitis and no asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT vs blended mix of current SCIT treatments	9 years	RCT
Sample size	**Outcome measure**	**Outcome discount rate**
?	QALYs mapped from Rhinitis Symptom Utility Index (RSUI)	3%
Cost data	**Cost year / currency**	**Cost discount rate**
Administrative data	2013/euros	3%
Results		**Sensitivity analysis**
ICER of SLIT vs SCIT is 12,593 euro per QALY with a probability of being cost effective at 20,000 euro per QALY of 76%		Probabilistic and deterministic sensitivity analysis as well as scenario analysis performed
General comments		
• This is a model based analysis that incorporates multiple different datasets and explores a number of different assumptions in sensitivity analysis • Comparator is a mix of SCIT treatments rather than one specific treatment • Unexplored assumption that 3 years of treatment give continued constant treatment effect for 9 years		

Data extraction of Asthma studies

Title: Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma

Author / Year: Reinhold / 2013[32]

Journal: Clinical and Translational Allergy

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Germany
Study population		
Children and adolescents with mite induced allergic asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SCIT / Standard Care	3 years	RCT 3 year mean follow up
Sample size	**Outcome measure**	**Outcome discount rate**
65	Mean morning peak flow (l/min)	0%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT – patient diary	2009 / Euro	0%
Results		**Sensitivity analysis**
ICER: 11 Euros per l/min mean morning peak flow		Bootstrapping performed but not used in cost effectiveness results
General comments		
• No hospital costs included • 5 SCIT and 1 non-SCIT patients excluded because of "outlier" levels of costs		

Data extraction of Asthma and Rhinitis studies

Title: Cost effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma

Author / Year: Nasser / 2008[14]

Journal: Allergy

Type of economic analysis	**Perspective**	**Countries**
CUA	Health system	UK
Study population		
Patients suffering from grass pollen induced rhinoconjunctivitis co-existing with asthma		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT (Grazax) / Standard Care	9 years	RCT 1 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
151	EQ5D - QALYs	3.5%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary linked to unit costs	2005 / GBP	3.5%
Results		**Sensitivity analysis**
ICER £8816 per QALY		One way sensitivity analysis to explore impact of changing time horizon
General comments		
• results based on patients in UK, Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy • treatment effect assumed to persist through 3 years of treatment and 6 years following treatment discontinuation		

Title: Economic evaluation of sublingual immunotherapy vs symptomatic treatment in allergic asthma

Author / Year: Ariano / 2009[13]

Journal: Annals of Allergy, Asthma & Immunology

Type of economic analysis	**Perspective**	**Countries**
CEA	Health system	Italy
Study population		
Patients with dust mite induced allergic asthma and rhinitis		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
SLIT / Standard Care	5 years	RCT 5 year follow up
Sample size	**Outcome measure**	**Outcome discount rate**
70	VAS symptom score	0%
Cost data	**Cost year / currency**	**Cost discount rate**
RCT patient diary and unit costs	? / Euros	0%
Results		**Sensitivity analysis**
Overall costs lower in SLIT patients and lower symptom score		NA
General comments		
• very little detail provided of the analysis performed • no real economic analysis or interpretation of the results provided		

Data extraction of Insect Venom Allergy study

Title: A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

Author / Year: Hockenhull / 2012[33]

Journal: NIHR HTA

Type of economic analysis	**Perspective**	**Countries**
CUA	Health System	England
Study population		
General population as well as high risk of sting subset of population		
Intervention / Comparator	**Time horizon**	**Effectiveness data**
PhVIT + HAD + AAI / HAD + AAI / avoidance advice only	10 years	Subset of RCT and survey data
Sample size	**Outcome measure**	**Outcome discount rate**
337	Systemic reaction or death following sting converted to QALYs	3.5%
Cost data	**Cost year / currency**	**Cost discount rate**
Administrative data and reference costs	? / GBP	3.5%
Results		**Sensitivity analysis**
PhVIT + HAD + AAI is cost saving and more effective when compared to either HAD + AAI or avoidance advice only for patients likely to be stung more than five times a year. In the general population the ICER for PhVIT + HAD + AAI against HAD + AAI is > £18 million per QALY and against avoidance advice only is > £ 7.6 million		Extensive sensitivity analysis on wide range of model parameters
General comments		
• Very little data available to base the model on • Extensive use of sensitivity and scenario analysis to explore all plausible assumption and demonstrate the robustness of the findings		

Appendix 2: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4/5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4/5/6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4/5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4/5/6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4/5/6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4/5/6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5/6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4/5/6

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5/6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5/6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, 15-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table2a-e 25-29
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12/13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12/13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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