



Impact of increasing treatment rates on cost-effectiveness of subcutaneous immunotherapy (SCIT) in respiratory allergy: a decision analytic modelling approach

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Abstract

Background Specific immunotherapy is the only causal treatment in respiratory allergy. Due to high treatment cost and possible severe side effects subcutaneous immunotherapy (SCIT) is not indicated in all patients. Nevertheless, reported treatment rates seem to be low. This study aims to analyze the effects of increasing treatment rates of SCIT in respiratory allergy in terms of costs and quality-adjusted life years (QALYs).

Methods A state-transition Markov model simulates the course of disease of patients with allergic rhinitis, allergic asthma and both diseases over 10 years including a symptom-free state and death. Treatment comprises symptomatic pharmacotherapy alone or combined with SCIT. The model compares two strategies of increased and status quo treatment rates. Transition probabilities are based on routine data. Costs are calculated from the societal perspective applying German unit costs to literature-derived resource consumption. QALYs are determined by translating the mean change in non-preference-based quality of life scores to a change in utility. Key parameters are subjected to deterministic sensitivity analyses.

Results Increasing treatment rates is a cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of 3484€/QALY compared to the status quo. The most influential parameters are SCIT discontinuation rates, treatment effects on the transition probabilities and cost of SCIT. Across all parameter variations, the best case leads to dominance of increased treatment rates while the worst case ICER is 34,315€/QALY. Excluding indirect cost leads to a twofold increase in the ICER.

Conclusions Measures to increase SCIT initiation rates should be implemented and also address improving adherence.

Keywords Cost-utility analysis · Markov process · State-transition model · Respiratory allergy · Subcutaneous immunotherapy

JEL Classification · I12 · I11 · I18

Introduction

Poorly controlled allergic disease can impact multiple quality of life domains like school performance, sleep, and daily activities [1–3]. To control symptoms regular medication during or even

outside symptomatic seasons is required. The number and type of sensitizations and symptoms often vary over time demanding patients to deal with frequently changing disease states. With an asthma prevalence of 5% (Poland) to 17% (Portugal) and a rhinitis prevalence of 17% (Italy) to 29% (Belgium) allergic respiratory diseases represent a relevant public health problem in Europe posing a significant burden on society [4, 5].

While allergen avoidance is rarely feasible, symptomatic pharmacotherapy induces good symptom control for a large share of patients. Still, allergen-specific immunotherapy (AIT) is the only causal treatment that is able to alter the natural course of the disease [6]. By applying increasing doses of an allergen sublingually (SLIT) or as subcutaneous

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injection (SCIT) over a period of 3–5 years the immunological mechanisms change and a sustained tolerance towards the specific allergen is achieved [7]. The benefits of AIT comprise reduced symptom severity leading to reduced medication needs and an improvement in quality of life during treatment [7–9]. There is some limited evidence on treatment effects lasting beyond AIT duration [8, 9] as well as on the prevention of new sensitizations and the onset of asthma symptoms in patients with allergic rhinitis [7, 10].

In Germany the most widely applied type of AIT is the subcutaneous injection route [11, 12]. Its effectiveness and cost-effectiveness has been well evaluated for a variety of allergens and indications [13–18]. Due to the risk of severe adverse reactions associated with SCIT, the high treatment cost, and the impact of patient compliance on treatment success a thorough patient selection prior to therapy is indicated [19].

For Germany reported treatment rates of SCIT are low (5–7%) compared to the estimated share of eligible patients [12, 20]. Therefore, this study aims to analyze the impact of increasing treatment rates (treating all eligible patients vs. actual treatment rates) on total quality-adjusted life years (QALYs), total costs and incremental cost-effectiveness based on a decision analytic state-transition Markov model.

Methods

Compared strategies

To assess the effects of increasing SCIT initiation rates in respiratory allergy patients the following strategies are

compared: increasing treatment rates to treat all respiratory allergy patients eligible for SCIT and the status quo treatment rates in respiratory allergy patients eligible for SCIT. Expected costs and QALYs for each strategy are estimated based on the decision analytic model described below.

Model structure and assumptions

The course of allergic respiratory disease in patients eligible for SCIT is simulated with a Markov state-transition model comprising the health states of rhinitis, asthma, both diseases concomitantly, symptom-free and death (absorbing Markov state). This model type was used as respiratory allergy is a chronic disease evolving over time that can be represented by disease-specific health states and transitions [21]. For the model development, we followed the international guidelines of the ISPOR-SMDM Modeling Good Research Practices Task Force [22].

Overall mortality is modelled by standardizing all-cause mortality of statistical life tables of the general German population [23] to the age- and gender-distribution of respiratory allergy patients [24, 25]. Asthma excess mortality is not considered due to its low rates [26].

All health states are distinguished by treatment strategy of symptomatic pharmacotherapy alone (no SCIT) and additional SCIT (SCIT). Within the model the following transitions are possible: death, progression (i.e., occurrence of new symptoms), remission of symptoms, relapse (i.e., reoccurrence of symptoms in symptom-free patients) and no change in health state. Figure 1 shows a simplified state-transition diagram of the model structure.

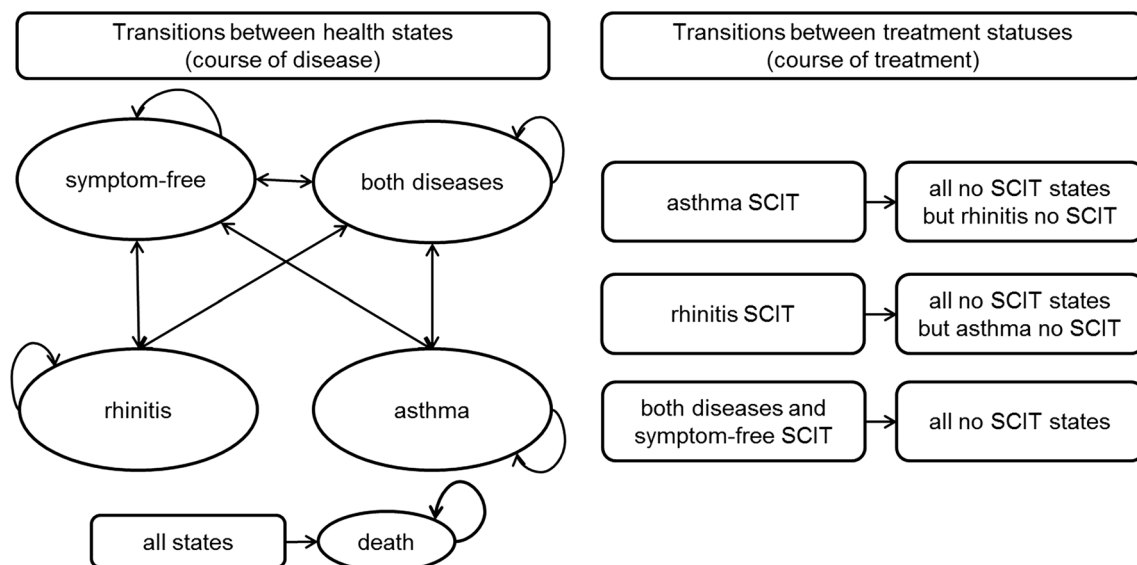


Fig. 1 State-transition diagram representing the structure of the Markov model. SCIT subcutaneous immunotherapy (in addition to pharmacotherapy); no SCIT no subcutaneous immunotherapy (pharmacotherapy alone)

The left side of Fig. 1 displays the movements between disease states in both treatment strategies. Symptom-free patients can relapse to any other health state and patients with both diseases can remit to any of the health states. Patients with either rhinitis or asthma can move to symptom-free or to having both diseases. The transitions between the treatment strategies are depicted on the right side of Fig. 1. In case of patient-induced treatment discontinuation or disease progression (during or after the treatment), patients receiving SCIT move to symptom treatment (no SCIT). Symptom treatment states comprise patients who never received SCIT, discontinued SCIT or no longer benefit from treatment effects. Patients cannot move from no SCIT to SCIT within the model.

According to German medical guidelines a 3-year period of SCIT [7] is assumed in the model, as a previous study based on German SHI routine data reported a treatment duration of 3 years for the majority of patients completing SCIT [27]. While the minimum required duration of AIT to achieve sustained treatment effectiveness is not clearly established [13, 28], current evidence supports the minimum treatment duration of 3 years set by medical guidelines [29]. Although there is limited evidence on the long-term effects of AIT some studies report treatment effects to last for up to 7 years [30, 31]. Therefore, to include all possible benefits of SCIT an analytic time horizon of 10 years has been chosen. To account for seasonal and perennial allergy a cycle length of 1 year is assumed.

Model input

Transition probabilities and treatment rates

The initial distribution of disease groups, the treatment rates of both strategies, treatment discontinuation rates and the annual transition probabilities (Online Resource 1) are derived from routine data of a nationwide German statutory health insurance company. The treatment effects of SCIT on transition probabilities are derived from the published literature in terms of relative risks (RR) of transition (Online Resource 2). The annual transition probabilities for SCIT eligible but untreated patients (no SCIT) are calculated by applying these relative risks to the routine data transition probabilities of SCIT patients.

The initial distribution of disease groups in the base case model is 70% allergic rhinitis, 11% allergic asthma, and 19% both diseases. The status quo treatment rates for patients eligible for SCIT with asthma, rhinitis, and with both diseases are 4, 16, and 50%, respectively, and 100% each in the increasing treatment rates strategy. Mean treatment discontinuation rate is about 26% in all health states (Online Resource 3).

Costs

The societal perspective is adopted and both direct costs and indirect costs due to productivity loss were included into the economic evaluation. Direct health state-specific costs include costs for physician visits, hospital admissions, symptomatic medication, and allergen extracts for SCIT injections. In general, the resource consumption for patients not receiving SCIT is quantified based on the published literature and valued with German unit costs [32] (details see below). The change in resource consumption during and after SCIT is also derived from the published literature [33–36]. All costs are adjusted [37] to reflect 2016 Euro values using the harmonized consumer price index [38] and the German labor cost index [39].

The number of physician visits per year in each disease group [40–42] is valued by published mean costs per visit calculated as average of general practitioners, pediatricians, ENT (ear, nose, and throat specialist) and dermatologists, because these specialties are typically consulted by respiratory allergy patients in Germany [20, 32]. Hospital stays are only considered for asthma patients and patients with both diseases. The average frequency and length of stay for hospital admissions due to asthma are taken from literature [43] and public statistics [44] whereas the cost per hospital day is derived from published unit costs [32]. The effects of SCIT in terms of improved symptom control leading to fewer physician visits and hospital admissions are reflected by applying the proportion of these costs between SCIT and no SCIT reported in the literature [34].

Resource consumption of SCIT comprises physician visits for the injections and allergen extracts. The number of injections and the amount of allergen extract per treatment year is derived from manufacturer dosing instructions for all extracts where this information is freely available [45–49]. In the base case analysis the mean injection interval is applied when a range is given in the instructions, for example, 4–8 weeks would translate to a 6-week interval. While the cost per injection visit is calculated as described above, the cost for allergen extracts is calculated by applying the price per package given in the Lauer-Taxe® pharmaceutical information system [50] (February 2017) to the number of packages consumed per year. The weighted mean costs across all extracts was calculated using the market share of each preparation within the relevant allergen group (i.e., grass or tree pollens, house dust mite and grass-tree-pollen mixtures) derived from the annual report of drug prescriptions [51].

To quantify the consumption of symptomatic asthma- and rhinitis-related medication, the symptom duration is defined by assuming an average allergy season of 91 days and combining this with the number of symptomatic seasons per year in patients with rhinitis and both diseases as

reported in literature [42]. For asthma controller medication, an adjustment was introduced following expert opinion: 40% of asthma patients are assumed to experience perennial symptoms, while for reliever medication the original seasonality of symptoms is maintained. On this basis the average number of symptomatic days per year is calculated using Eq. 1.

$$\begin{aligned} \text{Symptom days per year} = & 91 \times \text{share of patients}_{1\text{season}} \\ & + 91 \times 2 \times \text{share of patients}_{2\text{seasons}} \\ & + 91 \times 3 \times \text{share of patients}_{3\text{seasons}} \\ & + 91 \times 4 \times \text{share of patients}_{4\text{seasons}} \end{aligned} \quad (1)$$

For asthma-related medication, the intake of one daily defined dose (DDD) is assumed for each day of a symptomatic season. The share of patients taking a specific active ingredient is derived from routine data and multiplied by the average number of symptom days per year. For oral corticosteroids (OCS) the intake of one small package per year is assumed based on expert interviews. Due to the inability to determine allergy-related use of OCS in the routine data, the share of patients with OCS intake is derived from literature [42].

Rhinitis-related medication consumption is differentiated by seasonal and perennial disease. Lacking literature data on perennial rhinitis medication, nasal corticosteroids (NCS) are assumed to be required in 4 months per year in addition to one small package of oral antihistamines (OAH) based on expert interviews. For seasonal allergic rhinitis the number of intake days per season for OAH and NCS is reported in literature [52]. Based on expert interviews, it is assumed that patients need eye drops on 50% of OHA and on 15% of NCS intake days. Replacing the 91 days in Eq. 1 by the intake days per season gives the intake days per year for which one DDD is considered.

Symptomatic medication is valued by applying the mean cost per DDD for the largest package size available or the mean cost for one small package based on the Lauer-Taxe® [50]. The medication cost for a rhinitis patient is calculated as weighted mean of seasonal and perennial rhinitis medication cost applying a ratio of 70% seasonal and 30% perennial symptoms [1, 53]. Adding the cost of asthma medication to the cost of rhinitis medication derives the cost of a patient with both diseases. Medication reduction for SCIT is taken from the literature [33, 36]. For asthma patients medication reduction is reported not to occur before the second treatment year [33, 35].

Productivity loss in patients not receiving SCIT is determined for each disease group based on literature [54–56]. Working days lost due to absenteeism are distinguished from lost productivity caused by presenteeism. In the base case analysis, a conservative estimate is applied by restricting productivity loss to absenteeism. Increase of productivity

due to SCIT is reflected by applying different proportions of indirect costs in SCIT and no SCIT patients reported in the literature [13]. Each working day lost is valued by the average gross labor cost provided by the federal statistics office [37, 57–59].

Symptom-free patients are assumed to consume no resources and, therefore, cause no cost unless they receive SCIT over that period of time.

The resulting cost input for the health states and treatment strategies are displayed in Table 1. Disregarding the cost of SCIT the direct and indirect cost for SCIT patients are lower than for patients not receiving SCIT in the first year of treatment. However, the cost of SCIT exceeds these savings with the result of higher total cost in SCIT patients during active treatment. Treatment cost of SCIT is the most important cost parameter independent of disease causing 39%–75% of total cost. The second most important cost component in patients treated with SCIT and the most important component in patients not receiving SCIT is the productivity loss accounting for 20–41% of total cost in patients treated with SCIT and 40–79% in untreated patients.

Table 1 Annual cost by health state and treatment status (2016 values)

Type of service	Health state	Cost per year (€)	
		no SCIT	SCIT ^a
Physician visits	Rhinitis	79	32
	Both diseases	115	47
	Asthma	96	39
Hospital admissions	Both diseases	590	368
	Asthma	590	368
Medication	Rhinitis	75	52
	Both diseases	431	409
	Asthma	357	357
SCIT	Year 1	na	1424
	Years 2 and 3	na	1080
Total direct cost	Rhinitis	153	1508
	Both diseases	1136	2247
	Asthma	1043	2187
Productivity loss absenteeism	Rhinitis	579	477
	Both diseases	771	636
	Asthma	2043	1685
Productivity loss presenteeism	Rhinitis	2282	1611
	Both diseases	1727	1219
	Asthma	5352	3778
Total cost ^b	Rhinitis	732	1985
	Both diseases	1907	2883
	Asthma	3086	3872

SCIT subcutaneous immunotherapy, na not applicable

^aFor the first treatment year (other years see Online Resource 4)

^bTotal direct cost plus productivity loss due to absenteeism

Table 2 QALYs by health state and treatment status for base case and sensitivity analyses

Treatment and health state	QALY resulting from EQ-5D-based utility gain calculation			QALY resulting from RSUI/ASUI-based utility gain calculation		
	Base case	Best case	Worst case	Base case	Best case	Worst case
No SCIT						
Asthma	0.928	0.943	0.913	0.928	0.943	0.913
Rhinitis	0.902	0.908	0.893	0.902	0.908	0.893
Both diseases	0.899	0.904	0.894	0.899	0.904	0.894
SCIT						
Asthma	0.976	0.998	0.946	0.989	0.998	0.951
Rhinitis	0.944	0.958	0.93	0.953	0.966	0.936
Both diseases	0.940	0.951	0.929	0.949	0.963	0.935

RSUI/ASUI: Rhinitis/Asthma Symptom Utility Index, QALY quality-adjusted life year, SCIT subcutaneous immunotherapy

Quality of life

Lacking literature data on utilities in SCIT suited treated and untreated patients these parameters are estimated in two steps: first, the basis utility for each disease in untreated SCIT eligible patients is derived; second, the utility gain through SCIT is calculated and added to the basis utility.

As only patients with controlled asthma symptoms are eligible for SCIT according to the indication criteria (Online Resource 3), basis utilities are derived from asthma patients with controlled symptoms [60, 61]. For rhinitis and patients with both diseases the indication criterion of persistent symptoms (Online Resource 3) is translated into moderate to severe symptoms, because in the literature utilities for persistent symptoms are not reported. Based on the reported utility for each degree of severity [62–64], a weighted mean of moderate and severe symptoms is calculated according to their proportion reported in the literature (rhinitis [62, 63, 65–67]; rhinitis with asthma [66, 68, 69]).

The utility gain to be added to these basis utilities cannot be derived directly but needs to be translated from disease-specific non-preference-based instruments which are applied in clinical trials to a preference-based instrument [13]: The most widely used disease-specific instruments are the Rhinitis Quality of life Questionnaire (RQLQ) [70] and the Asthma Quality of Life Questionnaire (AQLQ) [71] and the two suitable preference-based instruments are the generic EQ-5D and the disease-specific rhinitis symptom utility index (RSUI) [63] and asthma symptom utility index (ASUI) [72]. To translate the change in RQLQ and AQLQ to a change in utility their best and worst scores are matched to referring states of the EQ-5D, RSUI and ASUI. Next, the difference between the utility of the worst and best states is divided by the difference of worst and best score. Thus, the utility change per change of score is calculated for each instrument. In the base case analysis, utilities based on EQ-5D values are applied. The change

in RQLQ and AQLQ under SCIT treatment is estimated by performing a fixed effects meta-analysis of randomized clinical trials (RCT) using these instruments (Online Resource 5). Multiplying this mean change by the utility change per score change and adding it to the basis utilities gives the utility for the referring disease state in SCIT treatment. The utility of a symptom-free patient is set to 1 because in this analysis only the allergy-related quality of life is considered and therefore symptom-free patients have no impairment (due to allergy) at all. Due to the lack of studies reporting the AQLQ score in patients with both diseases the utilities for these states are based on the RQLQ and the RSUI.

To calculate QALYs, the number of symptomatic and symptom-free days per year needs to be established for patients with and without SCIT treatment. Therefore, the number of symptom days reported for the control group of a RCT [73] (no SCIT) is extrapolated to a 91-day season and then imputed to Eq. 1 replacing the 91 days to calculate the symptom days per year. The reduction in symptom days under SCIT treatment is also derived from clinical trials [73–75]. The total QALY for a given SCIT state is then calculated as

$$QALY_{i,SCIT} = ((\text{Basis utility}_i + \text{utility gain}_i) \times \text{symptomatic days}_{i,SCIT}) + (1 \times \text{symptom-free days}_{i,SCIT}) \quad (2)$$

And for a no SCIT state the total QALY of a given state is calculated as

$$QALY_{i,no\ SCIT} = ((\text{Basis utility}_i \times \text{symptomatic days}_{i,no\ SCIT}) + (1 \times \text{symptom-free days}_{i,no\ SCIT})), \quad (3)$$

where i indicates the disease state, symptomatic and symptom-free days relate to 1 year, and SCIT and no SCIT indicate the treatment status.

Table 2 displays the resulting QALY model input for the health states and treatment options. For asthma, the QALYs of the no SCIT states are applied on the SCIT states in the first year of treatment. This is based on the assumption that if medication requirements do not change before the second year of SCIT it is unlikely that quality of life will change significantly in the same period. In the base case analysis the utility gain based on the generic EQ-5D instrument is used, whereas the larger utility gain based on the disease-specific RSUI and ASUI instruments is applied in sensitivity analysis.

Analyses

Base case

The cost-effectiveness analysis is performed using a deterministic cohort simulation. By assigning costs and QALYs to each health state in each cycle the model calculates the cumulative costs and benefits of the different strategies for the analyzed period of time. To assess the impact of increased treatment rates of SCIT, two strategies are compared: a strategy in which all eligible patients are treated and a strategy with the actual treatment rates (status quo). For each strategy, the treatment options of SCIT and no SCIT are included with different initial treatment uptakes (Online Resource 3). On this basis, the incremental cost-effectiveness ratio (ICER) comparing the two strategies is calculated as:

$$\text{ICER} = \frac{\text{costs}_{\text{increasing rates strategy}} - \text{costs}_{\text{status quo}}}{\text{QALYs}_{\text{increasing rates strategy}} - \text{QALYs}_{\text{status quo}}}, \quad (4)$$

where costs and QALYs are the cumulative values until year 10 after start of treatment in the referring strategy. The ICER indicates the additional cost per QALY gained when treating all eligible patients compared to status quo treatment rates.

To avoid bias arising from the assumption that costs and benefits occur at the beginning or the end of a cycle, a half-cycle correction is applied. Furthermore, to account for time preferences costs and QALYs are discounted with 3% per year as indicated in German guidelines [37].

All routine data analysis is conducted using IMB SPSS Version 24, the RevMan5 tool provided by the Cochrane Collaboration is used for the meta-analysis, and the Markov state-transition model is programmed and evaluated using the decision analytic software package TreeAge Pro 2015.

Sensitivity analysis

To assess the impact of parameter uncertainty and structural assumptions, a series of deterministic sensitivity one-way analyses are performed.

The discontinuation rates of SCIT, treatment effects on transition probabilities and the share of SCIT eligible patients which determines the status quo treatment rates are varied based on their range reported in the literature (see Table 4). The initial distribution of health states is derived based on SCIT treated rather than on all respiratory allergy patients in the routine data. Moreover, subgroup analysis is performed for each disease group by setting the other disease groups' initial probabilities to zero. The assumption of the longest treatment effect duration of SCIT reported in literature used in the base case is tested by assuming shorter time horizons of the model.

The cost per physician visit is altered by the span represented in the relevant specialties, where dermatologists present the lowest and ENT physicians present the highest cost per visit [32]. The cost of SCIT is further varied by adopting the minimum and maximum injection interval given in the manufacturers' information. From these changes a minimum and maximum of cost input is set up. Moreover, the productivity loss due to presenteeism is considered in addition to absenteeism, because it frequently occurs in respiratory allergy. Another analysis excludes productivity loss to assess the impact of indirect cost and therefore approximate a social health insurance (SHI) perspective.

The basis utilities are varied using their ranges found in literature. For asthma, this relates directly to the studies reporting the utilities, whereas for rhinitis the proportion of moderate and severe symptoms is taken from different studies with constant utilities for the degrees of severity. In a further analysis the utility gain is derived based on the RSUI and ASUI instruments to assess the influence of using a disease-specific instrument rather than the generic EQ-5D. Addressing the uncertainty of pooling data from different studies to calculate the mean change in RQLQ and AQLQ the lower and upper limits of the 95%-confidence interval (CI) are applied.

In two additional sensitivity analyses, the costs and QALYs are not discounted or discounted at 5% following German recommendations [37].

Results

In comparison to the status quo after 10 years there is a favorable population distribution with more symptom-free patients and fewer patients with asthma or with both diseases as well as a larger share of patients that still benefit from SCIT with the increasing treatment rate strategy (9% vs. 2%).

With an ICER of 3500 €/QALY (Table 3), the strategy increasing treatment rates can be considered cost-effective compared with other technologies in health and medicine in Germany.

Table 3 Base case results: Total costs, QALYs, and incremental cost-effectiveness ratio (ICER) over a time horizon of 10 years

	Cost	QALY	Increment		ICER
			Cost	QALY	
Status quo treatment rates	11,828 €	7.59			
Increased treatment rates	12,085 €	7.66	257 €	0.07	3484 €/QALY

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year

Table 4 Results of one-way sensitivity analyses in terms of incremental cost-effectiveness ratio (ICER)

Parameter	Variation	ICER (€/QALY)	Change in ICER
Base case		3484	
Minimal discontinuation rates	4 vs. 26% ^a	Dominant	– 142%
Maximal discontinuation rates	50 vs. 26% ^a	13,328	283%
Minimum SCIT treatment rate in status quo (Online Resource 3)	12% AR; 32% ARAA; 2% AA;	3093	– 11%
Maximum SCIT treatment rate in status quo (Online Resource 3)	23% AR; 57% ARAA; 9% AA	3597	3%
50% SCIT treatment rates in all status quo health states	50%	2608	– 25%
Initial population distribution of SCIT treated patients	70% AR; 26% ARAA; 4% AA	2769	– 21%
Maximum treatment effects of SCIT on transition probabilities	Online Resource 2	Dominant	– 183%
Minimum treatment effects of SCIT on transition probabilities	Online Resource 2	7683	121%
Minimum unit cost for SCIT and physician visit and best case utilities	Change to SCIT base case cost: AR – 9% (– 3% ^b); ARAA – 7% (– 2% ^b); AA – 5% (– 1% ^b)	1291	– 63%
Maximum unit cost for SCIT and physician visit and worst case utilities	Change to SCIT base case cost: AR + 23% (+ 1% ^b); ARAA + 22% (+ 1% ^b); AA + 16% (+ 1% ^b)	11,540	231%
Inclusion of productivity loss due to presenteeism	See Table 1	Dominant	– 416%
Exclusion of productivity loss (direct cost only)	See Table 1	9695	178%
Application of RSUI/ASUI based utility gain instead of EQ-5D	See Table 2	2971	– 15%
No discounting	0% instead of 3%	1693	– 51%
Discounting at 5%	5% instead of 3%	4657	34%

^aMean over all disease groups and treatment years

^bChange in cost of no SCIT states, AA allergic asthma, AR allergic rhinitis, ARAA allergic rhinitis and allergic asthma, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year, RSUI/ASUI Rhinitis/Asthma Symptom Utility Index, SCIT subcutaneous immunotherapy

The ICERs resulting from the conducted sensitivity analyses are summarized in Table 4. The most influential parameters are discontinuation rates, variation in cost and utility parameters and treatment effects of SCIT on transition probabilities (i.e., RR for the transitions). However, in all analyses the strategy of increasing treatment rates achieves ICERs lower than 14,000 €/QALY, which can be considered cost-effective.

Using RSUI and ASUI based utilities decreases the ICER to 2971 €/QALY. The inclusion of productivity loss due to presenteeism leads to dominance of the increasing treatment rates strategy, whereas the exclusion of productivity loss (i.e., approximation of an SHI perspective) still results in

ICERs below 10,000 €/QALY for increased treatment rates, which can be considered very cost-effective. Major savings due to improved productivity with SCIT treatment cause an increase of the ICER when productivity loss is not considered. Lower levels of discontinuation rates and higher levels of SCIT treatment effects on transition probabilities lead to dominance of the increasing treatment rates strategy.

In the worst case scenario analysis with maximum discontinuations rates, unit costs and SCIT treatment rates, minimum treatment effects on transition probabilities and base case initial population distribution the ICER is 34,315 €/QALY for increased treatment rates. In the best case

scenario analysis with minimum discontinuation rates, unit costs and SCIT treatment rates, maximum treatment effects on transition probabilities and alternative initial population distribution the strategy of increasing treatment rates is dominant over the status quo.

Figure 2 provides an overview of base case and sensitivity analyses results on the cost-effectiveness plane.

Assuming shorter time horizons for the analysis of 5 and 7 years instead of 10 years increases the ICER to 11,346 €/QALY at year 5 and to 5173 €/QALY at year 7. The subgroup analysis of the base case assumptions for each disease group shows cost-effectiveness for rhinitis and asthma with ICERs of 4788 €/QALY and 7375 €/QALY. For patients with both diseases increased treatment rates are dominant.

Discussion

Increasing treatment rates of SCIT in respiratory allergy can be considered very cost-effective from a societal perspective at base case assumptions with an ICER of 3484 € per QALY. Although in Germany there is no explicit cost-effectiveness threshold [76] it is likely that this low additional cost for gaining a QALY is deemed acceptable when compared with other well-accepted health technologies in Germany. Sensitivity analyses reveal discontinuation rates, treatment effects of SCIT on transition probabilities, cost of SCIT and productivity loss to have the strongest impact on the ICER. Overall, the results range from dominance to an ICER of 34,315 €/QALY. According to the WHO (World Health Organization) interventions with an ICER below the per capita gross domestic product (GDP) are judged to be highly cost-effective [77]. With a per capita GDP of 37,866 € in 2016 [78]

and taking into account the cost-effectiveness threshold currently used by the NICE (National Institute for Health and Care Excellence) of 30,000 £ (34,974 €; exchange rate 1.16 May 2017) [79] these are robust results as even in the worst case scenario ICERs remain below 35,000 €/QALY.

Additional costs within the healthcare budget for measures to increase SCIT treatment rates (e.g., patient information campaign, education programs for general practitioners, and pharmacists) have not been included in the model. An estimation of these costs per patient eligible for SCIT (i.e., the target population of the model) in Germany can be derived as follows: The absolute number of respiratory allergy patients in Germany ($n = 13,536,602$) is calculated by multiplying the prevalence of respiratory allergy reported in representative general population surveys [24, 25] with the German population in the referring age groups [80]. Apply the share of patients eligible for SCIT in each disease group (Online Resource 3) weighted by their distribution in the total respiratory allergy population to estimate the overall number of respiratory allergy patients eligible for SCIT ($n = 3,824,116$). Assuming a budget of ten million euro, the additional costs to increase SCIT treatment rates in Germany is 3 € per patient eligible for SCIT (range of 2 €–4 € for minimum and maximum share of eligible patients). Although such measures will not increase treatment rates to 100%, this will not be of major influence on cost-effectiveness of the increasing treatment rates strategy, as sensitivity analyses revealed that the difference in treatment rates between the two strategies induces only small changes in the ICER (− 11% and + 3%; see Table 4). Thus, including additional costs for increasing SCIT treatment rates does not lead to a relevant change in the cost-effectiveness of this strategy.

Patients who concomitantly suffer from allergic rhinitis and allergic asthma seem to benefit most from SCIT

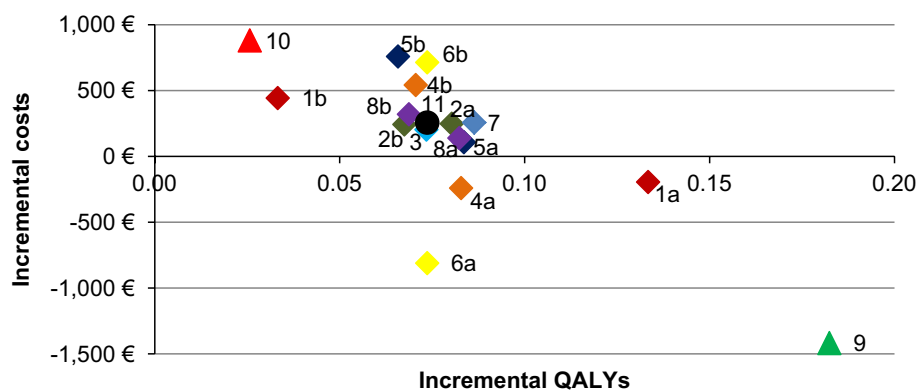


Fig. 2 Cost-effectiveness plane of base case and sensitivity analyses. 1 discontinuation rates (1a max.; 1b min.); 2 treatment rates (2a min.; 2b max.); 3 alternative initial population distribution; 4 treatment effects of SCIT on transition probabilities (4a max.; 4b min.); 5 cost and Quality-adjusted life years (QALYs) (5a cost min. QALYs max.;

5b cost max. QALYs min.); 6a inclusion of presenteeism (in addition to absenteeism); 6b exclusion of productivity loss; 7 Application of RSUI/ASUI (Rhinitis/Asthma Symptom Utility Index RSUI/ASUI) based utility gain instead of EQ-5D; 8 discounting (8a 0%; 8b 5%); 9 best case scenario; 10 worst case scenario; 11 base case

compared to patients with rhinitis or asthma alone. In part, this may be the result of some model assumptions (i.e., simply adding the cost of rhinitis and asthma, using RQLQ improvement), but since the modelled transitions are based on routine data effectiveness it is likely related to the clinically established concept that the improvement or remission of only one disease has a positive impact on the other disease and vice versa [81].

We identified only one published study examining the cost-effectiveness of different scenarios on allergy prevalence and SCIT treatment rates from a German statutory health insurance (SHI) perspective [17]. An increase of SCIT treatment rates to 75% in all disease groups is shown to be dominant over the status quo in terms of healed or avoided patients [17]. In our model the ICER of increased SCIT treatment rates to 100% from an approximated SHI perspective omitting productivity loss is 27 € per symptom-free patient. The comparison of the two models is hampered by several structural differences: Reinhold et al. simulate a 39-year time horizon where future patients are included as healthy subjects at the beginning of the modelling period and therefore the time horizon from onset of SCIT varies in each patient. Furthermore asthma has not been considered as a separate health state. Compared to our study the cost of SCIT and the cost of the different health states are considerably lower. The lack of detailed information about the cost calculation for the health states does not allow further exploration of these differences. The cost of SCIT is based on assuming an equally distributed application of pre-seasonal and perennial treatment of a specific SCIT preparation according to manufacturer information. In absence of evidence regarding the frequency of SCIT protocols the present model assumes a perennial SCIT protocol for all patients to obtain a conservative estimate of SCIT cost. Thus, both studies support the hypothesis that increased treatment rates of SCIT introduce relevant benefit to society and social health insurance with some uncertainty about the associated cost.

This study has several limitations. The chosen model type of a state-transition model is able to reflect all important aspects of the investigated decision problem as all relevant courses of disease, courses of treatment and differences in costs and outcomes have been captured [22]. However, while the real transition probabilities may depend on the previous disease course, the individual patient's disease history is not taken into account in our model due to the Markovian assumption. However, using a Markov process (allowing for time-dependent model parameters) rather than a simple Markov chain (with constant probabilities), we were able to simulate time-dependent transition probabilities more realistically. The cohort simulation enables the display of the cohort's course of disease over time and its distribution on the health states (i.e., Markov trace) rather than individual patient paths. With the research question of this study

focussing on the impact of increased SCIT treatment rates on the overall patient group the cohort calculation seems to be the appropriate method [22].

For many transition probabilities we used routine data as it was the only available source. An advantage of routine data is that they contain data on all disease groups from one source which increases internal validity in contrast to combining several different studies. However, probabilities derived from routine data are higher compared with those reported in literature and may depend on documentation habits and financial incentives. The assumptions made due to sparse literature on relative risks for transition probabilities in untreated SCIT eligible patients might not reflect the real proportions in some transitions. Considering the influence of this parameter on the overall result (ranging from dominance to a twofold increase of the ICER) more detailed and valid information would be valuable.

Another uncertain input parameter of the model is the health states' utility input which requires a number of assumptions in the calculation. The most fundamental assumption is the validity of translating a change of disease-specific non-preference-based quality of life score to a change in utility [13]. While there is reasonable doubt whether this represents the actual utility it appropriately reflects the increment of utility between increasing treatment rates and the status quo strategies. The uncertainty surrounding the change in RQLQ and AQLQ scores is deemed minor due to the application of validated methods of meta-analysis as recommended by the Cochrane Collaboration and the inclusion of 95%-CI values in sensitivity analysis which imposed only a moderate change in QALYs by less than 15% of the base case values.

The costs of SCIT are the main cost driver in all disease groups and have a considerable impact on the ICER. They might be overestimated because the applied average cost per physician visit is higher than the actual physician fee (SHI: 13–21 € per quarter year plus 10 € per injection < 26€ per injection) [82]. Furthermore the regular physician visits outside of SCIT might not be additive during SCIT. Yet, the cost of physician visits only amount to 25% of total SCIT cost. In the calculation of consumed allergen extract for an average patient, dose reductions during main allergen seasons or due to missed injections increasing the allergen extract consumption are not taken into account. Within the calculated number of required packages there might be some range of compensation in cases where not all the content of a vial is needed. Furthermore the variation of cost based on different injection intervals within sensitivity analysis is likely to cover the impact of these eventualities.

The cost of symptomatic medication strongly depends on the number of symptom or intake days per season and the number of seasons. Several choices of literature and

assumptions based on expert opinion have been made which might not reflect the real average medication need. Due to the cost of medication being a rather small part of the total cost and due the lack of alternative values no sensitivity analysis is conducted. By simply adding the calculated cost of rhinitis and asthma medication the cost of patients with both diseases is likely to be overestimated.

The period of time for which benefits of SCIT persist after treatment completion strongly determines its cost-effectiveness because the initial treatment costs are balanced by savings in the after-treatment period. To model the effects of SCIT for the 7-year period after treatment completion two basic assumptions have been made: (1) constance or trend continuation of treatment effects on transition probabilities after completion of SCIT through extrapolation of routine data (Online Resource 1); (2) costs and QALYs stay constant for patients in the SCIT states during and after successful completion of treatment due to limited availability of long-term data [8, 9]. The impact of applying the reported maximum duration of SCIT treatment effects has been assessed within sensitivity analyses. While a shorter time horizon increased the ICER the range of generally acceptable thresholds is not exceeded. Furthermore, only one course of SCIT is modelled, whereas respiratory allergy patients are likely to have more than one SCIT in their lifetime. Assuming a similar effectiveness of further courses of SCIT increased treatment rates are expected to be also cost-effective for a life-long time horizon. Moreover, this model excludes sublingual immunotherapy (SLIT) whose inclusion is unlikely to alter the results relevantly. Because SLIT is only applied in a small share of patients in Germany there will still be a considerable amount of untreated patients and a growing body of evidence suggests that SLIT is at least equally effective to SCIT.

In conclusion, an increase of SCIT treatment rates in respiratory allergy patients can be considered very cost-effective from a societal and SHI perspective. However, while increased treatment rates could be dominant (i.e., cost-saving) from a societal point of view, this is unlikely when a SHI perspective is adopted, as a major part of cost savings from SCIT are due to improved productivity not included in the SHI perspective. Further research should address reasons for low treatment rates to enable the development of measures to increase SCIT application. These measures should differentiate between disease groups and stakeholders and also aim at decreasing discontinuation rates which will considerably improve the cost-effectiveness of increased SCIT treatment.

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Compliance with ethical standards

Conflict of interest JB, JW and AKW declare that their institution has received funding from the Medical Association of German Allergologists (AeDA) outside the submitted work. LK reports personal fees from ALK Abelló, MEDA, Novartis, Allergopharma, Bionorica, Boehringer Ingelheim, GSK and Lofarma as well as grants from ALK Abelló, Novartis, Allergopharma, Bionorica, GSK, Lofarma, Biomay, HAL, Leti, Roxall and Bencard outside the submitted work. NM reports personal fees from ALK, AstraZeneca-Santis, Astellas, Bencard, Berlin Chemie, Boehringer Ingelheim, HAL, Leti, Novartis, and Medinfo outside the submitted work; NM is Secretary of UEMS Section and Board Allergy. HFM, HR, WW, WT, EH, US and GS declare that they have nothing to disclose.

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Impact of increasing treatment rates on cost-effectiveness of subcutaneous immunotherapy (SCIT) in respiratory allergy – a decision analytic modelling approach

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Online Resources

1 Transition probabilities

2 Relative Risks of transitions

3 Share of patients eligible for SCIT and SCIT discontinuation rates

4 Costs per health state and cycle

5 Calculation of Utilities

Online Resource 1

In the routine data analysis diagnosis of respiratory allergy is defined as at least one assured outpatient diagnosis of J30.1 “allergic rhinitis due to pollen “, J30.2 “other seasonal allergic rhinitis “, J30.3 “other allergic rhinitis “ or J30.4 “allergic rhinitis, unspecified “ for allergic rhinitis or J45.0 “predominantly allergic asthma” or J45.8 “mixed asthma” for allergic asthma in the referring year [1].

Routine data derived transition probabilities for a maximum five year period are extrapolated by linear trend or assumed to remain constant at the level of the latest year. In some of the rare transitions in the fourth or fifth year the number of observations in the routine data is too small to generate reliable probabilities. Further there might be extreme or implausible values in years four and five due to documentation bias after completion of SCIT. In general the extrapolation methods are based on unbiased years and chosen to reflect the most plausible course over time and conservative estimates in order to avoid favouring SCIT. Table 1 displays the methods used for each transition.

Health state	Transition	Extrapolation method
Rhinitis	remission	assume value from year 3
	progression	linear trend based on years 1 to 5
Asthma	remission	linear trend based on years 1 to 3
	progression	linear trend based on years 1 to 4
Both diseases	no remission	assume value from year 3
	remission both diseases	assume value from year 3
	remission asthma	linear trend based on years 1 to 5
Symptom-free	no relapse	assume value from year 4
	relapse both diseases	linear trend based on years 1 to 2
	relapse asthma	linear trend based on years 1 to 2

Table 1 Extrapolations methods used to derive transition probabilities for the time horizon not covered by routine data

The following tables 2 to 11 show the resulting transition probabilities for SCIT states and the probabilities for no SCIT states calculated by application of relative risks for transition as described in Online Resource 2.

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	74.39%	75.21%	87.49%	75.21%
2	70.10%	70.87%	82.44%	70.87%
3	70.68%	71.46%	83.12%	71.46%
4	70.68%	71.46%	83.12%	71.46%
5	70.68%	71.46%	83.12%	71.46%
6	70.68%	71.46%	83.12%	71.46%
7	70.68%	71.46%	83.12%	71.46%
8	70.68%	71.46%	83.12%	71.46%
9	70.68%	71.46%	83.12%	71.46%
10	70.68%	71.46%	83.12%	71.46%

Table 2 Transition probability both diseases no remission

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	8.62%	8.52%	5.63%	8.52%
2	8.83%	8.73%	5.77%	8.73%
3	8.77%	8.68%	5.73%	8.68%
4	8.77%	8.68%	5.73%	8.68%
5	8.77%	8.68%	5.73%	8.68%
6	8.77%	8.68%	5.73%	8.68%
7	8.77%	8.68%	5.73%	8.68%
8	8.77%	8.68%	5.73%	8.68%
9	8.77%	8.68%	5.73%	8.68%
10	8.77%	8.68%	5.73%	8.68%

Table 3 Transition probability both diseases remission to symptom-free

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	84.11%	55.82%	16.65%	75.63%
2	84.14%	55.84%	16.65%	75.66%
3	85.00%	56.41%	16.82%	76.43%
4	80.00%	53.10%	15.83%	71.94%
5	70.65%	46.89%	13.98%	63.53%
6	71.46%	47.43%	14.14%	64.26%
7	68.36%	45.37%	13.53%	61.47%
8	65.25%	43.31%	12.91%	58.68%
9	62.15%	41.25%	12.30%	55.88%
10	59.04%	39.19%	11.68%	53.09%

Table 4 Transition probability both diseases remission of asthma

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	4.88%	4.82%	3.19%	4.82%
2	5.68%	5.62%	3.71%	5.62%
3	5.01%	4.95%	3.27%	4.95%
4	5.01%	4.95%	3.27%	4.95%
5	5.01%	4.95%	3.27%	4.95%
6	5.01%	4.95%	3.27%	4.95%
7	5.01%	4.95%	3.27%	4.95%
8	5.01%	4.95%	3.27%	4.95%
9	5.01%	4.95%	3.27%	4.95%
10	5.01%	4.95%	3.27%	4.95%

Table 5 Transition probability rhinitis remission

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	6.22%	10.47%	12.84%	8.65%
2	8.43%	14.19%	17.40%	11.72%
3	10.45%	17.58%	21.56%	14.53%
4	13.27%	22.34%	27.39%	18.46%
5	16.46%	27.71%	33.97%	22.90%
6	18.56%	31.24%	38.31%	25.82%
7	21.10%	35.50%	43.53%	29.34%
8	23.63%	39.77%	48.76%	32.86%
9	26.16%	44.03%	53.98%	36.38%
10	28.69%	48.29%	59.21%	39.90%

Table 6 Transition probability rhinitis progression

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	10.63%	7.06%	2.10%	9.56%
2	11.99%	7.95%	2.37%	10.78%
3	9.30%	6.17%	1.84%	8.36%
4	9.31%	6.18%	1.84%	8.37%
5	8.64%	5.74%	1.71%	7.77%
6	7.98%	5.30%	1.58%	7.17%
7	7.31%	4.85%	1.45%	6.58%
8	6.65%	4.41%	1.32%	5.98%
9	5.98%	3.97%	1.18%	5.38%
10	5.32%	3.53%	1.05%	4.78%

Table 7 Transition probability asthma remission

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	29.46%	49.58%	60.79%	40.97%
2	34.04%	57.29%	70.25%	47.34%
3	36.75%	61.85%	75.84%	51.11%
4	29.41%	49.50%	60.69%	40.90%
5	33.06%	55.63%	68.21%	45.97%
6	33.31%	56.06%	68.74%	46.33%
7	33.57%	56.49%	69.27%	46.68%
8	33.82%	56.93%	69.80%	47.04%
9	34.08%	57.36%	70.33%	47.40%
10	34.34%	57.79%	70.85%	47.75%

Table 8 Transition probability asthma progression

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	0.00%	0.00%	0.00%	0.00%
2	58.28%	34.63%	28.24%	41.91%
3	68.67%	40.81%	33.28%	49.38%
4	78.57%	46.69%	38.08%	56.50%
5	88.89%	52.82%	43.08%	63.92%
6	88.89%	52.82%	43.08%	63.92%
7	88.89%	52.82%	43.08%	63.92%
8	88.89%	52.82%	43.08%	63.92%
9	88.89%	52.82%	43.08%	63.92%
10	88.89%	52.82%	43.08%	63.92%

Table 9 Transition probability symptom-free no relapse

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	0.00%	0.00%	0.00%	0.00%
2	11.03%	18.56%	22.76%	15.34%
3	23.08%	38.84%	47.62%	32.09%
4	23.08%	38.84%	47.62%	32.09%
5	23.08%	38.84%	47.62%	32.09%
6	23.08%	38.84%	47.62%	32.09%
7	23.08%	38.84%	47.62%	32.09%
8	23.08%	38.84%	47.62%	32.09%
9	23.08%	38.84%	47.62%	32.09%
10	23.08%	38.84%	47.62%	32.09%

Table 10 Transition probability symptom-free relapse to both diseases

SCIT subcutaneous immunotherapy

Cycle	SCIT	No SCIT base case	No SCIT best case	No SCIT worst case
1	0.00%	0.00%	0.00%	0.00%
2	8.26%	13.91%	17.05%	11.49%
3	10.00%	16.83%	20.64%	13.91%
4	11.74%	19.75%	24.22%	16.32%
5	13.47%	22.67%	27.80%	18.73%
6	15.21%	25.59%	31.38%	21.15%
7	16.94%	28.51%	34.96%	23.56%
8	18.68%	31.43%	38.54%	25.98%
9	20.41%	34.35%	42.12%	28.39%
10	22.15%	37.28%	45.70%	30.80%

Table 11 Transition probability symptom-free relapse to asthma

SCIT subcutaneous immunotherapy

Online Resource 2

Relative risks for the transitions are derived from literature by calculation of an annual rate r as:

Equation 1

$$r = -\ln(1 - P)/t$$

With $\ln$ = natural logarithm and P =event rate in time period t

Based on the annual rates the annual probability p is calculated according to the following equation:

Equation 2

$$p = 1 - e^{-r*t}$$

With e = Euler's number, r = annual rate derived from equation 2 and t = reference time period for the probability.

The relative risk for each transition is then derived from the thus calculated annual probabilities.

Relative risks could only be found for progression [2-4] and remission [5-10] of rhinitis and remission of asthma [11,12]. Therefore the probabilities for all transitions in the symptom-free no SCIT states (i.e. relapse) are adjusted using the relative risks calculated for progression in rhinitis lacking data on symptom-free transitions. The transitions of no remission and complete remission in the both diseases state are based on the relative risks of remission in rhinitis while for remission of asthma in both diseases the relative risk of remission of asthma is used.

Table 12 displays the relative risks used for the adjustment of transition probabilities for untreated SCIT suited patients. The routine data derived transition probabilities for the SCIT states are given in Online Resource 1.

	Relative risk for transition in SCIT eligible untreated vs. treated patients		
	base case	best case	worst case
Rhinitis progression	1.68	2.06	1.39
Rhinitis remission	0.99	0.65	0.99
Asthma remission	0.66	0.20	0.90

Table 12 Relative risks of transitions in SCIT eligible untreated patients

SCIT subcutaneous immunotherapy

Online Resource 3

The share of patients eligible for SCIT is estimated based on German medical guideline criteria and their frequency reported in literature or estimated in expert interviews. The criteria include therapy refusal, medical contraindication, persistent rhinitis symptoms and controlled asthma symptoms. The share of patients receiving SCIT is derived from routine data. These two shares relate to the population of all respiratory allergy patients. With the target population of the model comprising patients eligible for SCIT these rates need to correspond to this population. In the increasing treatment rates strategy all eligible patients are treated and therefore treatment rates are 100%. The treatment rates in the status quo are then related to the SCIT-eligible population by:

Equation 1

$$\frac{\text{Share of treated patients on all respiratory allergy patients}_{(Routine\ data)}}{\text{Share of eligible patients on all respiratory allergy patients}_{(Treatment\ assignment\ scheme)}}$$

Table 13 displays the share of eligible and treated patients in all respiratory allergy patients and in SCIT eligible patients by disease group.

Disease group	All respiratory patients				Patients eligible for SCIT			
	Increasing treatment rate strategy*			Status Quo**	Increasing treatment rate strategy	Status Quo***		
	base	best	worst			base	best	worst
Rhinitis	31%	41%	22%	5%	100%	16%	12%	23%
Both diseases	18%	28%	16%	9%	100%	50%	32%	57%
Asthma	27%	59%	11%	1%	100%	4%	2%	9%

Table 13 Share of patients eligible for SCIT and referring treatment rates

*calculated from the treatment assignment scheme, **derived from routine data, ***calculated by applying equation 1, SCIT subcutaneous immunotherapy

The discontinuation rates of SCIT which are being derived from the routine data indicated documentation bias in the third year of treatment where the rate doubled compared to years one and two. This might be caused by patients who get a new package of allergen extract at the end of year three which is sufficient to complete the three year course of injections without needing further prescription in the last treatment year. This is especially plausible for patients having initiated SCIT in the first half of the year. To account for this bias adjusted discontinuation rates for the third year are calculated as average rate over all years. The values used in the worst sensitivity analysis lie above the original discontinuation rates of year three and therefore cover any influence of these adjustments.

Table 14 displays the adjusted base case discontinuation rates of SCIT by disease group.

Treatment year	Rhinitis	Both diseases	Asthma	Symptom-free
1	26%	26%	28%	0%*
2	21%	19%	19%	19%
3 (original)	45%	44%	42%	46%
3 (adjusted)**	31%	30%	30%	33%

Table 14 Raw and adjusted discontinuation rates of SCIT based on routine data

*initially there are no patients in this state **mean of years one to three of the original data; SCIT subcutaneous immunotherapy

Online Resource 4

The following tables 15 to 17 display the base case cost per health state and cycle (i.e. year) in 2016 Euro values.

	No SCIT**	SCIT			
		year 1	year 2	year 3	years 4 to 10
Physician visits	78.60 €	31.89 €	31.89 €	31.89 €	31.89 €
Medication	74.59 €	52.21 €	25.06 €	9.52 €	9.52 €
SCIT	0 €	1,423.54 €	1,080.39 €	1,080.39 €	0€
Total direct cost	153.20 €	1,507.64 €	1,137.34 €	1,121.80 €	41.41 €
Productivity loss*	578.95 €	477.40 €	477.40 €	477.40 €	477.40 €
Total cost	732.14 €	1,985.04 €	1,614.74 €	1,599.20 €	518.81 €

Table 15 Base case cost per year and treatment strategy in rhinitis patients (2016 Euro)

*only absenteeism **cost in no SCIT states stay constant in all years SCIT subcutaneous immunotherapy

	No SCIT**	SCIT			
		year 1	year 2	year 3	years 4 to 10
Physician visits	114.87 €	46.60 €	46.60 €	46.60 €	46.60 €
Hospitalization	589.80 €	367.59 €	367.59 €	367.59 €	367.59 €
Medication	431.38 €	409.01 €	292.66 €	223.60 €	223.60 €
SCIT	0 €	1,423.54 €	1,080.39 €	1,080.39 €	0 €
Total direct cost	1,136.06 €	2,246.73 €	1,787.23 €	1,718.17 €	637.79 €
Productivity loss*	771.08 €	635.83 €	635.83 €	635.83 €	635.83 €
Total cost	1,907.13 €	2,882.56 €	2,423.06 €	2,354.00 €	1,273.62 €

Table 16 Base case cost per year and treatment strategy in patients with rhinitis and asthma (2016 Euro)

*only absenteeism **cost in no SCIT states stay constant in all years SCIT subcutaneous immunotherapy

	No SCIT**	SCIT			
		year 1	year 2	year 3	years 4 to 10
Physician visits	96.26 €	39.05 €	39.05 €	39.05 €	39.05 €
Hospitalization	589.80 €	367.59 €	367.59 €	367.59 €	367.59 €
Medication	356.79 €	356.79 €	267.59 €	214.07 €	214.07 €
SCIT	0 €	1,423.54 €	1,080.39 €	1,080.39 €	0 €
Total direct cost	1,042.86 €	2,186.97 €	1,754.62 €	1,701.10 €	620.71 €
Productivity loss*	2,043.34 €	1,684.94 €	1,684.94 €	1,684.94 €	1,684.94 €
Total cost	3,086.19 €	3,871.91 €	3,439.56 €	3,386.04 €	2,305.65 €

Table 17 Base case cost per year and treatment strategy in asthma patients (2016 Euro)

*only absenteeism **cost in no SCIT states stay constant in all years SCIT subcutaneous immunotherapy

Online Resource 5

The EQ-5D is a widely used and well validated generic preference-based quality of life instrument including the dimensions of mobility, self-care, usual activities, pain/ discomfort and anxiety/ depression. The health states are comprised by a value of 1 to 3 for each dimension where 1 indicates no impairment and 3 the most severe impairment. These states are then valued in a general population sample with the time trade-off method. [13,14]

The Asthma symptom utility index (ASUI) and Rhinitis symptom utility index (RSUI) are disease specific preference-based quality of life instruments. They comprise five different symptoms (S1 to S5) and define the health states through severity (none, mild, moderate, severe) and frequency (1-3, 4-7 and 8-14 days in the last two weeks) for each symptom. [15,16] The symptoms in the RSUI are stuffy nose, runny nose, itchy eyes, itchy throat and sneezing while the ASUI symptoms are cough, wheeze, dyspnea, awaken at night and medication side effects. [15,16] The health states are valued by patient samples using the standard gamble method. [15,16] Since 52% of the RSUI patients reported concomitant asthma the use of RSUI values to derive utilities for the both diseases population seems plausible. [16]

To measure the improvement of quality of life in patients receiving SCIT RCTs applying the Rhinitis Quality of Life Questionnaire (RQLQ) and/ or the Asthma Quality of Life Questionnaire (AQLQ) are identified in systematic searches of the data bases Medline and Embase. Suitable studies are then pooled by conducting a fixed effects meta-analysis using the RevMan5 tool provided by the Cochrane Collaboration. The results of the meta-analyses based on 12 studies for rhinitis [17-28], 11 studies for both diseases [18-28] and two for asthma [29,30] are displayed in figures 1 to 3.

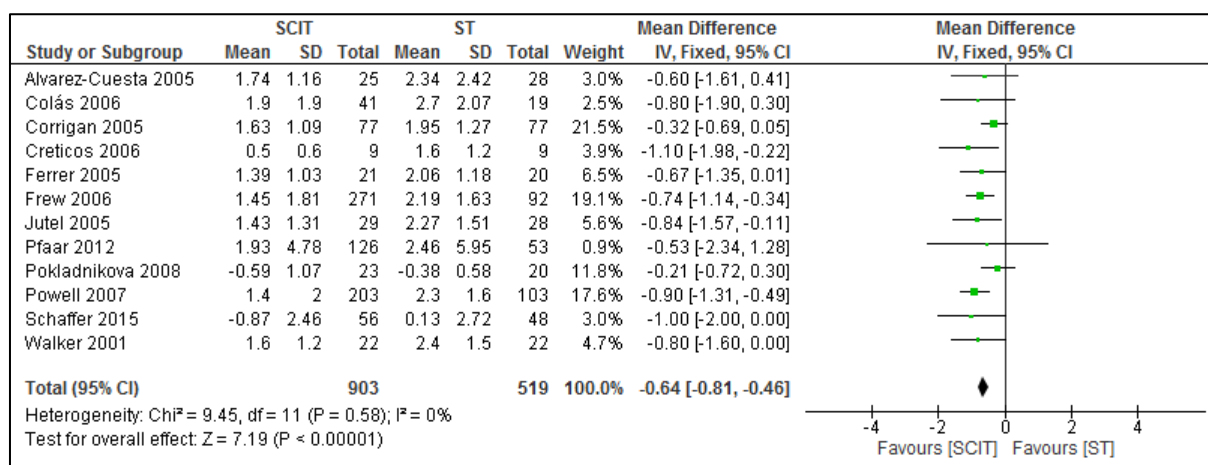


Figure 1 Mean difference in RQLQ score in allergic rhinitis patients

SCIT subcutaneous immunotherapy, ST symptom treatment

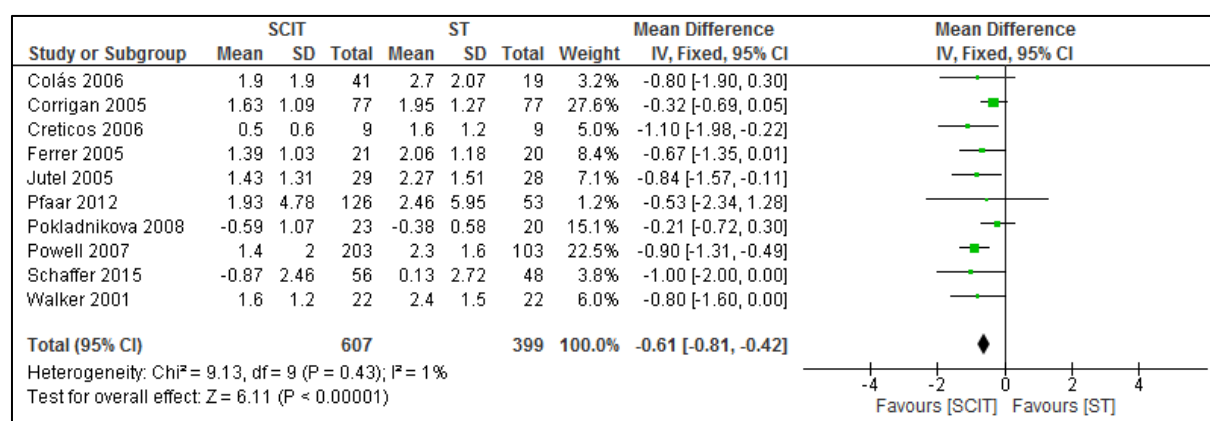


Figure 2 Mean difference in RQLQ score in patients with allergic rhinitis and allergic asthma

SCIT subcutaneous immunotherapy, ST symptom treatment

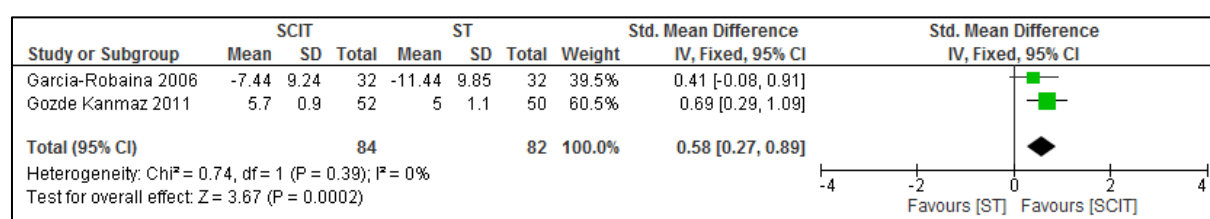


Figure 3 Mean difference in AQLQ score in allergic asthma patients

SCIT subcutaneous immunotherapy, ST symptom treatment

The RQLQ includes 28 questions in the seven domains activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function whereas each question is scored on a scale from 0 (no impairment) to 6 (severe impairment). [31] The AQLQ comprises 38 questions on the four domains symptoms, activity limitation, emotional function and environmental stimuli with each question being scored from 7 (no impairment) to 1 (severe impairment). [32] In both instruments the overall score is the mean score of all questions. [31,32]

Only one RCT using the AQLQ defined by Juniper et al. could be identified [30] while another RCT [29] applied the AQLQ defined by Marks et al. [33] which was included in the meta-analysis. Due to the different quality of life instruments the standardized mean difference was calculated and retranslated into the Juniper AQLQ by multiplication with the pooled variance of the SCIT and control group. This proceeding follows the recommendations of the Cochrane Collaboration. [34]

The translation of a change in RQLQ or AQLQ score to a change in utility is adopted from a published HTA report which includes a decision analytic model on SCIT in patients with seasonal allergic rhinitis. [35] First the range of the RQLQ and AQLQ is determined by subtracting the best from the worst possible score (RQLQ 6-0=6; AQLQ 1-7=-6). Thus the range of both scores is 6. In all preference-based instruments the best possible state is valued 1. For the RSUI and ASUI the worst states are severe symptoms in 8-14 days of two weeks in all symptom domains. The utilities for these states are given in one study for the ASUI (0.0397) [15] and in two studies for the RSUI whose mean value is used (0.0224) [36,16]. It is assumed that allergic rhinitis and allergic asthma do not lead to

impairments in the EQ-5D domains of mobility and self-care. [35] Therefore the worst rhinitis- or asthma-related EQ-5D state is “11333” which reflects no impairment in mobility and self-care and severe impairment in usual activities, severe pain and anxiety. Applying the German time trade-off value set this state has a utility of (0.296). [37] The change in utility by change of RQLQ and AQLQ score calculated by division by the utility range is 0.1173 for the EQ-5D, 0.160 for the ARSUI and 0.63 for the RSUI. Table 18 shows the mean utility gain derived by multiplication of the mean score difference from the meta-analysis with the utility change per score point.

EQ-5D	Rhinitis	Both diseases	Asthma
Base case	0.075	0.072	0.083
Best case*	0.095	0.095	0.127
Worst case**	0.054	0.049	0.039
RSUI/ ASUI			
Base case	0.104	0.099	0.113
Best case*	0.132	0.132	0.173
Worst case**	0.075	0.068	0.053

Table 18 Utility gain for the disease states by instrument

*based on the upper limit of the 95% confidence interval (CI) of the mean difference in RQLQ or AQLQ ** based on the lower limit of the 95%-CI of the mean difference in RQLQ or AQLQ

For asthma a capping was required in the best case utility gain scenario because the sum of basis utility and utility gain exceeded the maximum value of 1. This is caused by several factors: because of the assumption that only well controlled asthma patients are eligible for SCIT the basis utilities for asthma are high. Moreover the utility gain is based on the improvement of RQLQ or AQLQ in clinical trials which will include a certain share of patients becoming symptom-free and therefore does not adequately reflect the concept of improvement within the state of asthma applied here. The capping was designed to result in a utility of 0.998 which is just below the value of symptom-free patients (i.e. 1).

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