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Cost-effectiveness of grass pollen allergen immunotherapy in adults

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Abstract

Background: Major scientific societies, such as the EAACI or the AAAAI, do not express any suggestion on which form of allergen immunotherapy (AIT) is to be preferred (subcutaneous immunotherapy, SCIT, vs sublingual immunotherapy, SLIT). This choice could depend on their relative pharmacoeconomic value.

Objective: To assess the cost-effectiveness of AIT for grass pollen, administered as SCIT or SLIT.

Methods: We created a Markovian Model, to evaluate, in a hypothetical cohort of adult patients suffering from moderate-to-severe rhino-conjunctivitis with or without allergic asthma, the cost-effectiveness of SLIT (tablets, Grazax[®] and Oralair[®]) or SCIT (various currently available products, plus indirect nonmedical costs, such as travel and productivity costs) in addition to pharmacological therapy, assuming a 9-year horizon to capture AIT long-term effects. The incremental cost-effectiveness ratio (ICER) was calculated assuming pharmacological therapy as the reference comparator.

Results: In the base case, SCIT was slightly more expensive, but more effective than SLIT, being the most cost-effective option (ICER for SCIT, €11 418; ICER for SLIT, €15 212). ICERs greater than €120 000 for both SCIT and SLIT were demonstrated in a scenario assuming that low treatment persistence rates, which are common in real-life, lead to absence of long-term AIT clinical benefit. Considering indirect non-medical costs SLIT resulted more cost-effective than SCIT (ICER for SCIT, €17 318; ICER for SLIT, €15 212).

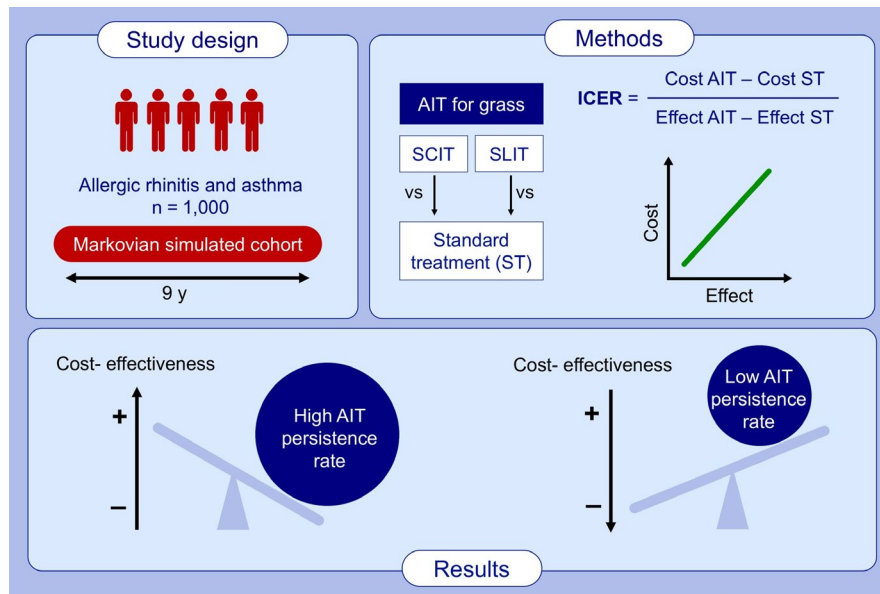
Conclusion: In daily practice, AIT for grass pollens may be a cost-effective option only in patients with low discontinuation rates. SCIT, which is less affected by this limitation than SLIT, seems the most cost-effective AIT form.

KEYWORDS

costs, QALY, SCIT, SLIT

Abbreviations: AIT, allergen immunotherapy; ICER, incremental cost-effectiveness ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

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GRAPHICAL ABSTRACT

Both SCIT and SLIT for grass pollen are more effective, but also more expensive than standard pharmacological treatment. AIT treatment persistence (ie, completion of the minimal recommended duration of 3 years) significantly affects cost-effectiveness. In daily practice, AIT for grass pollens may be a cost-effective option only in patients with high treatment persistence rates.

1 | INTRODUCTION

Subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT) are established treatment modalities for patients with moderate-to-severe allergic rhino-conjunctivitis (ARC) with or without allergic asthma.¹ The main limit of SCIT, the classic subcutaneous route of allergen immunotherapy (AIT), is that treatment requires repeated visits to physician's office for administration, representing an investment of time and effort from patients. To address this shortcoming, SLIT was developed. The self-administration of SLIT by the patients makes this treatment time-saving relative to SCIT.

A benefit from both SCIT and SLIT compared with placebo has been consistently demonstrated in randomized controlled trials (RCTs), but the extent of this effectiveness in terms of clinical benefit is unclear.²⁻⁵ Pharmacoeconomic studies, mainly based on the results of RCTs, suggested that both forms of AIT are cost-effective relative to placebo.⁶⁻¹⁵ However, discrepancies between the clinical settings of RCTs and those of real clinical practice make the assumptions of these modeling studies uncertain and limit the validity of their conclusions.^{5,16} Furthermore, data on the relative cost-effectiveness of SCIT vs SLIT are scarce, owing to the lack of efficacy studies aiming at head-to-head comparison between SLIT and SCIT.

Although prominent scientific societies in the field, such as the European Academy of Allergy and Clinical Immunology or the American Academy of Asthma, Allergy, and Immunology, express no preference on which form of AIT (either SLIT or SCIT) is to be chosen, physicians, patients, insurers, or National Health Systems may be interested in choosing the option with the best value.^{1,17}

In fact, a recent review on pharmacoeconomic studies on AIT concluded that the evidence supporting AIT cost-effectiveness is limited and of a low methodological quality and appears to suggest that AIT may be cost-effective from an English NHS perspective only in very high-risk subgroups.¹⁶

To assess the strategy with the best value, we used a nonstationary Markov model to compare the cost-effectiveness of SCIT and SLIT for grass pollens to standard pharmacological treatment using an independent model (in the absence of support by any pharmaceutical company). Extensive scenario analyses were implemented to mirror plausible real-life situations in order to increase the reliability of the conclusions. The results are intended to provide healthcare professionals and policymakers with information useful for cost-effective interventions.

2 | METHODS

2.1 | Model structure

A Markovian state-transition model was used, considering the Italian societal perspective, including payments of the National Health Service and additional payments by the patients, and assuming a 9-year horizon, to capture the possible long-term effects of grass pollen AIT in adults suffering from ARC with/without mild/intermittent asthma (Figure 1).¹⁸⁻²³

We compared cost-effectiveness of the following 3 strategies: (a) standard treatment (no AIT); (b) SLIT added to standard treatment; and (c) SCIT added to standard treatment (Figure 1). The "no

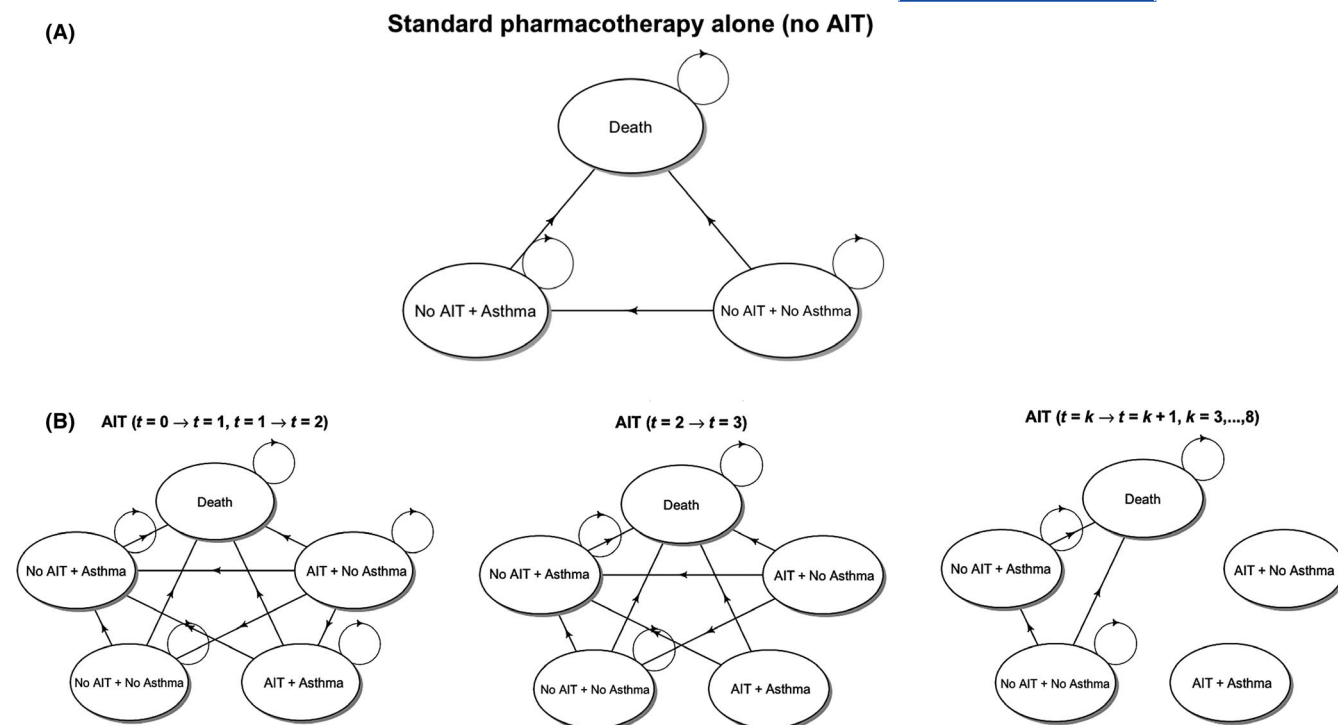


FIGURE 1 Markovian model structure. Patients enter the simulation receiving (A) standard pharmacotherapy alone (no AIT) or (B) AIT (SCIT or SLIT) added to standard pharmacotherapy. The cycle length is 1 y. Model input parameters are reported in Table 1. Detailed calculations of transition probabilities are reported in Appendix S1

AIT" strategy included symptomatic pharmacotherapy alone (antihistamines, topical corticosteroids). The SLIT strategy included only tablets for grass pollens (Grazax[®], Oralair[®]),^{24,25} which were showed to be more efficacious than SLIT products administered as drops.² The SCIT strategy included marketed SCIT products (unmodified native-conjugated extracts and allergoids: Allergovit[®], Purethal[®], Lais In[®], Tyrosin TU[®], Pangramin Ultra[®]), representative of those used in RCTs.²

The SLIT strategy included 1 daily dose for 3 consecutive years for Grazax[®] and 1 daily dose for 7 months per year for Oralair[®] for 3 consecutive years. The SCIT strategy included a monthly dose for 3 consecutive years after the initial build-up period consisting in 1 weekly dose up to maintenance (4-week course on average).

The model was designed to simulate cohorts of adult patients, (mean age, 35.9 years), with moderate-to-severe ARC with/without mild or intermittent allergic asthma, as included in the RCTs for grass pollen SCIT and SLIT, respectively.^{2,3,26} The model for "no AIT" strategy comprised three health states: "No Asthma," including patients with ARC without asthma; "Asthma," including patients with ARC and asthma, and "Death." SCIT and SLIT strategies comprised other two additional health states: "No AIT + No Asthma" and "No AIT + Asthma," including patients that prematurely abandon AIT or that have completed the 3-year course of treatment. Asthma occurrence was accompanied by an increased risk of dying.²⁷ At entry, we assumed that no patient suffered from allergic asthma (Figure 1 and Table 1). After the start of treatment, patients were followed up in 1-year Markov cycles. Each year, they could experience symptom improvement, bronchial asthma

development, death, or abandon treatment before reaching a mutually exclusive health state for the next cycle. After AIT completion (in $t = 2$; we start to count time in $t = 0$) or after its premature discontinuation, solely standard treatment was continued in the model (from $t = 3$ onwards). However, it was assumed that AIT effects remain constant after AIT (for a total simulation horizon of 9 years).

The length of the grass pollen season was estimated at 60 days per year on average, as assessed in RCTs.²

Output included costs and quality-adjusted life-years (QALYs). The incremental cost-effectiveness ratio (ICER) between strategies was calculated as incremental costs divided by incremental QALYs ($\text{ICER} = \text{Cost of AIT} - \text{Cost of No AIT} / \text{Effect of AIT} - \text{Effect of No AIT} = \Delta\text{Cost} / \Delta\text{Effect}$), assuming no AIT as the reference comparator. Costs and QALYs were discounted at 3.5% per year. We did not choose a decision threshold to avoid misleading conclusions. Analyses were performed by R 3.6.0.²⁸

2.2 | Intervention effect and model assumptions

Model input parameters used in the base case and scenario analyses are listed in Table 1. Compared to patients treated with standard therapy, vaccinated counterparts experience lower symptoms (leading to QALY increase) during the pollen season in proportion to efficacy of each AIT strategy. Annual incidence of asthma and death was also inserted to the model.^{27,29,30} Patients could withdraw from AIT (Table 1).³¹ The counts related to the evolution of the cohort (1000

TABLE 1 Epidemiologic, quality of life, and cost inputs: Baseline values used in the base case and scenario analyses

Variable	Baseline value	Source
AIT persistence, rate (%)		
SLIT		
1st year	52	Eggert-Schmidt et al (2014) ³¹
2nd year	25	
3rd year	15	
SCIT		
1st year	100	
2nd year	47	
3rd year	26	
Incidence of asthma per year		
No AIT	0.00463	Shaaban et al (2008) ²⁹
AIT	0.00231	Jacobsen et al (2007) ³⁹
Deaths per 1000 cases		
Asthma	0.92	Huovinen et al (1997) ²⁷
No Asthma (all cause mortality)	0.61	ISTAT, Tavole di Mortalità ³⁰
Utility inputs, QALYs adjusted for age		
No AIT – No Asthma	0.7402	Di Bona et al (2012) ² Di Bona et al (2015) ³ Reviky et al (1998) ³² Bernert et al (2009) ³³
No AIT – Asthma	0.5461	
SLIT – No Asthma	0.7891	
SLIT – Asthma	0.5822	
SCIT – No Asthma	0.8083	
SCIT – Asthma	0.5964	
Direct medical costs, € per case		
Rounded average AIT prize, € per year course		
SLIT (tablets)	992.2	AIFA ^{24,25}
SCIT	473.4	Producer Price List (yr 2018) ^a
Rounded average anti-symptomatic drug costs, € per dose		
Anti-H1 (desloratadine, 5 mg)	0.21	Italian National Formulary
Nasal corticosteroids (budesonide 50 mg)	0.08	AIFA (year 2018)
Average daily drug use, number of tablets or puffs		
Anti-H1 (desloratadine, 5 mg)		
No AIT	0.31	Bona et al (2015) ³
SLIT	0.23	
SCIT	0.19	
Nasal corticosteroids (budesonide 50 mg)		
No AIT	0.46	
SLIT	0.29	
SCIT	0.23	
First visit cost, €	30.66	Ministry of Health, Nomenclatore Tariffario Regionale ³⁶
Skin-prick test cost, €	44.86	Ministry of Health, Nomenclatore Tariffario Regionale, ³⁶ Di Bona et al (2015) ^{3,4}
Control visit, €	22.91	
Number of tests and control visits per treatment course		
No AIT	1	

(Continues)

TABLE 1 (Continued)

Variable	Baseline value	Source
SLIT	3	
SCIT	3	
AIT administration costs (SCIT), € per injection	11.96	Ministry of Health Nomenclature Tariffario Regionale ³⁶
Average number of administrations per year		
1st year	12 (4 + 8)	
2nd year	10	
3rd year	10	
Average direct costs of asthma, €	594	Accordini et al (2013) ³⁸
Direct nonmedical costs, € per case		
Travel cost of SCIT, €	5	Assumption
Indirect nonmedical costs, € per case		
Average hourly labor cost, €	14.6	Istat (2014) ³⁷
Time lost due to SCIT administration, h	2	Assumption
Average indirect costs of asthma, € per case/y	989	Accordini et al (2013) ³⁸

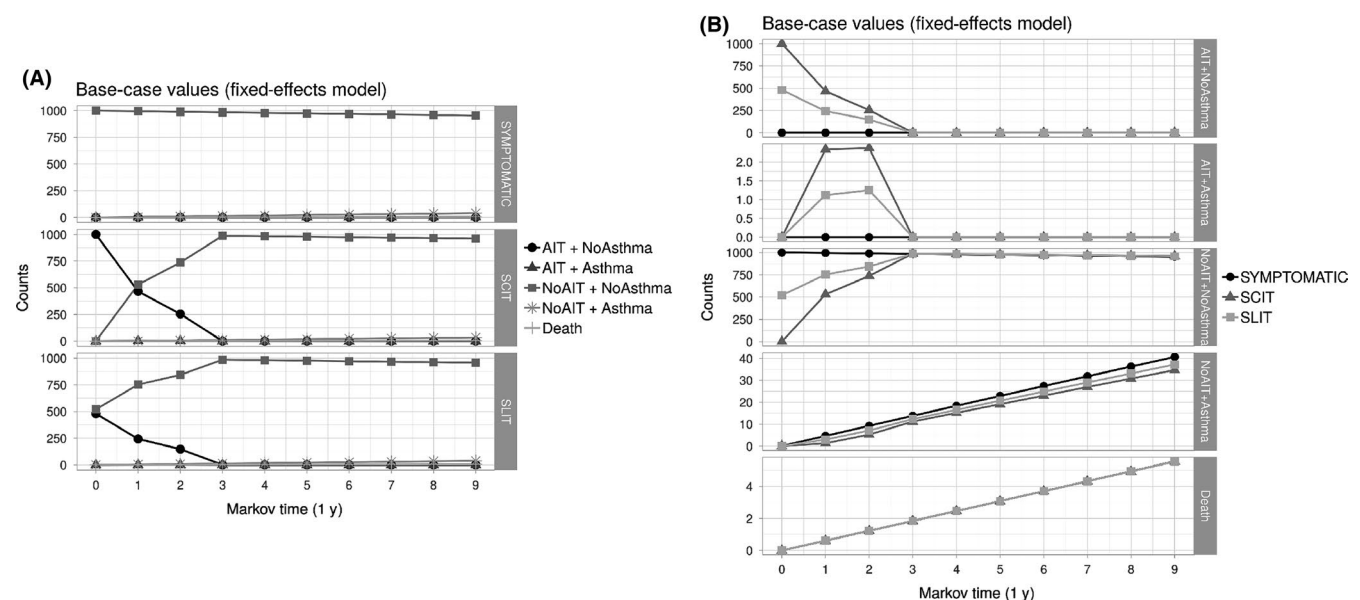
^aPersonal communication.

FIGURE 2 Markovian simulation, for the base case, of the cohort over the 10-y time horizon per 1000 patients, according to the 5 mutually exclusive health states (A) or the therapeutic strategy (B)

patients) of the base case in the 9-year time horizon are reported in Figure 2A,B. In the base case, we assumed that efficacy of AIT was not affected by withdrawal.

2.3 | Quality-adjusted life-years

Our estimates on efficacy of all treatment strategies are based on the pooled rhino-conjunctivitis total symptom scores (RTSS) reported in the available meta-analyses of RCTs comparing SCIT or SLIT tablets to placebo.^{2,3} In these meta-analyses, differences among the studies

were assessed as standardized mean differences (SMD), since different scales were used in the original RCTs to assess clinical benefit. Therefore, a back-transformation procedure was used to convert SMD to RTSS for each strategy. The multiattribute Rhinitis Symptom Utility Index (RSUI)^{32,33} was then used to convert symptom severity (RTSS) to utilities. Utilities were further adjusted by patient's age and co-existing asthma (Table 1).^{2,3,32,33} In the base case, the fixed-effects model was used to obtain the pooled estimates. Under this assumption, differences in efficacy between SCIT and SLIT appear to be lower than the random-effects model, which shows a greater efficacy of SCIT.³⁴ The literature review, indirect comparisons between

SCIT and SLIT, and the abovementioned back-transformation procedure are described in detail in Appendix S1.

2.4 | Costs

Costs of vaccines used for SLIT (Grazax[®], Oralair[®]) were based on the private sector price of the Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco).^{24,25} For SCIT grass products (Allergovit[®], Purethal[®], Lais In[®], Tyrosin TU[®], Pangramin Ultra[®]), an average cost was calculated based on the respective pharmaceutical companies prices for the Italian market, obtained from the manufacturers (personal communication). Costs for symptomatic medications were calculated by multiplying the unit costs for desloratadine and budesonide (obtained from the Italian National Formulary) by the number of actuations, which estimation was based on data presented in Bachert et al (see Appendix S1 for detailed calculations).^{8,35}

Health interventions, such as visits or diagnostic tests, were valued and the corresponding costs attributed.³⁶

Indirect nonmedical costs were estimated as travel costs, averaging public transport (equal to a round-trip bus ticket in Rome, Italy) and private transport, and productivity costs equal to 2 hours of working time (not adjusted for age-specific wage-rate and workforce participation), based on ISTAT data.³⁷ Intangible costs, such as pain, discomfort, or suffering, were not evaluated in the present analyses. Annual costs of asthma estimates were based on results of an international population-based study (Table 1).³⁸ Costs are given in 2018 Euros.

2.5 | Scenario analyses

Uncertainty about the model assumptions was assessed generating a set of different plausible scenarios, each based on a specification representing alternative assumptions, in order to match relevant clinical data. In all the scenarios, efficacy was assessed by pooled estimates from meta-analysis under the fixed-effect model, unless differently specified.

We considered the following variations of the base case:

- #1: Same assumptions as the base case; efficacy calculated based on the same studies as the base case meta-analyzed but using the random-effects model, showing a greater benefit with SCIT relative to SLIT;
- #2: SCIT and SLIT have the same efficacy relative to standard treatment²⁶;
- #3: No clinical improvement after AIT premature discontinuation^{19,23};
- #4: No AIT preventive effects on asthma^{39,40};
- #5: Preventive effect on asthma only by SCIT⁴¹;
- #6: Full societal perspective;
- #7: Full societal perspective, considering efficacy calculated under the random-effects model);

- #8: Symptoms only during the peak of the pollen season.

Assumptions for each scenario are reported in details in Appendix S1.

3 | RESULTS

3.1 | Base-case analysis

Table 2 shows costs and QALY gain for each strategy. Both forms of AIT contributed to gains in QALY and increased costs relative to standard treatment. SCIT was slightly more expensive, but also more effective than SLIT, resulting the most cost-effective option (ICER for SCIT, €11 418; ICER for SLIT, €15 212) (Table 2; Figure 3). The lower costs of SLIT relative to SCIT were due to higher discontinuation rate with SLIT. Hence, SLIT costs dramatically decrease precisely because of withdrawal. Nonetheless, we assumed that the efficacy of AIT was not diminished by treatment withdrawal. QALY differences are mainly explained by different efficacy among the strategies in terms of RTTS, calculated by meta-analysis under the fixed-effects model in the base case to reduce the efficacy of SCIT relative to SLIT (conservative model). Also, asthma occurrence and death contribute to QALY calculation.

3.2 | Scenario analyses

We varied model parameters to test whether our conclusions were robust under different circumstances: In general, high level of uncertainty in ICER estimation was found when the core model parameters were changed in order to mirror plausible clinical assumptions (Table 3).

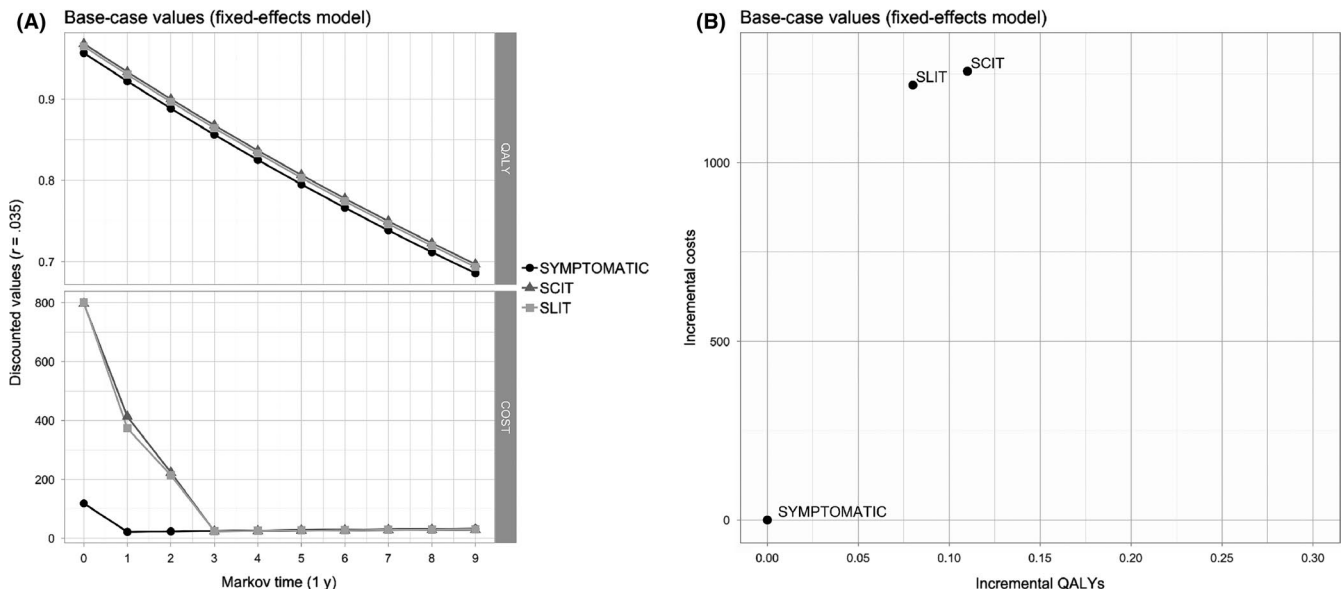
The cost-effectiveness of SCIT was sensitive to changes in RTSS and consequently to changes in QALY estimates. In the scenario #1, RTSS was estimated using the same studies as the base case, but meta-analyzed under the random-effects model, which shows a substantial increased benefit with SCIT, but not with SLIT relative to standard treatment. Under this assumption, the differences in cost-effectiveness between SCIT and SLIT markedly increased (ICER for SCIT, €4319; ICER for SLIT, €15 121), owing to increased efficacy estimates for SCIT. Conversely, assuming no difference between SCIT and SLIT efficacy, SLIT was marginally more cost-effective than SCIT (ICER €15 212 vs €15 700, respectively; scenario #2).

The main model assumption in the base case was that efficacy observed after one season of AIT administration was sustained for 9 years. Scenario #3 tested the hypothesis that only subjects who complete the minimum required period of 3 years of AIT were expected to have short-term and long-term clinical benefit.^{18,23} Under these circumstances, the ICER of SCIT and SLIT dramatically increased far over any acceptable willingness to pay threshold (€125 600 and €121 700, respectively). We also found an increase

TABLE 2 Cumulative cost and QALYs per patient of 3 strategies in the base case^a

Strategy	Cost, €	Incremental cost, €	QALYs	Incremental QALYs	ICER, € per QALY
No AIT	365.3	NA	8.15	NA	NA
SCIT	1621.5	1256	8.26	0.11	11 418
SLIT	1582.2	1217	8.23	0.08	15 212

^aCosts are given in 2018 euros (€). Cumulative QALYs and costs were discounted at an annual rate of 3.5%.

**FIGURE 3** Evolution of costs and QALYs, for the base case scenario, over the 10-y time horizon of the Markovian simulation (A), and the corresponding cost-effectiveness plane (B)

in the ICER estimates when we assumed a lack of preventive effect on asthma development by both forms of AIT or by SLIT alone (scenarios #4 and #5).

The cost-effectiveness of SCIT was sensitive to increased costs as assessed in a societal perspective including indirect nonmedical costs. Under these circumstances, SLIT was slightly more cost-effective than SCIT only when efficacy was estimated by meta-analysis using the fixed-effects model (scenarios #6; conservative, favorable to SLIT), not when the random-effects model was used (scenario #7; favorable to SCIT).

Finally, the cost-effectiveness of both AIT strategies was sensitive to the duration of pollen exposure as shown in scenario #8, assuming symptom occurrence only during the peak of pollen season (estimated 15-day length).

4 | DISCUSSION

Our conclusions on cost-effectiveness of AIT for grass pollens compared to standard treatment are based on several reasons that will be clarified throughout the discussion.

The base-case model revealed that SCIT costs €11 418 per QALY gained and SLIT costs €15 212 per QALY gained relative to standard

treatment. These results apparently suggest that both strategies are cost-effective relative to standard treatment, considering the general accepted societal thresholds for willingness to pay.⁴² This is actually the conclusion of several pharmacoeconomic studies on this subjects, which estimated ICERs similar to ours.

However, there are several points that need to be addressed. The first problem is precisely related to the choice of a reliable threshold value for cost-effectiveness.⁴³⁻⁴⁷ In the United States, values ranging from \$50 000 to \$100 000 are sometimes used as threshold. In the UK, NICE adopted a much lower threshold, ranging from £20 000 to £30 000 per QALY gained. In the Netherlands, the threshold for a drug to be considered cost-effective varies from €10 000 to €80 000 depending on the severity of the disease.

As a consequence, adopting the US or UK threshold, both SCIT and SLIT could be considered cost-effective relative to standard treatment, but adopting the threshold proposed in the Netherlands for low severity diseases (€10 000), neither of the two strategies would be cost-effective.

Besides the threshold value, a clarification on the meaning of the results of ours (and other) studies should be done. In the base case, SLIT led to 0.08 QALY gain per patient, whereas SCIT led to 0.11 QALY gain per patient compared to standard treatment over the 10 Markov one-year cycles. This means that for each patient

TABLE 3 Scenario analyses

Scenario	Incremental costs, € ^a	Incremental QALYs	ICER, € ^a per QALY
#1: Efficacy calculated with the REM			
SCIT vs standard treatment	1123	0.26	4319
SLIT vs standard treatment	1217	0.08	15 212
#2: No difference between SLIT and SCIT			
SCIT vs standard treatment	1256	0.08	15 700
SLIT vs standard treatment	1217	0.08	15 212
#3: No clinical benefit after premature discontinuation			
SCIT vs standard treatment	1256	0.01	125 600
SLIT vs standard treatment	1217	0.01	121 700
#4: No asthma prevention by AIT			
SCIT vs standard treatment	1286	0.09	14 289
SLIT vs standard treatment	1232	0.07	17 600
#5: No asthma prevention by SLIT			
SCIT vs standard treatment	1256	0.11	11 418
SLIT vs standard treatment	1232	0.07	17 600
#6: Full societal perspective (FEM)			
SCIT vs standard treatment	1905	0.11	17 318
SLIT vs standard treatment	1217	0.08	15 212
#7: Full societal perspective (REM)			
SCIT vs standard treatment	1905	0.26	7327
SLIT vs standard treatment	1217	0.08	15 212
#8: Symptoms only during the peak of the pollen season (15 d)			
SCIT vs standard treatment	1256	0.04	31 400
SLIT vs standard treatment	1217	0.03	40 567

^aCosts are given in 2018 euros (€). Cumulative QALYs and costs were discounted at an annual rate of 3.5%. REF, random-effects model; FEM, fixed-effects model.

SLIT led to 0.008 QALY gain/y (365 days), which is equivalent to: $0.008 \times 365 = 2.9$ well days (days without symptoms) per year. Hence, one must be willing to pay additional €15 212 for a patient to be in perfect health for 3 more days per year compared to standard treatment (more than €500 per 1 day without symptoms). Regarding SCIT, one must be willing to pay additional €11 418 for a patient to be in perfect health 4 more days per year compared to standard treatment ($0.011 \times 365 = 4$; €285 per 1 day without symptoms). These results show that AIT is not expensive, but its modest clinical benefit,^{2-4,48} lower than the minimally clinically important difference (1.1-1.3 RTSS points) for SLIT (0.83 RTSS points on average), greatly reduces its cost-effectiveness relative to standard treatment.

This aspect must be further clarified. With regard to clinical benefit and costs, the results of the base case are overly favorable to AIT relative to standard treatment, because the key assumptions of the model are favorable to AIT, particularly to SLIT. Firstly, efficacy of AIT was not assumed to be affected by treatment withdrawal; therefore, efficacy was the same regardless the fact that patients were treated for 6 months or 3 years, for example. Conversely, costs were reduced in proportion to treatment duration. This also means that SLIT costs less than SCIT, owing to its higher dropout rate. Secondly,

a preventive effect of AIT on incident cases of asthma was assumed, even if it was inconsistently demonstrated.

These assumptions, which are shared by all pharmacoeconomic analyses on this subject, are hardly realistic. Therefore, in scenario analyses, we varied key model parameters in order to mirror alternative plausible real-life situations.

With regard to the first point, that is, AIT treatment persistence, we estimated treatment persistence 26% at 3 years for SCIT and 15% for SLIT.³¹ These estimates are consistent with those reported in other studies.^{49,50} This is not a trivial point. Retrospective studies and RCTs with SLIT and SCIT provided evidence that 3 years of AIT may be associated with long-term clinical benefit. Moreover, AIT courses of less than 3 years' duration may be associated with a greater relapse rate.^{18,23} Actually, current guidelines recommend at least 3 years of treatment for both forms of AIT.^{1,17} If AIT is discontinued before the minimal recommended duration of 3 years, long-term effects are not expected, with consequence on the cumulative QALYs over 10 years.⁵¹

Hence, in the scenario #3, assuming no improvement after premature treatment discontinuation, the incremental costs per QALY gained raised dramatically, in comparison

with the base case (where AIT long-term effect is assumed), from €11 418 to €125 600 with SCIT and from €15 212 to €121 700 with SLIT relative to standard treatment. Thus, in this scenario modeled to reflect a real-life situation, ICERs of both SCIT and SLIT rise far above any plausible cost-effective threshold. Notably, this situation could be even worse in the real-life, owing to possibly poor adherence rates. The average adherence reported in RCTs is greater than 85%.⁵² However, in chronic diseases, including diabetes, hypertension, HIV infection, and asthma, the adherence is estimated 10%-50%.⁵³⁻⁵⁵ Thus, a low adherence rate can be expected for AIT too,⁵⁶ further impacting treatment efficacy, particularly for SLIT (which is self-administered by the patients, without periodic scheduled administration visits).

The other long-term effect of AIT we included in our modeling study is the prevention of incident cases of asthma in patients with allergic rhinitis. One caveat is that the evidence of AIT preventive effect on the occurrence of new cases of asthma is supported only by observational studies and there is a high level of inconsistency among the study results.^{39-41,57} A recent high-quality RCT of 812 children with grass pollen rhino-conjunctivitis treated with SLIT tablets for 3 years failed to demonstrate an effect on the time of onset of asthma compared to placebo after 2 years of follow-up.⁴¹ The absence of AIT preventive effect on asthma development was explored in two specific scenarios (#4; #5), which showed a decrease of cost-effectiveness. These results again highlight that cost-effectiveness is conditioned by assumptions based on uncertain findings, especially if one consider that the AIT preventive effect of asthma development has been shown only in children and adolescent studies.

Despite the results of our study were questionable respect to AIT cost-effectiveness overall, we sought to assess which of the 2 strategies could be the most cost-effective. Scenario analysis results were all favorable to SCIT, except the full societal perspective scenario (only when efficacy was calculated using the fixed-effect model), incorporating indirect nonmedical costs. This scenario aimed at weighing the main difference between SLIT and SCIT, which is the possibility of self-administration only for SLIT, critically reducing time lost for administration visits. This analysis showed that SLIT, although less effective,² is also less expensive than SCIT, resulting slightly more cost-effective than SCIT (scenario #6). However, calculation of indirect costs raises legitimate concerns: Firstly, people outside the labor force, such as students or homemakers, have the same impact as workers in this analysis; secondly, full employment in the labor market is not realistic. As a consequence indirect costs in this scenario are likely overestimated. On the other hand, there are other intangible costs that were not included in this analysis, such as school absence or study impairment or other sources of productivity loss.^{58,59} A recent study of Swedish patients suffering from allergic rhinitis estimated that the mean productivity loss was due not only to absenteeism, but also to presenteeism (lacking performance of present employees), although to a lesser extent.⁶⁰

4.1 | Limitations and strengths

Our study has several limitations. Firstly, the relative efficacy of SCIT and SLIT was never assessed in head-to-head comparisons, but only by indirect comparisons by meta-analysis. This limitation is common to all cost-effectiveness studies, and it is currently not possible to overcome this obstacle.

Second, the accuracy of the efficacy estimates of AIT compared to standard treatment is uncertain.^{2,5,26} Published meta-analyses provide different estimates depending on which studies are included.

For example, in the Verheggen study,⁶ only the studies assessing the efficacy of Oralair® (as representative of SLIT, 4 studies) were compared, by meta-analysis, to a mix of allergoid products (as representative of SCIT, 5 studies). This can be considered a subgroup of the available studies on grass AIT (both SCIT and SLIT). In contrast, we compared the efficacy of both Grazax® and Oralair® (11 studies) to that of all the 11 available studies using SCIT for grass (allergoid and native-conjugated products).^{2,3}

Moreover, given the high degree of the between-study heterogeneity reported in the SCIT meta-analyses, the efficacy estimates varied greatly depending on whether the fixed-effects model or the random-effects model was used to analyze the same studies. The random-effects model should be the most appropriate. Uncertainty in efficacy estimates bears consequences on QALY estimates, as highlighted by the comparison between the base case and scenario #1 and between scenario #6 and scenario #7.

Finally, in this study we did not perform sensitivity and probabilistic analyses to better define uncertainty and provide a probability of cost-effectiveness as a function of willingness to pay (these analyses are ongoing). In that sense, the use of input parameters (costs) specifically related to the Italian perspective must be seen as a mere starting point, that must be further validated by letting all these parameters vary simultaneously according to a set of suitably defined probability distributions, encompassing the variability existing among different Countries and Health Services.

The strength of this analysis resides in the fact that we used data from already published meta-analyses synthesizing multiple data sources to improve precision of pooled estimates and, most importantly, to increase generalizability. The main reason for the differences between the results of ours and other studies is that the other studies did not include all the available studies, but different subgroups of studies, leading to variability in efficacy and QALY estimates.⁶⁻¹⁵

Nonetheless, whatever the best strategy was (SLIT or SCIT), it must be highlighted that the cost-effectiveness estimates of our study and the others are similar in their magnitude. Hence, the same conclusions reached with this study that AIT cost-effectiveness relative to standard treatment is uncertain, applies also to other cost-effectiveness analyses. Our conclusions are in accordance with those of the Meadows study, which estimated SCIT as more cost-effective than SLIT, with both strategies possibly becoming cost-effective at a threshold of £30 000 per QALY at around 6 years from the beginning of treatment.⁵ However, the study underlines that little

evidence exists as to the duration of clinical benefit beyond treatment cessation.⁵

Finally, we used an independent model without any pharmaceutical funding, differently from other studies on this topic, which were either performed in most (if not all) cases by employees of competing manufacturers or funded by them. This inevitably biased the utility estimates and consequently ICERs leading to results always favorable to one or the other form of AIT relative to standard treatment.^{5,42} This is also the conclusion of the Meadows systematic review of the available pharmacoeconomic studies, which underlined that all the studies reporting that both SLIT and SCIT are likely cost-effective at thresholds of £20 000 were funded by a manufacturer of a AIT product.⁵

5 | CONCLUSIONS

This study highlights the need for head-to-head comparative studies estimating the relative efficacy of SCIT and SLIT in order to perform reliable comparative cost-effectiveness evaluations. We made reasonable assumptions about AIT benefits and prices, but our results are not of sufficient strength to conclude that both forms of AIT for grass pollens are cost-effective strategies compared to standard treatment. AIT modest clinical benefit and high rate of treatment discontinuation before the recommended 3 years, which affects long-term post-treatment efficacy, weigh heavily with AIT cost-effectiveness. Nonetheless, SCIT might be the most cost-effective option as it is less affected than SLIT by problems related to adherence and treatment persistence. Patients should be informed about how AIT works and the need for regularity in the administration schedule and completion of the course of treatment. Furthermore, strategies of systematic follow-up promoting adherence should be implemented, as shown,⁶¹ to increase cost-effectiveness.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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COST-EFFECTIVENESS OF GRASS POLLEN ALLERGEN IMMUNOTHERAPY IN ADULTS – **SUPPLEMENTARY MATERIAL**

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All the calculations used for the definition of the transition probability matrices and the relative parameters, as well as for the simulation of the cohort through a Markovian model, have been obtained through R 3.6.0 (R Core Team, 2019). Here below we report only a few fragments of code (and its output) necessary to understand the text: the code in its entirety is available on request from the authors, in the form of an RStudio project (RStudio Team, 2016).

Assumptions and study arms

As in Verheggen et al. (2015), we consider a cohort of patients, whose inclusion criteria are as follows:

- *“suffered from grass pollen rhino-conjunctivitis”.*
- *“positive grass allergen-specific skin prick test and/or elevated serum grass pollen specific IgE”.*
- We will assume that the average age of patients is 35.9 years, in agreement with the meta-analysis of Di Bona et al. (2015). Since the studies included in the meta-analysis in question refer to a period from 1999 to 2014, the probability of death for an individual in the general population can be inferred from the ISTAT mortality tables for general mortality in the year 2010 (considering an individual who was 36 years old in 2010, regardless of gender). We will also assume that the duration of a Markovian cycle is one year, and that, after the beginning of therapy in $t = 0$, the follow-up was 9 years. The beginning of therapy (both immunotherapy – indicated from now on with AIT – and symptomatic therapy) takes place in $t = 0$, and the subsequent periods are numbered as $t = 1, 2, \dots, 9$, for a total of 10 years.
- Similarly, in agreement with Verheggen et al. (2015), we will assume that *“at entry time, none of the patients suffered from co-existing chronic asthma”.*

The possible relationships of the individuals belonging to the cohort with the available treatments are the following (these relationships influence the graphic structure of the transition probabilities between the states of the Markovian model):

- **SYMPTOMATIC:** purely symptomatic treatment, that is antihistamine (desloratadine 5mg/die) + nasal corticosteroid (Budesonide nasal spray 200 mcg/die; two 50 mcg puffs twice a day). Symptomatic treatment lasts from the beginning of the simulation in $t=0$, during the pollen season, and is continued for the entire duration of the follow-up. As in Verheggen et al. (2015), asthmatic disease can complicate rhino-conjunctivitis even in $t = 0$.
- **SCIT** (subcutaneous immunotherapy): the therapy is administered for a maximum of three years, superimposed to symptomatic therapy. After a maximum of three Markov cycles (i.e. $t = 0,1,2$), immunotherapy is stopped, and patients continue with symptomatic therapy alone. The discontinuation of immunological therapy can occur since the first Markovian cycle in $t=0$: also in this case, patients continue with symptomatic therapy until the end of follow-up. None of the patients enter the cohort with coexisting asthmatic disease.
- **SLIT** (sublingual immunotherapy): the same assumptions stated for SCIT apply here.

Transition probabilities

We detail, for each of the three arms of the study, the graphic structure of the transition matrices and the calculation of the relative transition probabilities.

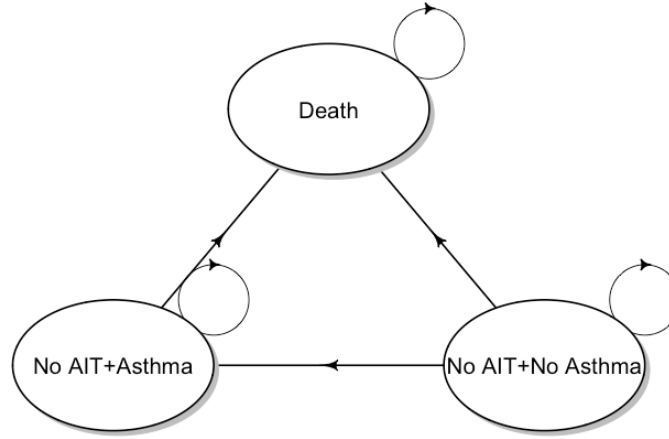
SYMPTOMATIC

SYMPTOMATIC arm is structurally the simplest. In this branch we have three possible states (their meaning is obvious, since no patient of the cohort included in this arm is given any form of immunotherapy):

- NO AIT + NO Asthma
- NO AIT + Asthma
- Death

The Markov chain modelling the temporal evolution of this arm is a homogeneous Markov chain (time-invariant), having the following transition diagram (valid for the whole time horizon considered for the simulation):

Standard pharmacotherapy alone (no AIT)



The following transition probabilities:

$$\Pr(\text{Death} \mid \text{No AIT} + \text{NO Asthma}) = \Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{Death})$$

$$\Pr(\text{Death} \mid \text{No AIT} + \text{Asthma}) = \Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{Death})$$

will differ from each other, because the latter should reflect the specific mortality due to asthma (slightly higher than the mortality for all causes in the general population). Moreover, since the hypothesis is that none of the patients is asthmatic at entry time, the initial distribution on the states is as follows:

$$\Pr(\text{No AIT} + \text{NO Asthma}) = 1, \Pr(\text{No AIT} + \text{Asthma}) = 0, \Pr(\text{Death}) = 0$$

For the calculation of $\Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{No AIT} + \text{Asthma})$ we will use the data reported by Shaaban et al. (2008), in particular (pag. 1052): “The probability of having asthma at the end of follow-up (mean 8.8 years) was 4,0% in patients with allergic rhinitis”. For this subpopulation of $N = 6461$ patients at risk of onset of asthma, we have: $N = 1217$, mean age = 33.4 years. The duration of the follow-up is comparable with that assumed for our simulation. Since this is an incidence probability referring to a period of 8.8 years, and assuming that events occur at a constant rate during a single Markovian cycle (lasting one year), we can transform this probability spanning a time horizon of 8.8 years in a incidence probability referring to a time horizon of one year through the two following step:

- I. conversion of the probability over a horizon of 8.8 years to an annual incidence rate (in the expression below $\rightarrow prAsthma = 0.040, t = 8.8$):

$$rate = - \frac{\log(1 - prAsthma)}{t}$$

II. conversion of the annual incidence rate to an annual incidence probability as follows:

$$prAsthma1yr = 1 - \exp(-rate \times 1)$$

We show the calculations, which lead to results perfectly comparable to those of Verheggen et al. (2015):

```
> prAsthma <- 0.040
> rate <- -((log(1-prAsthma))/8.8)
> rate
[1] 0.004638863
> prAsthma1yr <- 1 - exp(-rate)
> prAsthma1yr
[1] 0.00462812
> round_preserve_sum(prAsthma1yr, 5)
[1] 0.00463
```

The probability of death within 1 year for all causes in the absence of asthma can be derived from the ISTAT mortality tables for general mortality. The reference on which to calibrate the data is the meta-analysis by Di Bona et al. (2015), which is used extensively throughout the paper, where the average age of the patients was 35.9 years. Considering that the studies included in the above-mentioned meta-analysis were published from 1999 to 2014 (for a total of 16 years), we considered the probability of death in the year 2010 that, regardless of gender, assumed the following value (source: ISTAT, 2019):

```
> prDeath <- 0.61492/1000
> prDeath
[1] 0.00061492
> round_preserve_sum(prDeath, 5)
[1] 0.00061
```

For the probability of death within 1 year for asthmatic patients we can use Table 3 reported in the study by Huovinen et al. (1997), according to which the age-adjusted relative risk (asthmatic patients vs. non-asthmatic patients) of death for all causes is equal to 1.49. Therefore the probability of death (within one year) for all causes in an asthmatic patient is equal to:

```
> RRDeathAsthma <- 1.49
> prDeathAsthma <- RRDeathAsthma * prDeath
> prDeathAsthma
[1] 0.0009162308
> round_preserve_sum(prDeathAsthma, 5)
[1] 0.00092
```

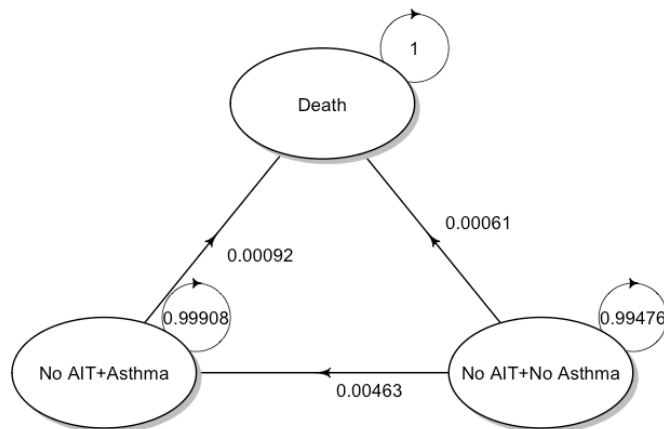
Obviously, this probability is slightly higher than that of a non-asthmatic patient (9.2 against 6.1 deaths per 100,000 person years).

Below, we show the transition probability matrix for the SYMPTOMATIC arm:

```
> round_preserve_sum(sympt@transitionMatrix, 5)
      No AIT+No Asthma No AIT+Asthma Death
No AIT+No Asthma      0.99476      0.00463 0.00061
No AIT+Asthma         0.00000      0.99908 0.00092
Death                 0.00000      0.00000 1.00000
```

and the structure graph of the transitions, with the transition probabilities superimposed:

Standard pharmacotherapy alone (no AIT)



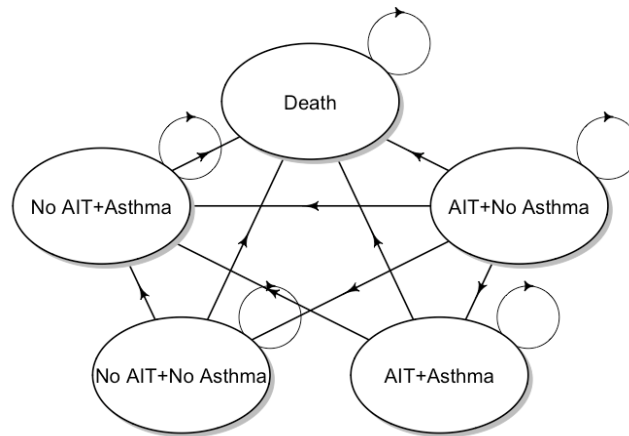
AIT (SCIT/SLIT)

The SCIT and SLIT arms are modelled through a non-homogeneous Markov chain (one for each of the two SCIT and SLIT arms). For convenience we will refer generically to this chain as AIT (of course, the transition probabilities will vary between the two SCIT/SLIT arms). There are five possible states:

- NO AIT + NO Asthma
- AIT + NO Asthma
- NO AIT + Asthma
- AIT + Asthma
- Death

Up to $t = 2$ (i.e. for transitions $t = 0 \rightarrow t = 1$ and $t = 1 \rightarrow t = 2$) the structure of the state transition diagram is shown below:

AIT ($t = 0 \rightarrow t = 1, t = 1 \rightarrow t = 2$)

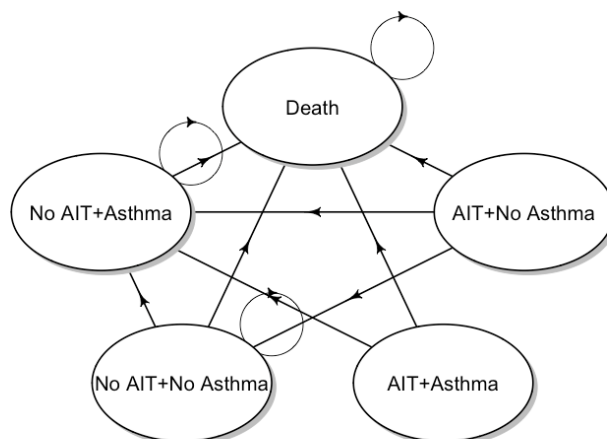


Up to $t = 2$ (i.e. when the transitions between states are governed by the diagram above) the following transitions:

- $\text{AIT} + \text{No Asthma} \rightarrow \text{No AIT} + \text{No Asthma}$
- $\text{AIT} + \text{Asthma} \rightarrow \text{No AIT} + \text{Asthma}$

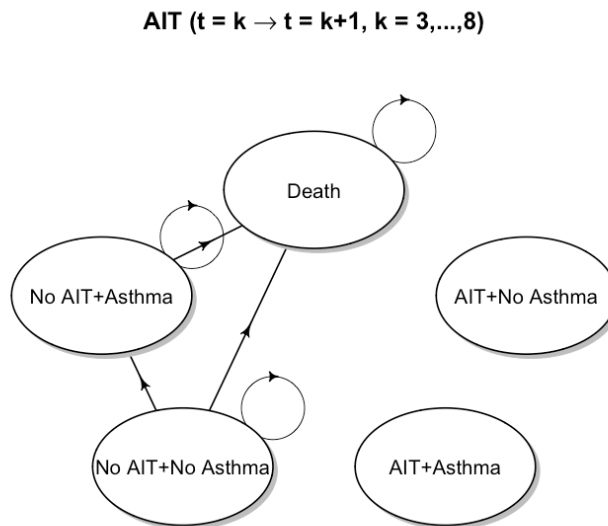
correspond to the discontinuation of therapy. As we said before, at the end of the third cycle (year) all patients have finished immunotherapy. Therefore, the probabilities of transition from $t = 2$ to $t = 3$ must take into account the fact that the probability of remaining in the AIT state must be forced to zero (immunotherapy ends). Therefore, the diagram of state transitions changes as follows:

AIT ($t = 2 \rightarrow t = 3$)



For subsequent transitions, the two states $\text{AIT} + \text{No Asthma}$ and $\text{AIT} + \text{Asthma}$ are no longer reachable and become isolated: the underlying Markov chain becomes observationally equivalent to that used for the SYMPTOMATIC arm. Of course in $t = 3$ we have a probability distribution of

states that is not equal to the initial distribution that we set for the SYMPTOMATIC arm, but that reflects the distribution between asthmatic and non-asthmatic patients that has been reached through the state transitions that occurred in previous cycles.



SCIT

We show how the calculations of the transition probabilities for the SCIT arm were carried out. For the calculation of the discontinuation probabilities we use the results reported in Egert-Schmidt et al. (2014), Tables 2 and 3:

For the calculation of the probability of discontinuation we use the following parameters:

- Pollen, preseasonal
- age ≥ 18 years (adults)
- N = 38576

Therefore, we have:

```

> # patients who have completed one year of therapy (t = 0)
> round_preserve_sum(38576 - (0 * 38576))
[1] 38576
> # patients who have completed two years of therapy (t = 1)
> round_preserve_sum (38576 - (0.53 * 38576))
[1] 18131
> # number of patients who completed the first year of therapy but discontinued
during the second year
> 38576 - 18131
[1] 20445
> # probability of discontinuation during the second year of therapy (in t = 1)
> round_preserve_sum(20445/38576, 2)
[1] 0.53 # ← probability of discontinuation

> # patients who completed three years of therapy (t = 2)
> round_preserve_sum(38576 - (0.74 * 38576))

```

```
[1] 10030
> # number of patients who completed the second year of therapy but discontinued
during the third year
> 18131 - 10030
[1] 8101
> # probability of discontinuation during the third year of therapy (in t = 2)
> round_preserve_sum(8101/18131, 2)
[1] 0.45 # ← probability of discontinuation
```

According to these data, the probability of discontinuation during the first year (in $t = 0$) is zero, i.e. the adherence to SCIT is maximum during the first year of therapy.

We will now discuss each transition probability (row by row):

→ 1st row

$\Pr(AIT + No\ Asthma \rightarrow AIT + Asthma)$: indicates the likelihood of developing asthma in the next cycle for patients receiving SCIT immunotherapy. For the calculation of this probability we used a set of parameters already used in the work of Verheggen et al (2015), and in particular the probability of developing asthma at 1 year according to the data of Shaaban et al. (2008) → 0.0046 (see the calculations we have presented before), and the relative risk (AIT versus symptomatic treatment) of developing asthma → $RR = 0.505$, according to Novembre et al. (2004) and Möller et al. (2002). Therefore, this transition probability can be estimated as:

```
> round_preserve_sum(0.505 * prAsthma1yr, 5)
[1] 0.00234
```

$\Pr(AIT + No\ Asthma \rightarrow No\ AIT + No\ Asthma)$: in this case we have a discontinuation at the next cycle and therefore, considering the transition from $t = 0$ to $t = 1$, this probability coincides with the probability of discontinuation during the second year that we have calculated before (→ 0.53), while in the transition from $t = 1$ to $t = 2$ it coincides with the probability of discontinuation during the third year (→ 0.45).

$\Pr(AIT + No\ Asthma \rightarrow No\ AIT + Asthma)$: in this case, we have as much a discontinuation during the next cycle as the onset of asthma. Although the two events have a clear relationship, since the interruption of immunotherapy can promote the development of asthma, in the absence of data the easiest thing to do is to consider them as independent events. Therefore, this transition probability can be calculated as follows:

$$\begin{aligned}
P(AIT + No Asthma \rightarrow No AIT + Asthma) &= \Pr(No AIT + Asthma \mid AIT + No Asthma) \\
&\approx \Pr(asthma \text{ onset within 1 yr during the next cycle}) \\
&\times \Pr(discontinuation \text{ during the next cycle})
\end{aligned}$$

Therefore, for state transitions occurring from $t = 0$ to $t = 1$ (bearing in mind that the 1-year probability of developing asthma that we must consider is that valid for patients who have undergone immunotherapy in previous cycles) we have:

```
round_preserve_sum(prAsthma1yr * 0.505 * 0.53, 5)
[1] 0.00124
```

while for the state transitions from $t = 1$ to $t = 2$ we have:

```
round_preserve_sum(prAsthma1yr * 0.505 * 0.45, 5)
[1] 0.00105
```

For the next cycle this probability is simply obtained as the 1-year probability of developing asthma for subjects who have undergone immunotherapy (since the probability of discontinuation becomes 1), that is:

```
round_preserve_sum(prAsthma1yr * 0.505, 5)
[1] 0.00234
```

For transitions from $t = 3$ onwards this probability of transition is zero, since immunotherapy is no more administered to any patient.

$\Pr(AIT + No Asthma \rightarrow AIT + No Asthma)$: the patient remains in the same state in the next cycle. Obviously this probability is calculated as a complement to unity (since the rows of a transition probability matrix must sum to 1) of the remaining four probabilities, and therefore from $t = 0$ to $t = 1$ we have:

```
rest1SCIT_2ndyear <-
+   RRAitAsthma * prAsthma1yr + prStopSCIT_2ndyr +
+   prStopSCIT_2ndyr * (RRAitAsthma * prAsthma1yr) + prDeath
+   round_preserve_sum(1 - rest1SCIT_2ndyear, 5)
[1] 0.46581
```

while from $t = 1$ to $t = 2$ we have:

```
rest1SCIT_3rdyear <-
+   RRAitAsthma * prAsthma1yr + prStopSCIT_3rdyr +
+   prStopSCIT_3rdyr * (RRAitAsthma * prAsthma1yr) + prDeath
+   round_preserve_sum(1 - rest1SCIT_3rdyear, 5)
[1] 0.546
```

As we know, for subsequent cycles the probability of remaining in a state in which immunotherapy is administered is 0, since all patients end their immunotherapy.

$\Pr(AIT + No\ Asthma \rightarrow Death)$: here we can use 1-year the probability of death valid for non-asthmatic individuals of ($\rightarrow 0.00061$).

→ 2nd row

$\Pr(AIT + Asthma \rightarrow AIT + No\ Asthma) = 0$, since we assume that the onset of asthma is an irreversible condition. This probability is zero in all cycles, and a fortiori it is zero when the immunotherapy is terminated.

$\Pr(AIT + Asthma \rightarrow No\ AIT + No\ Asthma) = 0$, for the same reason as above (it is irrelevant that a discontinuation also occurred).

$\Pr(AIT + Asthma \rightarrow No\ AIT + Asthma)$: in this case we have a discontinuation, and therefore we will use the discontinuation probabilities that we have calculated before. Obviously, when the immunotherapy ends, this probability will be calculated taking into account that all patients stop assuming the immunotherapy (and therefore all patients will be pushed into the “No AIT” state, except those who have died). Therefore, in the following cycles this probability is null, since no patient can come from a state in which immunotherapy was administered.

$\Pr(AIT + Asthma \rightarrow Death)$: in this case we can use the 1-year probability of death for an asthmatic patient ($\rightarrow 0.00092$).

$\Pr(AIT + Asthma \rightarrow AIT + Asthma)$: also this probability of remaining in the same state is calculated by difference, taking into account that the 2nd row must sum 1 (and also taking into account the fact that when the immunotherapy is terminated this probability becomes zero).

→ 3rd row

$\Pr(No\ AIT + No\ Asthma \rightarrow AIT + No\ Asthma) = 0$ for all cycles, as no patient of the cohort who does not assume the immunotherapy in $t = 0$ start assuming it in $t = 1$, as well as no patient who has suspended the immunotherapy in $t = 1$ then resumes it in $t = 2$. In addition, no patient who has completed three years of immunotherapy resumes it later.

$\Pr(No\ AIT + No\ Asthma \rightarrow AIT + Asthma) = 0$ for the same reason as above.

$\Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{No AIT} + \text{Asthma})$, is the 1-year probability of developing asthma. Up to $t = 2$ (that is for transitions from $t = 0$ to $t = 1$, or from $t = 1$ to $t = 2$), a patient reaches a “No AIT” state because she/he has suspended immunotherapy. Starting from $t = 3$, after the transition from $t = 2$ to $t = 3$, the patient who has not prematurely interrupted the treatment has completed a full immunotherapy cycle in $t = 2$, and with probability 1 she/he moves towards any state where the label “No AIT” is present. Therefore, for the transition probability matrices from $t = 0$ to $t = 1$ and from $t = 1$ to $t = 2$, this probability only concerns patients who have not completed an immunotherapy cycle, and therefore we can set it equal to 0.00463 (assuming that if immunotherapy is not administered for at least three years, it does not have a protective effect on asthma, and therefore this probability coincides with the 1-year probability of asthma for individuals not undergoing immunotherapy). On the other hand, for the transition probability matrix from $t = 2$ to $t = 3$, we must take into account that the “no AIT” state will be reached by patients who have completed a full cycle of immunotherapy (three years) as well as by those who had already interrupted AIT before. Based on the data reported in Egert-Schmidt et al. (2014), Table 3, those who carry out SCIT for at least three years are 26% of the individuals in the sample (pollen, preseasonal), and therefore this probability of transition can be estimated as:

```
> round_preserve_sum(0.74 * prAsthma1yr + 0.26 * (0.505 * prAsthma1yr), 5)
[1] 0.00403
```

taking into account the non-adherence to therapy for the calculation of the probability of onset of asthma during the next cycle.

$\Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{Death})$: this probability is equal to the 1-year probability of death in the general population ($\rightarrow 0.00061$).

$\Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{No AIT} + \text{No Asthma})$: as in the other cases, the probability of remaining in the same state in the next cycle is calculated as the complement to unity of the other probabilities of this row.

→ 4th row

Obviously, for the first three probabilities of this row we have:

$$\Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{AIT} + \text{No Asthma}) = 0$$

$$\Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{AIT} + \text{Asthma}) = 0$$

$$\Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{No AIT} + \text{No Asthma}) = 0$$

The first and third are zero because the asthma condition is not reversible, while the second is zero because no patient who has suspended or completed the immunotherapy resumes it afterwards.

$\Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{Death})$, this probability is equal to the 1-year probability of death in an asthmatic patient ($\rightarrow 0.00092$).

$\Pr(\text{No AIT} + \text{Asthma} \rightarrow \text{No AIT} + \text{Asthma})$, as usual this probability is obtained by taking the complement to unity of the other probabilities in this row.

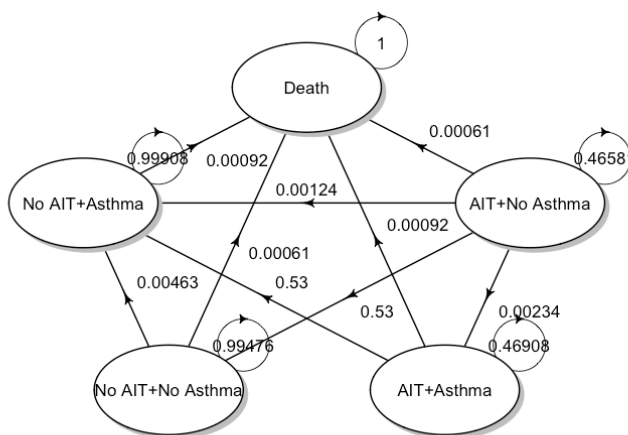
→ 5th row

Death is an absorbing state, to which corresponds the only non-zero probability of this row.

At this point we report the diagram of the transition probability matrices with transition probabilities superimposed, plus the corresponding transition probability matrix:

→ from $t = 0$ to $t = 1$

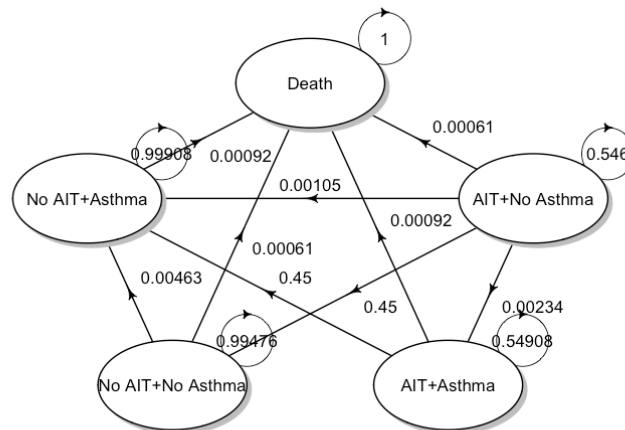
SCIT (t=0 -> t=1)



```
> round_preserve_sum(SCITt0_t1@transitionMatrix, 5)
      AIT+No Asthma AIT+Asthma No AIT+No Asthma No AIT+Asthma Death
AIT+No Asthma      0.46581      0.00234      0.53000      0.00124 0.00061
AIT+Asthma         0.00000      0.46908      0.00000      0.53000 0.00092
No AIT+No Asthma   0.00000      0.00000      0.99476      0.00463 0.00061
No AIT+Asthma      0.00000      0.00000      0.00000      0.99908 0.00092
Death              0.00000      0.00000      0.00000      0.00000 1.00000
```

→ from t = 1 to t = 2

SCIT (t=1 -> t=2)

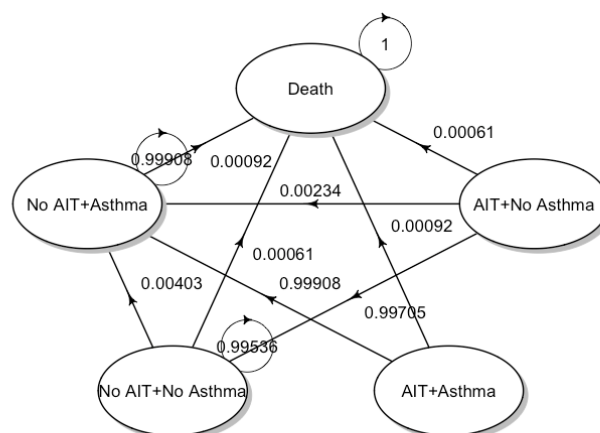


```
> round_preserve_sum(SCITt1_t2@transitionMatrix, 5)
```

	AIT+No Asthma	AIT+Asthma	No AIT+No Asthma	No AIT+Asthma	Death
AIT+No Asthma	0.546	0.00234	0.45000	0.00105	0.00061
AIT+Asthma	0.000	0.54908	0.00000	0.45000	0.00092
No AIT+No Asthma	0.000	0.00000	0.99476	0.00463	0.00061
No AIT+Asthma	0.000	0.00000	0.00000	0.99908	0.00092
Death	0.000	0.00000	0.00000	0.00000	1.00000

→ from t = 2 to t = 3

SCIT (t=2 -> t=3)



→ from $t = k$ to $t = k + 1$, for $k = 3, 4, \dots, 8$

Figure 1 is a directed acyclic graph (DAG) illustrating the causal relationships between AIT, Asthma, and Death. The nodes represent different states: 'No AIT+Asthma', 'AIT+No Asthma', 'No AIT+No Asthma', 'AIT+Asthma', and 'Death'. The edges represent causal effects with associated probabilities: 0.99998, 0.00092, 0.00403, 0.00061, and 0.99536. Each node has a self-loop with a probability of 1.

The main input parameters used for this arm are as follows

14

SLIT

For the SLIT arm, the methods for calculating the transition probabilities are identical to those already seen for the SCIT arm. Obviously, some input parameters change, and in particular the discontinuation rates that reflect the adherence to therapy. The initial parameters to be used with SLIT for the calculation of these probabilities are:

- age ≥ 18 years (adulti)
- N = 570

As we did with SCIT, we obtained:

```
> # patients who have completed one year of therapy (t = 0)
> round(570 - (0.48 * 570))
[1] 296
> # patients who have completed two years of therapy (t = 1)
> round(570 - (0.75 * 570))
[1] 142
> # number of patients who completed the first year of therapy but discontinued
during the second year
> 296 - 142
[1] 154
> # probability of discontinuation during the second year of therapy (in t = 1)
> round(145/296, 2)
[1] 0.49 <- probability of discontinuation

> # patients who have completed two years of therapy (t = 1)
> round(570 - (0.75 * 570))
[1] 142
> # patients who have completed three years of therapy (t = 2)
> round(570 - (0.85 * 570))
[1] 86
> # number of patients who completed the second year of therapy but discontinued
during the third year
> 142 - 86
[1] 56
> # probability of discontinuation during the third year of therapy (in t = 2)
> round(56/142, 2)
[1] 0.39 <- probability of discontinuation
```

Based on Table 3 of Egert-Schmidt et al (2014), in the first year we have a probability of discontinuation ($t = 0$) of 0.52. In other words, the initial probability distribution in $t = 0$ for the SLIT arm will have to take into account that only 52% are in the “AIT + No Asthma” state, while the remaining 48% will be in the “No AIT + No Asthma” state (because these patients started the therapy but discontinued within the first year). This, of course, influences the cost calculation for the first Markovian cycle. The lower adherence of SLIT with respect to SCIT is confirmed in the literature; see, for example, Incorvaia, et al. (2016); Kiel et al. (2013); Sieberet al. (2011).

As we did for the SCIT arm, keeping in mind that only 15% end a complete cycle for SLIT immunotherapy, we have that $\Pr(\text{No AIT} + \text{No Asthma} \rightarrow \text{No AIT} + \text{Asthma})$ from $t = 2$ to $t = 3$ (and afterwards) is calculated as:

```
> round_preserve_sum(0.85 * prAsthmalyr + 0.15 * (0.505 * prAsthmalyr), 5)
[1] 0.00428
```

We report only the transition probability matrices (the diagrams are identical to those already showed for the SCIT arm):

→ from $t = 0$ to $t = 1$

```
> round_preserve_sum(SLITt0_t1@transitionMatrix, 5)
      AIT+No Asthma AIT+Asthma No AIT+No Asthma No AIT+Asthma Death
AIT+No Asthma      0.5059    0.00234      0.49000    0.00115 0.00061
AIT+Asthma         0.0000    0.50908      0.00000    0.49000 0.00092
No AIT+No Asthma   0.0000    0.00000      0.99476    0.00463 0.00061
No AIT+Asthma      0.0000    0.00000      0.00000    0.99908 0.00092
Death              0.0000    0.00000      0.00000    0.00000 1.00000
```

→ from $t = 1$ to $t = 2$

```
> round_preserve_sum(SLITt1_t2@transitionMatrix, 5)
      AIT+No Asthma AIT+Asthma No AIT+No Asthma No AIT+Asthma Death
AIT+No Asthma      0.60614    0.00234      0.39000    0.00091 0.00061
AIT+Asthma         0.00000    0.60908      0.00000    0.39000 0.00092
No AIT+No Asthma   0.00000    0.00000      0.99476    0.00463 0.00061
No AIT+Asthma      0.00000    0.00000      0.00000    0.99908 0.00092
Death              0.00000    0.00000      0.00000    0.00000 1.00000
```

→ from $t = 2$ to $t = 3$

```
> round_preserve_sum(SLITt2_t3@transitionMatrix, 5)
      AIT+No Asthma AIT+Asthma No AIT+No Asthma No AIT+Asthma Death
AIT+No Asthma      0      0      0.99705    0.00234 0.00061
AIT+Asthma         0      0      0.00000    0.99908 0.00092
No AIT+No Asthma   0      0      0.99511    0.00428 0.00061
No AIT+Asthma      0      0      0.00000    0.99908 0.00092
Death              0      0      0.00000    0.00000 1.00000
```

→ from $t = k$ to $t = k + 1$ for $k = 3, 4, \dots, 8$

```
> round_preserve_sum(SLIT_geq3@transitionMatrix, 5)
      AIT+No Asthma AIT+Asthma No AIT+No Asthma No AIT+Asthma Death
AIT+No Asthma      1      0      0.00000    0.00000 0.00000
AIT+Asthma         0      1      0.00000    0.00000 0.00000
No AIT+No Asthma   0      0      0.99511    0.00428 0.00061
No AIT+Asthma      0      0      0.00000    0.99908 0.00092
Death              0      0      0.00000    0.00000 1.00000
```

The main input parameters for the SLIT arm are:

```
> prAsthmalyr
[1] 0.00462812 # approx. to 0.00463
> prDeath
[1] 0.00061492 # approx. to 0.00061
> RRDeathAsthma
[1] 1.49
> RRAitAsthma
[1] 0.505
> prDeathAsthma <- RRDeathAsthma * prDeath
> prDeathAsthma
[1] 0.0009162308 # approx. to 0.00092
> prStopSLIT_1styr
```

```
[1] 0.52
> prStopSCIT_2ndyr
[1] 0.49
> prStopSCIT_3rdyr
[1] 0.39
```

Mapping RTSS onto utility scores

The severity of allergic rhinoconjunctivitis is based on the RTSS (Rhinoconjunctivitis Total Symptom Score; EMA, European Medicines Agency, 2008), based on patient reported outcomes. RTSS takes into account the six symptoms most commonly associated with pollinosis (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes). The self-attributed score to each symptom varies from 0 to 3, namely: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The total of the scores attributed to these six symptoms results in a daily RTSS that can vary from 0 to 18. The final Rhinoconjunctivitis Total symptom score was calculated as the mean of the total daily scores recorded throughout the whole pollen season.

The utilities associated with seasonal allergic rhinoconjunctivitis have been estimated in Revichi et al. (1998), who developed a multiattribute utility index for symptoms of this disease, called RSUI (Rhinitis Symptom Utility Index). This index has been constructed based on the interplay between the two standard approaches existing to assign an utility score to an health state, i.e. the VAS (Visual Analog Scale) and SG (Standard Gamble) methods (Gray et al., 2010; Torrance, 1986). The symptoms considered differ slightly from those used for the construction of the RTSS, and the resulting utility scores (based on the degree of severity of the symptom) are the following:

```
> revichi
```

	stuffy_nose	runny_nose	itchy_eyes	itchy_throat	sneezing
1 None	1.00	1.00	1.00	1.00	1.00
2 Mild 1-3	0.99	0.98	0.96	0.97	0.98
3 Mild 4-7	0.97	0.96	0.94	0.95	0.96
4 Mild 8-14	0.95	0.94	0.91	0.93	0.94
5 Moderate 1-3	0.96	0.95	0.82	0.94	0.94
6 Moderate 4-7	0.93	0.92	0.89	0.91	0.92
7 Moderate 8-14	0.89	0.88	0.85	0.88	0.88
8 Severe 1-3	0.88	0.86	0.81	0.85	0.86
9 Severe 4-7	0.82	0.80	0.75	0.80	0.82
10 Severe 8-14	0.75	0.73	0.68	0.73	0.73

Mapping of RTSS scores to utilities was partly based on the same procedure used by Verheggen et al. (2015), as communicated by one of the authors (K.Y. Westerhout, personal communication, 2016-03-10). The algorithm consists of the following steps:

1. Firstly, in order to create correspondence between the symptoms used in the table of estimated utilities by Revichi et al. (1998) and the RTSS index, the values relating to the symptom “itchy eyes” were duplicated in “watery eyes”. We used the following vocabulary:

- a. stuffy nose → nasal congestion
- b. runny nose → rhinorrhea
- c. sneezing → sneezing
- d. itchy throat → nasal pruritus
- e. watery eyes → watery eyes
- f. itchy eyes → ocular pruritus

2. Secondly, we calculated the average of each symptom for each level of severity, taking the average with respect to symptom durations, and obtaining:

```
> avg_revichi
      None avg. Mild avg. Moderate avg. Severe avg.
stuffy_nose      1      0.970      0.927      0.817
runny_nose       1      0.960      0.917      0.797
sneezing         1      0.960      0.913      0.803
itchy_throat     1      0.950      0.910      0.793
itchy_eyes       1      0.937      0.853      0.747
watery_eyes      1      0.937      0.853      0.747
```

3. Finally, we calculated the empirical distribution of symptom severity for each possible value of RTSS. For example, to obtain this distribution in the case of RTSS = 0, we enumerated all possible combinations of symptom severity levels that can result in that RTSS value, obtaining the following table (0 = none, 1 = mild, 2 = moderate, 3 = severe):

RTSS	Stuffy	Runny	Sneezing	Itchy throat	Itchy eyes	Watery eyes
0	0	0	0	0	0	0

Therefore, out of six possible cases, all of these are favourable to 0 = none, while we have no cases favourable to other severity levels, and therefore we obtain the following probability distribution on symptom severity for RTSS = 0:

	None	Mild	Moderate	Severe
Count	6	0	0	0
Probability	1.0000	0.0000	0.0000	0.0000

We can also say that in a patient chosen at random among those for whom RTSS = 0, we have a 100% probability that a symptom chosen at random presents severity level 0 = none.

In the same way, when $RTSS = 1$ we have 36 possible cases arranged in the following table:

RTSS	Stuffy	Runny	Sneezing	Itchy throat	Itchy eyes	Watery eyes
1	1	0	0	0	0	0
	0	1	0	0	0	0
	0	0	1	0	0	0
	0	0	0	1	0	0
	0	0	0	0	1	0
	0	0	0	0	0	1

Therefore, out of 36 possible cases, 6 are favourable to 0 = none while 30 are favourable to 1 = mild, while we have no possibility that any symptom has a severity level of 2 = moderate or 3 = severe (because, if so, it would not be possible that $RTSS = 1$). We have the following probability distribution:

	None	Mild	Moderate	Severe
Count	30	6	0	0
Probability	0.8333	0.1667	0.0000	0.0000

We can also say that in a patient chosen at random among those for whom $RTSS = 1$, there is a probability of 83% that a symptom occurs with a severity level of 0 = none, and a probability of 17% that it occurs with a severity level of 1 = mild.

By repeating the same calculation on all possible levels of $RTSS$, we obtain the following ensemble of probability distributions:

```
> rtssFrequency
      None    Mild Moderate Severe
RTSS=0 1.0000 0.0000  0.0000 0.0000
RTSS=1 0.8333 0.1667  0.0000 0.0000
RTSS=2 0.7143 0.2381  0.0476 0.0000
RTSS=3 0.6250 0.2679  0.0893 0.0179
RTSS=4 0.5417 0.2917  0.1250 0.0417
RTSS=5 0.4676 0.3009  0.1620 0.0694
RTSS=6 0.4018 0.3006  0.1935 0.1042
RTSS=7 0.3399 0.2961  0.2215 0.1425
RTSS=8 0.2839 0.2839  0.2473 0.1850
RTSS=9 0.2328 0.2672  0.2672 0.2328
RTSS=10 0.1850 0.2473  0.2839 0.2839
RTSS=11 0.1425 0.2215  0.2961 0.3399
RTSS=12 0.1042 0.1935  0.3006 0.4018
RTSS=13 0.0694 0.1620  0.3009 0.4676
RTSS=14 0.0417 0.1250  0.2917 0.5417
RTSS=15 0.0179 0.0893  0.2679 0.6250
RTSS=16 0.0000 0.0476  0.2381 0.7143
RTSS=17 0.0000 0.0000  0.1667 0.8333
RTSS=18 0.0000 0.0000  0.0000 1.0000
```

We are now ready to map each RTSS into a utility score by taking, for each symptom, the weighted mean of the utility scores in `avg_revichi`, weighted by the corresponding probability distribution on symptom severity. For example, for $RTSS = 2$ we get:

$$\bar{s}_1 = 1.000 \times 0.7143 + 0.970 \times 0.2381 + 0.927 \times 0.0476 + 0.817 \times 0.000 = 0.9894$$

$$\bar{s}_2 = 1.000 \times 0.7143 + 0.960 \times 0.2381 + 0.917 \times 0.0476 + 0.797 \times 0.000 = 0.9865$$

$$\bar{s}_3 = 1.000 \times 0.7143 + 0.960 \times 0.2381 + 0.913 \times 0.0476 + 0.803 \times 0.000 = 0.9863$$

$$\bar{s}_4 = 1.000 \times 0.7143 + 0.950 \times 0.2381 + 0.910 \times 0.0476 + 0.793 \times 0.000 = 0.9838$$

$$\bar{s}_5 = 1.000 \times 0.7143 + 0.937 \times 0.2381 + 0.853 \times 0.0476 + 0.747 \times 0.000 = 0.9780$$

$$\bar{s}_6 = 1.000 \times 0.7143 + 0.937 \times 0.2381 + 0.853 \times 0.0476 + 0.747 \times 0.000 = 0.9780$$

The final utility value was obtained using the following formula, as proposed by Revichi et al. (1998):

$$u_i = 1.198(\bar{s}_1 \times \bar{s}_2 \times \bar{s}_3 \times \bar{s}_4 \times \bar{s}_5 \times \bar{s}_6) - 0.198$$

The coefficients of this expression were originally obtained by Revichi et al. (1998), are based on a multi-attribute multiplicative function that take as input the utility values assigned to each symptom present in the Revichi table. Note that u_i can range from a maximum value of 1, when no symptoms are present, up to a minimum value of 0 in the worst possible case. On the ground of this expression, we get the following utility scores for each possible RTSS score (from 0 to 18):

```
> RSUI
      util
RTSS=0  1.0000
RTSS=1  0.9440
RTSS=2  0.8873
RTSS=3  0.8255
RTSS=4  0.7640
RTSS=5  0.7027
RTSS=6  0.6442
RTSS=7  0.5864
RTSS=8  0.5314
RTSS=9  0.4773
RTSS=10 0.4265
RTSS=11 0.3769
RTSS=12 0.3301
RTSS=13 0.2846
RTSS=14 0.2421
RTSS=15 0.2006
RTSS=16 0.1612
RTSS=17 0.1210
RTSS=18 0.0792
```

Unlike the procedure we have described so far, which therefore coincides with that used in Verheggen et al. (2015), we have introduced some variations that take into account the fact that the RTSS score used in pharmacoeconomic studies is almost never an integer number. In fact, RTSS often estimated from meta-analyses that provide an average value calculated over selected populations. Therefore, the first operation that is usually carried out is to round the average RTSS

score to the nearest integer. This rounding operation can introduce substantial bias. To better justify this observation, we note that Devillier et al. (2014) estimate that the Minimally Important Difference (MID, i.e. the smallest difference in the RTSS score that corresponds to a clinical improvement actually perceived by the patient) is equal to a reduction of about 1.1 - 1.3 of the RTSS of patients suffering from allergic rhino-conjunctivitis (this value can be safely rounded to 1, according to Devillier et al., 2014). For example, let us assume that we have found a mean score $RTSS = 4.51$ in the treatment group, rounded to $RTSS = 5$, and a mean score $RTSS = 4.49$ in the control group, rounded to $RTSS = 4$. In this way, we have introduced a fictitious clinical improvement between the control and the treatment group, corresponding to a fictitious improvement in the utilities associated with the two states, equal to approximately 8.00% (in the sense that the utility of treated patients would be 0.7640, while that of untreated patients would be 0.7027). To avoid biases of such kind, we have considered an interpolation procedure capable of mapping RTSS scores one-on-one and onto utilities even for non-integer values of the RTSS score. The procedure we have introduced consists of the following steps:

1. For each degree of symptom severity ($SSev \rightarrow 0 = \text{none}, 1 = \text{mild}, 2 = \text{moderate}, 3 = \text{severe}$), we overfitted the relationship between $X = RTSS$ and $Y = p_{SSev}$, where p_{SSev} is the probability of occurrence shown in the `rtssFrequency` table (pag. 20), using the following polynomial regression model:

$$p_{SSev} = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p + noise$$

Choosing $p = 9$ we are able to control the overall root mean square (RMS) prediction error to a level of less than 10^{-3} . In this way, the probabilities estimated by the model in correspondence of an integer RTSS score are indistinguishable from the respective empirical probabilities reported in `rtssFrequency` table. This polynomial regression model, of course, can be used to interpolate probabilities at any non-integer RTSS value as follows:

$$\hat{p}_{SSev} = \hat{\beta}_0 + \hat{\beta}_1 \times RTSS + \dots + \hat{\beta}_p RTSS^p$$

2. Since the probabilities on the four severity levels must sum 1, the probabilities relative to 0 = none, 1 = mild and 2 = moderate are obtained by interpolation, while the probabilities relative to 3 = severe are calculated by difference:

$$\hat{p}_{severe} = 1 - \hat{p}_{none} - \hat{p}_{mild} - \hat{p}_{moderate}$$

3. Given these values, we can estimate the utility score in correspondence of any non-integer RTSS value. For example, for $RTSS = 4.50$ we get $u_{interp} = 0.7332$, which is roughly similar to the midpoint of the interval (0.7027, 0.7640).

For the reader's convenience, here below we report the theoretical utilities estimated by the model in correspondence of the integer RTSS scores:

```
> RSUI_interp
      util_interp
RTSS=0      0.9999
RTSS=1      0.9444
RTSS=2      0.8864
RTSS=3      0.8255
RTSS=4      0.7638
RTSS=5      0.7029
RTSS=6      0.6437
RTSS=7      0.5864
RTSS=8      0.5310
RTSS=9      0.4775
RTSS=10     0.4261
RTSS=11     0.3769
RTSS=12     0.3298
RTSS=13     0.2848
RTSS=14     0.2419
RTSS=15     0.2007
RTSS=16     0.1608
RTSS=17     0.1212
RTSS=18     0.0790
```

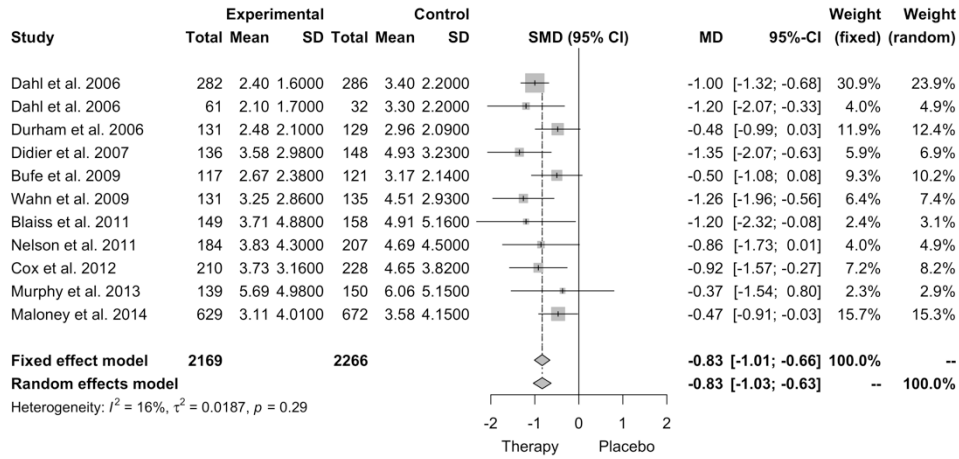
Using the mean square error as a measure of interpolation accuracy, we have an overall error value of 9×10^{-4} . The differences between the values contained in the `RSUI_interp` table and those contained in the `RSUI` table are marginal.

RTSS estimation and utility calculation

For estimating the effects of immunotherapy, we used the following meta-analyses (the results of which we report for convenience):

- SLIT: data source is the study by Di Bona et al. (2015), on the efficacy of SLIT versus placebo for seasonal allergic rhino-conjunctivitis due to grass pollens.
- SCIT: data source is the study by Di Bona et al. (2012), on the efficacy of SCIT versus placebo for seasonal allergic rhino-conjunctivitis due to grass pollens.

The first meta-analysis (SLIT) provides data on symptom score (SS), taking the mean differences in the two groups (MD) as the effect size. The graph below reproduces the original graph shown in section B (MD for symptom score) of Figure 1 in Di Bona et al. (2015):



Based on this meta-analysis, we estimated an average score for each of the two groups: the average score of each group obtained through the fixed effects model was used to back-transform the pooled effect size of the SCIT meta-analysis (which is expressed in terms of standardized average differences, and therefore it is not immediately interpretable in clinical terms, neither it can be transformed into utilities).

In general, the pooled effect size is estimated using the following weighted average:

$$M = \frac{\sum_{i=1}^K w_i y_i}{\sum_{i=1}^K w_i} = \frac{\sum_{i=1}^K w_i (\bar{x}_i^{(e)} - \bar{x}_i^{(c)})}{\sum_{i=1}^K w_i} = \frac{\sum_{i=1}^K w_i \bar{x}_i^{(e)}}{\sum_{i=1}^K w_i} - \frac{\sum_{i=1}^K w_i \bar{x}_i^{(c)}}{\sum_{i=1}^K w_i}$$

where:

- $\bar{x}_i^{(e)}$ represents the average in the experimental group of the i -th study.
- $\bar{x}_i^{(c)}$ represents the average in the control group of the i -th study.
- w_i indicates the weight, which differs depending on whether a fixed or random effects model is used (for example, in the random effects model each weight is obtained as the inverse of the within-study variance of the i -th study).

Therefore, in order to keep consistency with the estimated pooled effect size, the average score in each of the two groups was calculated as:

$$\text{average score in the experimental group} = \bar{x}_{SLIT}^{(e)} = \frac{\sum_{i=1}^K w_i \bar{x}_i^{(e)}}{\sum_{i=1}^K w_i}$$

$$\text{average score in the control group} = \bar{x}_{SLIT}^{(c)} = \frac{\sum_{i=1}^K w_i \bar{x}_i^{(c)}}{\sum_{i=1}^K w_i}$$

For the SLIT study, we obtained the following results using the fixed effects model:

```
> # control
> fixed.control.2015 <-
+   sum(meta_dibona2015_MD$w.fixed * meta_dibona2015_MD$mean.c) /
+   sum(meta_dibona2015_MD$w.fixed)
> # experimental
> fixed.experimental.2015 <-
+   sum(meta_dibona2015_MD$w.fixed * meta_dibona2015_MD$mean.e) /
+   sum(meta_dibona2015_MD$w.fixed)
> fixed.experimental.2015 <- round_preserve_sum(fixed.experimental.2015, 4)
> fixed.control.2015 <- round_preserve_sum(fixed.control.2015, 4)
> fixed.experimental.2015
[1] 2.9176
> fixed.control.2015
[1] 3.7507
```

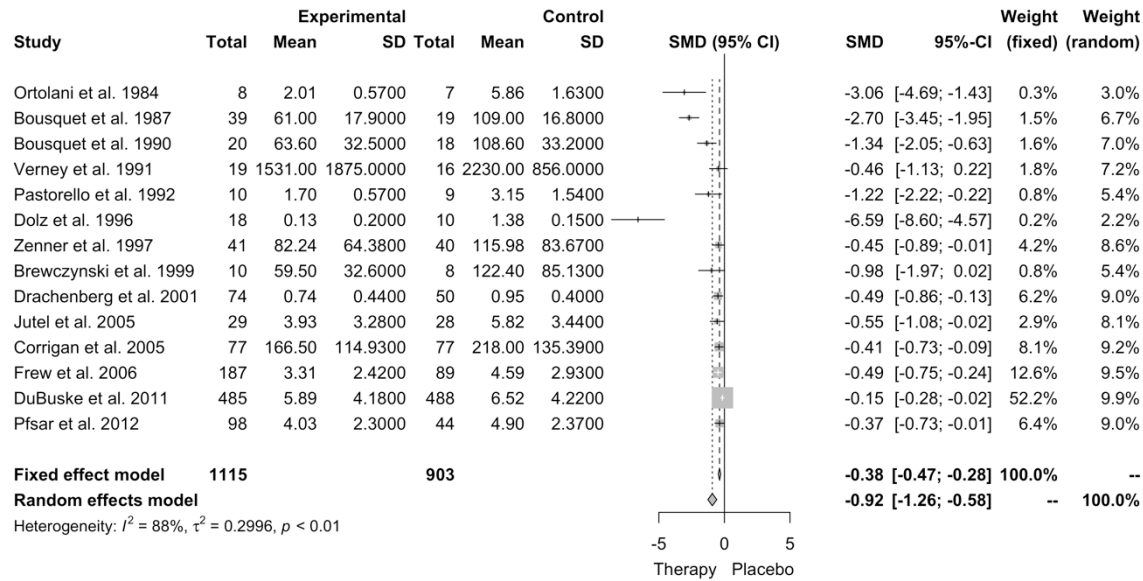
For the random effects model we obtained the following estimates (which differ slightly from the previous one, because the weights are slightly different):

```
> # control
> random.control.2015 <-
+   sum(meta_dibona2015_MD$w.random * meta_dibona2015_MD$mean.c) /
+   sum(meta_dibona2015_MD$w.random)
> # experimental
> random.experimental.2015 <-
+   sum(meta_dibona2015_MD$w.random * meta_dibona2015_MD$mean.e) /
+   sum(meta_dibona2015_MD$w.random)
> random.experimental.2015 <- round_preserve_sum(random.experimental.2015, 4)
> random.control.2015 <- round_preserve_sum(random.control.2015, 4)
> random.experimental.2015
[1] 2.9891
> random.control.2015
[1] 3.8208
```

On the basis of the interpolation procedure we have described above, which allows to transform the RTSS scores into utilities, we obtained the following utility estimates for each of the two groups (experimental and control), for each of the two models used (fixed and random effects):

```
> fixed.control.utility2015 <- interpRSUI(fixed.control.2015)
> fixed.control.utility2015
[1] 0.7792
> random.control.utility2015 <- interpRSUI(random.control.2015)
> random.control.utility2015
[1] 0.7748
> fixed.experimental.utility2015 <- interpRSUI(fixed.experimental.2015)
> fixed.experimental.utility2015
[1] 0.8306
> random.experimental.utility2015 <- interpRSUI(random.experimental.2015)
> random.experimental.utility2015
[1] 0.8262
```

In the second meta-analysis (SCIT), the effect size considered is the standardised mean difference (SMD) of the SS in the two groups:



The figure shown above equivalent to the third meta-analysis contained in Figure 1 of Di Bona et al., (2012). In this case, the effect-size used is the standardised mean difference, since the scores used in the studies included in the meta-analysis are not comparable (they do not represent the same symptom measurement scale, except in a small subset of studies): this makes it impossible to calculate an average score for each group, since we cannot sum up values expressed on heterogeneous measurement scales (we would obtain an average without any clinical or practical meaning).

To solve this problem, we first recall the standardized mean difference of the i -th study is obtained through the following linear transformation:

$$SMD_i = \frac{\bar{x}_i^{(e)} - \bar{x}_i^{(c)}}{S_i^{within}}$$

where S_i^{within} represents the within standard deviation for the i -th study, i.e. the pooled standard deviation of the sample standard deviations in the two groups.

Therefore, we used the inverse of this transformation on the pooled effect size to back-transform it on a non-standardised scale, comparable with the average scores for RTSS that we have obtained before from the SLIT meta-analysis. The basic idea, expressed in Higgins and Green (2008), section 12.6.4, is to use a reference standard deviation for the particular measurement scale on which we want to back-trasform the pooled effect size, reformulating the previous expression as follows:

$$\hat{x}_{SLIT}^{(e)} = \bar{x}^{typical} + (SMD \times SD^{typical})$$

where:

- $\hat{x}_{SLIT}^{(e)}$ is the average score of the experimental group back-transformed on the scale of measurement of interest (in our case the RTSS).
- $\bar{x}^{typical}$ represents the ‘typical’ average level of the measurement scale on which we want to back-transform the average score of the SLIT experimental group.
- $SD^{typical}$ represent the ‘typical’ standard deviation of the measurement scale on which we want to back-transform the average score of the SLIT experimental group.
- SMD is the average effect size (pooled) of the SLIT meta-analysis (in our case, equal respectively to -0.38 for the fixed effects model, and -0.92 for the random effects model).

Based on the above discussion, it is apparent that the natural choice for calculating $\bar{x}^{typical}$ is the control group of the SLIT meta-analysis. With this choice we have that:

$$\bar{x}^{typical} = \bar{x}_{SLIT}^{(c)} = 3.7507 \rightarrow \text{fixed effects model}$$

$$\bar{x}^{typical} = \bar{x}_{SLIT}^{(c)} = 3.8208 \rightarrow \text{random effects model}$$

For the choice of $SD^{typical}$, in Higgins and Green (2008) is suggested that “... *the standard deviation could be obtained as the pooled standard deviation of baseline scores in one of the studies*”. As it is not clear which studies have to be used to calculate this pooled standard deviation, we have chosen to calculate $SD^{typical}$ as follows:

$$SD^{typical} = \frac{\sum_{i=1}^K w_i s_i^{(c)}}{\sum_{i=1}^K w_i}$$

where $s_i^{(c)}$ is the sample standard deviation of the score for the i -th study in the control group of the SLIT meta-analysis. In other words, rather than calculating a pooled average, weighted by degrees of freedom as is usually done (which, however, requires that the variances at the population level are the same for all studies), we have taken a weighted average using the weights from the estimated model, so as to make less important the effect of those studies that have a higher sample variability (which is most likely due to a high heterogeneity of the experimental material).

With this choice, we have the following values for $SD^{typical}$ (both for the fixed effects and the random effects model):

```
> SDtypical_fixed.2015 <-
+   as.numeric(sqrt((meta_dibona2015_MD$w.fixed  %*%
+               sdctrl_2015 ^ 2) / sum(meta_dibona2015_MD$w.fixed)))

> SDtypical_fixed.2015 <- round_preserve_sum(SDtypical_fixed.2015, 4)
> SDtypical_fixed.2015
[1] 3.1012
```

```

> SDtypical_random.2015 <-
+   as.numeric(sqrt((meta_dibona2015_MD$w.random  %*%
+                   sdctrl_2015 ^ 2) / sum(meta_dibona2015_MD$w.random)))

> SDtypical_random.2015 <- round_preserve_sum(SDtypical_random.2015, 4)
> SDtypical_random.2015
[1] 3.1871

```

We are ready to back-transform using the parameters of the fixed effects model, obtaining::

```

> fixed_experimental.2012 <- fixed_control.2015 +
+   SDtypical_fixed.2015 * meta_dibona2012_SMD$TE.fixed

> fixed_experimental.2012 <- round_preserve_sum(fixed_experimental.2012, 4)
> fixed_experimental.2012
[1] 2.5876

```

while we obtain the following result for the random effects model:

```

> random_experimental.2012 <- random_control.2015 +
+   SDtypical_random.2015 * meta_dibona2012_SMD$TE.random

> random_experimental.2012 <- round_preserve_sum(random_experimental.2012, 4)
> random_experimental.2012
[1] 0.8768

```

It is worth noting that we could back-transform the average score in the experimental group of the 2015 meta-analysis (SLIT) as well, since also in this case we have a meta-analysis based on the SMD (for details see Di Bona et al., 2015). In this way, we could back-transform the untransformed average score of the experimental group treated with SLIT on the same measurement scale used to back-transform the average score related to the SCIT meta-analysis. However, if we perform the calculations for the fixed effects model we get:

```

> fixed_experimental.2015.back <- fixed_control.2015 +
+   SDtypical_fixed.2015 * meta_dibona2015_SMD$TE.fixed

> fixed_experimental.2015.back <-
+   round_preserve_sum(fixed_experimental.2015.back, 4)
> fixed_experimental.2015
[1] 2.9176
> fixed_experimental.2015.back
[1] 2.9630

```

We therefore have a minimal difference, far below the minimal clinically significant difference.

Hence, for the experimental group of the SLIT meta-analysis we can continue to use

`fixed_experimental.2015 = 2.9176`. We have the same results with the random effects model, since the difference between the original and the back-transformed average scores is minimal even in this case:

```

> random_experimental.2015.back <- random_control.2015 +
+   SDtypical_random.2015 * meta_dibona2015_SMD$TE.random

> random_experimental.2015.back <-
+   round_preserve_sum(random_experimental.2015.back, 4)

```

```
> random.experimental.2015
[1] 2.9891
> random.experimental.2015.back
[1] 2.9183
```

At this point we can estimate the utilities for each state using the interpolation procedure detailed before. Summarizing:

- for the SYMPTOMATIC arm, the utilities are obtained from the quantity $\bar{x}_{SLIT}^{(c)}$, calculated on the SLIT meta-analysis control group (Di Bona et al., 2015) – we have two estimates, one for the fixed effects model and one for the random effects model.
- for the SLIT arm, the utilities are obtained from $\bar{x}_{SLIT}^{(e)}$ using the same meta-analysis as above – we have two estimates, one for the fixed effects model and one for the random effects model.
- for the SCIT arm, the utilities are obtained through the back transformation of $\bar{x}_{SCIT}^{(e)}$, obtained through the SCIT meta-analysis reported Di Bona et al. (2012) - also in this case we have two estimates, one for the fixed effects and one for the random effects model.

The utilities for each state are as follows:

```
> standard_utilities
SYMPT_fixed SYMPT_random SLIT_fixed SLIT_random SCIT_fixed SCIT_random
0.7792      0.7748      0.8306      0.8262      0.8509      0.9513
```

These utilities refer to a single condition. To estimate the utilities in cohorts with varying age classes, we used a multi-utility multiplicative function as described in Ara and Wailoo (2012), taking as reference a baseline value of utility of perfect health condition valid for each age class, that is:

$$U_{A,B} = U_A \times U_B$$

where U_A indicates the utilities referred to a single condition, while U_B indicates the average utility of age class B in the absence of any pathological dimension. U_B utilities were derived from scores valid for Spain reported in Bernert et al. (2009). In addition, we considered a further adjustment to incorporate the presence/absence of allergic asthma into the utility. For this purpose we used the utility of 0.7378, attributed by Brüggjenjürgen et al. (2008) to patients in whom “*allergic rhinitis and mild allergic asthma*” (and intermittent use of beta-agonists) was present.

In this way, we obtained the following set of age-adjusted utilities:

```
> age_adjusted_utilities
      25-34  35-49  50-64  > 65
SYMPT_fixed 0.7558 0.7402 0.7013 0.7091
SYMPT_random 0.7516 0.7361 0.6973 0.7051
SLIT_fixed   0.8057 0.7891 0.7475 0.7558
SLIT_random  0.8014 0.7849 0.7436 0.7518
```

```
SCIT_fixed      0.8254 0.8083 0.7658 0.7743
SCIT_random    0.9228 0.9037 0.8562 0.8657
```

as well as the following set of age- and asthma-adjusted utilities:

```
> ageasthma_adjusted_utilities
      25-34  35-49  50-64  > 65
SYMPT_fixed 0.5576 0.5461 0.5174 0.5232
SYMPT_random 0.5545 0.5431 0.5145 0.5202
SLIT_fixed   0.5945 0.5822 0.5515 0.5576
SLIT_random  0.5913 0.5791 0.5486 0.5547
SCIT_fixed   0.6090 0.5964 0.5650 0.5713
SCIT_random  0.6808 0.6668 0.6317 0.6387
```

Given the hypothesis of our study, the utilities of our interest are those that fall into the age group 35 – 49.

Costi

The cost of the medical resources used in the simulation was obtained, directly or indirectly, from various data sources. None of the patients included in the simulated cohort is hospitalized. We used a societal perspective (Garrison et al., 2010). We have, therefore, quantified the direct costs due to the consumption of medicines or medical resources, either those paid by the patient or by the provider of the service (the Regions and then, ultimately, the Italian State), and the direct non medical costs, such as transport costs to reach the local hospital where the treatment is administered (the entire cost is borne by patients). We also considered indirect non-medical costs, that is the loss of income due to the number of working hours lost as a consequence of treatment administration. We have decided not to consider the intangible costs arising from the physical or psychological distress associated with the disease, given their difficult quantification (Walley and Haycox, 1997). All the costs are in 2018 Euros, except those for asthma medication (which are in 2010 Euros; however, the small amount of inflation over the last 10 years makes the this issue of little practical relevance).

A. Symptomatic treatment

1. Desloratadine: 5 mg orally once a day per os, the daily cost is 0.2055 Eur per 5 mg tablet (Desloratadina DOC – generic drug - 4.11 Eur per pack, 20 tablets). To estimate the average daily consumption of Desloratidine during the entire pollen season we used the combined data from Dahl et al. (2006) and Bachert et al. (2007); Bachert et al. (2007) report an average consumption per season of 17.9 tablets in the control group and 12.2 tablets in the experimental group (treated with SLIT immunotherapy for rhino-conjunctivitis), while Dahl et al. (2006) claim that these differences in Desloratadine consumption between the two groups correspond to a reduction in the RTSS from 3.4 (control group) to 2.4 (treated group with SLIT immunotherapy). To transform the average consumptions reported in these studies into average

consumptions corresponding to the RTSS scores that we estimated for the different arms of our simulation we used a proportion, assuming that there is a linear relationship between the RTSS and the average Desloratadine consumption during the pollen season. For both SLIT and SCIT the average RTSS reduction between the two groups (control and experimental, treated with AIT) is:

```
> diffEffectsSLITFixed <- 2.9176 - 3.7507
> diffEffectsSLITRandom <- 2.9891 - 3.8208
> diffEffectsSLITFixed
[1] -0.8331
> diffEffectsSLITRandom
[1] -0.8317

> diffEffectsSCITRandom <- 0.8768 - 3.8208
> diffEffectsSCITFixed
[1] -1.1631
> diffEffectsSCITRandom
[1] -2.944
```

For the SLIT arm (in both models, fixed and random effects) the reduction is significantly below the minimum clinically significant difference, while for the SCIT arm the reduction of the RTSS exceeds the minimum clinically significant difference. Since the consumption of Desloratidine decreased on average by 5.7 tablets in the control group with respect to the treated one, according to data from Bachert et al. (2007), and the corresponding reduction in the mean RTSS was equal to 1 according to Dahl et al. (2006), we calculated the reduction x in the consumption of Desloratidine for the SLIT arm (for which the reduction in RTSS was equal on average to 0.8331) as follows (for brevity, we report the calculations with reference only to the SLIT arm, fixed effects model):

$$(-5.7) : (-1) = x : \text{diffEffectsSLITFixed}$$

obtaining an average reduction of 4.75 tablets (for the arm treated with SLIT, compared to the arm not treated with immunotherapy), which therefore corresponds to a total of $17.9 - 4.75 = 13.15$ cpr of Desloratidine on average during the entire pollen season for the SLIT arm.

Repeating the same calculations for all possible combinations (SLIT and SCIT, fixed effect model and mixed effect model), and dividing by the mean duration of a pollen season (58 days; Dahl et al., 2006), we obtain the following average daily consumption of (tablets per day) of Desloratadine:

```
> final1day_2sign
               SCIT SLIT
Desloratadine_FIXED 0.19 0.23
Desloratadine_RANDOM 0.02 0.23
```

For the SYMPTOMATIC arm we assume an average consumption in the control arm equal to that reported in the study by Bachert et al. (2007) for the entire pollen season, that is 17.9

tablets, corresponding to an average daily consumption of 0.31 tablets per day during the entire pollen season.

2. Budesonide: two 50 mcg puffs per nostril twice a day (total 200 mcg per day), the cost per inhalation is 0.0775 Eur (15.50 Eur per 200 inhalations, Kesol[®] Spray 50Mcg 10ml/200D), the daily cost is $0.0775 * 4 = 0.31$ Eur (200 mcg per die). The data reported in the study by Bachert et al. (2007) indicate an average consumption of 26.6 50mcg inhalations for the control group over the entire pollen season, and 15.2 inhalations for the treated group. Using the same method described that we have described above for determining the consumption of Desloratidine, we obtain the following average number of inhalations per day during the entire pollen season, for the two arms of the study:

```
> final1day_2sign
      SCIT SLIT
Budesonide_FIXED 0.23 0.29
Budesonide_RANDOM 0.00 0.30
```

Also in this case, for the SYMPTOMATIC arm we assume the same average consumption in the control arm for the entire pollen season as reported in the Bachert et al. study (2007), i.e. 26.6 inhalations, corresponding to an average daily consumption of 0.46 inhalations per day during the entire pollen season.

B. Consumption of medical resources

In this case the costs changes from from year to year as the simulation scenarios unfolds.

- SYMPTOMATIC arm:
 - 1st year (t = 0)
 - i. first access visit: 30.66 Eur = for the ticket of the first specialist visit + 10 EUR additional fixed fee to access public healt services
 - ii. control specialist visit = 22.91 EUR
 - iii. allergy testing: 11.92 Eur up to 7 allergens for a total of 16 allergens, giving a total cost of 11.92×3 Eur + 10 Eur (additional fixed fee) = 44.86 EUR
 - from the 2nd year onwards: no further use of medical resources

Therefore, for the SYMPTOMATIC arm we have the following costs during the simulation horizon:

```
> costHealthSymptomatic <- c(30.66 + 22.91 + 44.86, rep(0, 9))
> costHealthSymptomatic
[1] 98.43 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00
```

The calculations were made using the ticket prices valid for the Apulia Region. Assuming an average duration of 20 minutes for each specialist visit, we can conclude (with a good level of

approximation) that the cost of the ticket for specialist visits incurred by the patients covers the remuneration that the Apulia Region must pay to the specialist doctor. Therefore, in line with the societal perspective used, we do not have to charge any other cost for the specialist visits. The cost incurred by the patients for paying the allergy testing ticket covers the entire cost of the service (and therefore, also in this case we do not have to add any other cost to be borne by the Health Authority. For the Apulia Region, the maximum ticket price cannot exceed 36.15 Eur, plus a fixed fee of 10 Eur for each prescription, regardless of the real value of the service. This additional fixed fee is not charged by all Italian Regions, or varies from Region to Region in a specific way. In addition, in some Regions the maximum ticket amount is different from that valid for Apulia. However, any variation of ticket amounts would change in the same way in each of the three arms of the simulation. Therefore, without losing in generality, we can use the ticket amounts valid for the Apulia Region.

- SCIT arm:
 - 1st year ($t = 0$)
 - i. same costs as SYMPTOMATIC arm: first specialistic visit (30.66 Eur) + control specialistic visit (22.91 Eur) + allergy testing (44.86 Eur)
 - ii. 12 immunotherapy administrations, 4 administrations for induction phase during the 1st month + 8 additional administrations in the course of the year. The total cost of this therapeutic regime must be calculated in blocks of 8 administrations, at a unit cost of 11.96 each, for a total of $11.96 \times 8 = 92.69 + 10$ Eur (fixed fee) = 102.69 Eur. Since 8 administrations are not enough in the first year (we have 12 administrations), we will suppose to consume two blocks of 8 administrations, for a total cost equal to $102.69 + 102.69 = 205.38$ Eur
 - 2nd year
 - i. control specialist visit (22.91 Eur)
 - ii. 10 administrations during the year. Part of the cost of the therapy incurred in the previous year is used residually in this year, and therefore we charge the cost of a single block of immunotherapy, i.e. 92.69 Eur + 10 Eur (fixed fee) = 102.69 Eur
 - 3rd year
 - i. control specialistic visit (22.91 Eur)
 - ii. allergy testing (44.86 Eur)
 - iii. 10 administrations during the year, 102.69 Eur as above
 - from 4th years onwards,: no further consumption of medical resource.

The costs of the SCIT arm from year to year as the simulation unfolds are as follows:

```
> costHealthSCIT <-
+   c(30.66 + 22.91 + 44.86 + 205.38,
+     22.91 + 102.69,
+     22.91 + 44.86 + 102.69,
+     rep(0, 7))
> costHealthSCIT
[1] 303.81 125.60 170.46  0.00  0.00  0.00  0.00  0.00  0.00  0.00
```

- **SLIT arm:** the costs of this section are absolutely identical to those of the SCIT arm, with the only difference that the patients do not incur in administration costs:

```
> costHealthSLIT <-
+   c(30.66 + 22.91 + 44.86, 22.91, 22.91 + 44.86, rep(0, 7))
> costHealthSLIT
[1] 98.43 22.91 67.77 0.00  0.00  0.00  0.00  0.00  0.00  0.00
```

C. Costs of immunotherapy

The regimes used for the two treatments are as follows:

- **SCIT:** the administration is carried out for three years, with administration frequency described in the previous section
- **SLIT:** in this case the administration regime varies depending on the drug used:
 - GRAZAX®:** three years continuously, 1 sublingual tablet per day
 - ORALAIR®:** 7 months per year, starting from 4 months before the beginning of the pollen season, 1 sublingual tablet per day

The prices of boxes of tablets used to administer SLIT are as follows:

- GRAZAX Os 30 Liof 75 000 Sq-t: 99.02 Eur
- GRAZAX Os 100 Liof 75 000 Sq-t: 330.08 Eur

For a full year of therapy with GRAZAX we therefore need 100 + 100 + 100 + 30 + 30 tablets, corresponding to a total annual cost of:

$$330.08 \times 3 + 99.02 \times 3 = 1289.46 \text{ Eur}$$

For ORALAIR we have:

- ORALAIR 30 Cpr Subl 300 lr: 99.28 Eur
- ORALAIR 30 Cpr Subl 300 lr: 297.83 Eur

For 7 months of therapy with ORALAIR we therefore need 90 + 90 + 30 tablets, which corresponds to a total annual cost of:

$$297.83 \times 2 + 99.28 = 694.94 \text{ EUR}$$

Therefore, the overall annual average cost for SLIT is obtained by taking an average of the two prices we have calculated, obtaining:

$$(1289.46 + 694.94) / 2 = 992.2 \text{ Eur}$$

The therapy is entirely borne by the Puglia Region, and there are no ticket costs borne by the patients.

The preparations we have considered to determine the average annual cost borne by patients for SCIT immunotherapy are those marketed by the following pharmaceutical companies (we report the average cost per pack containing 1 vial for 5 administrations; the initial pack also containing the vials used for induction response has the same cost):

- Allergofarma (Allergovit[®]): 265 Eur
- Hal-Allergy (Purethal[®]): 225 Eur
- Lofarma (Lais In[®]): 214.50 Eur
- Allergy Therapeutics (Tyrosin TU[®]): 199 Eur
- Alk-Abellò (Pangramin Ultra[®]): 250 Eur

Taking an average, and bearing in mind that we need 2 packs to obtain 10 annual administrations, the total average annual cost for SCIT is therefore equal to:

$$(2 * 265 + 2 * 225 + 2 * 214.50 + 2 * 199 + 2 * 250) / 5 = 473.4 \text{ Eur}$$

The cost of the therapy is entirely borne by the patient but, as we know, this information is irrelevant, given the perspective that we have adopted for the analysis.

D. Costs for asthma

The costs for asthma were derived from Table 2 in Accordini et al. (2013). Costs have been estimated on the basis of: "... 462 subjects included in the analysis, that had mild (22.3%), moderate (34.0%) or severe (43.7%) persistent asthma ...". The average annual direct healthcare cost (constant 2010 prices) includes specialist medical examinations, clinical and laboratory examinations, medicines and hospital admissions, and has been estimated at 594 Eur. The average annual indirect non-healthcare cost reflects the loss of productivity due to both lost working days, and limitations in activities not directly related to work. Its has been estimated at 989 Eur.

E. Other costs

They should be charged for SCIT immunotherapy only, as its administration involves a temporary interruption of work and additional transport costs. In the first case, these are indirect non-healthcare costs (the same as the indirect costs incurred for asthma), while in the second case we have direct non-healthcare costs that are borne entirely by the patient.

Using the human-capital method, indirect costs are evaluated as the loss of income that could have been produced, but which was not actually produced because of the onset of the morbid event (Liljas, 1998). To obtain an hourly monetary valuation of the loss of productivity, we have

considered the amount of gross domestic product per capita at current prices for the year 2014 (source: ISTAT, 2019) equal to 26697.6 Eur, which divided first over 52 weeks and then over an amount of 35 hours per working week, gives an average hourly value of 14.66 Eur. The indirect costs of lost productivity due to the administration of SCIT are, therefore, as follows (taking into account the total number of administrations over the three years):

```
> costProductivitySCIT <-
+   c(14.66 * 2 * 12, 14.66 * 2 * 10, 14.66 * 2 * 10,
+     rep(0, 7))
> costProductivitySCIT
[1] 351.84 293.20 293.20  0.00  0.00  0.00  0.00  0.00  0.00  0.00
```

These costs are borne by all patients of the simulated cohort, and this somehow compensates for the underestimation resulting from not having calculated the indirect costs (resulting from the inability to perform daily activities) borne by those individuals who are not included into the Italian workforce. On the other hand, the human capital method overestimates real productivity losses, because if the work is interrupted for a short time, colleagues can replace those who are temporarily absent.

As far as direct transport costs are concerned, we have hypothesized a public/private mix with a cost of 5 Euro per administration, obtaining:

```
> costTransportSCIT <- c(5 * 12, 5 * 10, 5 * 10, rep(0, 7))
> costTransportSCIT
[1] 60 50 50  0  0  0  0  0  0  0
```

Results

Base case scenario (fixed effects model)

In this scenario, the parameters to calculate the utilities are those obtained on the basis of the fixed effect model. Both the indirect costs of lost productivity and the direct transport costs associated with SCIT therapy will not be considered: these costs will be included in another scenario, in order to better evaluate their impact.

For the pollen season we have, as we know, an average duration of 58 days, as assessed in RCTs (Di Bona et al., 2012). However, from now on, the average duration will always be approximated to 60 days, without any substantial change in the subsequent calculations. The calculation of QALYs gained in each year by each patient is done according to the following formula:

$$QALY = \frac{10}{12} \times 1 + \frac{2}{12} \text{utility}_{\text{arm}}$$

Calculations for the SYMPTOMATIC arm are as follows:

```

> qaly_NoAIT_NoAsthma_SYMPOMATIC <- (10/12) * 1 + (2/12) *
age_adjusted_utilities[1, 2]
> qaly_NoAIT_NoAsthma_SYMPOMATIC
[1] 0.9567
> qaly_NoAIT_Asthma_SYMPOMATIC <- ageasthma_adjusted_utilities[1, 2]
> qaly_NoAIT_Asthma_SYMPOMATIC
[1] 0.5461
> qaly_Death <- 0

```

For the SCIT arm, we have:

```

> qaly_NoAsthma_SCIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[5, 2], n + 1)
> qaly_NoAsthma_SCIT
[1] 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805
> qaly_Asthma_SCIT <- rep(ageasthma_adjusted_utilities[5, 2], n + 1)
> qaly_Asthma_SCIT
[1] 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964
> # in caso di discontinuazione
> qaly_NoAsthma_NoSCIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[5, 2], n + 1)
> qaly_Asthma_NoSCIT <- rep(ageasthma_adjusted_utilities[5, 2], n + 1)
> qaly_Asthma_NoSCIT
[1] 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964

```

It is worth noting that:

- QALYs have been defined as vectors in order to let them vary, in other scenarios, between one Markovian cycle and another.
- In case of discontinuation of the therapy, the QALYs gained by each patient stop increasing, and remain constant as the simulation unfolds.

In the same way, for the SLIT arm we have:

```

> qaly_NoAsthma_SLIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[3, 2], n + 1)
> qaly_NoAsthma_SLIT
[1] 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485
> qaly_Asthma_SLIT <- rep(ageasthma_adjusted_utilities[3, 2], n + 1)
> qaly_Asthma_SLIT
[1] 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822
> # in caso di discontinuazione
> qaly_NoAsthma_NoSLIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[3, 2], n + 1)
> qaly_Asthma_NoSLIT <- rep(ageasthma_adjusted_utilities[3, 2], n + 1)
> qaly_Asthma_NoSLIT
[1] 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822

```

Here we present the definition of the costs for all the three arms:

```

> # Symptomatic treatment
> costSeasonalSYMPOMATIC <- costList$costSeasonalSymptomaticTotal
> costSeasonalSYMPOMATIC
[1] 19.65

> costSeasonalSCIT <- costList$CostSeasonalTotal_FIXED["SCIT"]
> attributes(costSeasonalSCIT) <- NULL
> costSeasonalSCIT
[1] 19.65

> costSeasonalSLIT <- costList$CostSeasonalTotal_FIXED["SLIT"]
> attributes(costSeasonalSLIT) <- NULL
> costSeasonalSLIT
[1] 19.65

```

```

> # costs of immunotherapy
> costAitSCIT <- costList$costAitSCIT
> costAitSCIT
[1] 473.4
> costAitSLIT <- costList$costAitSLIT
> costAitSLIT
[1] 992.2

> # consumption of medical resources
> costHealthSYMPTOMATIC <- costList$costHealthSymptomatic
> costHealthSYMPTOMATIC
[1] 98.43 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00

> costHealthSCIT <- costList$costHealthSCIT
> costHealthSCIT
[1] 303.81 125.60 170.46 0.00 0.00 0.00 0.00 0.00 0.00 0.00

> costHealthSLIT <- costList$costHealthSLIT
> costHealthSLIT
[1] 98.43 22.91 67.77 0.00 0.00 0.00 0.00 0.00 0.00 0.00

> # costs for asthma
> costAsthmaDirect <- costList$costAsthmaDirect
> costAsthmaDirect
[1] 594
> costAsthmaIndirect <- costList$costAsthmaIndirect
> costAsthmaIndirect
[1] 989

> # indirect costs due to lost productivity (SCIT)
> costProductivitySCIT <- costList$costProductivitySCIT
> costProductivitySCIT
[1] 351.84 293.20 293.20 0.00 0.00 0.00 0.00 0.00 0.00 0.00

> # direct transportation costs (SCIT)
> costTransportSCIT <- costList$costTransportSCIT
> costTransportSCIT
[1] 60 50 50 0 0 0 0 0 0 0

```

As already said before, indirect lost productivity costs and direct non-medical transport costs for SCIT are not included in this scenario. Here is the evolution of the cohort in each of the three arms:

- SYMPTOMATIC

```

> outSYMPTOMATIC
# A tibble: 10 x 4
  Cycle `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl> <dbl>
1     0      1000         0     0
2     1       995.       4.63 0.615
3     2       990.       9.23 1.23
4     3       984.      13.8 1.85
5     4       979.      18.3 2.47
6     5       974.      22.9 3.08
7     6       969.      27.3 3.70
8     7       964.      31.8 4.33
9     8       959.      36.2 4.95
10    9       954.      40.6 5.57

```

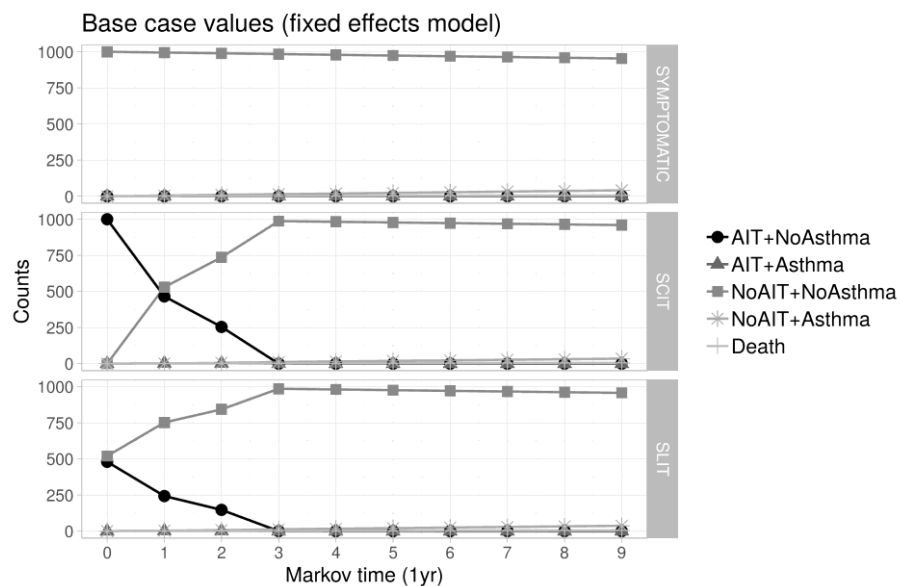
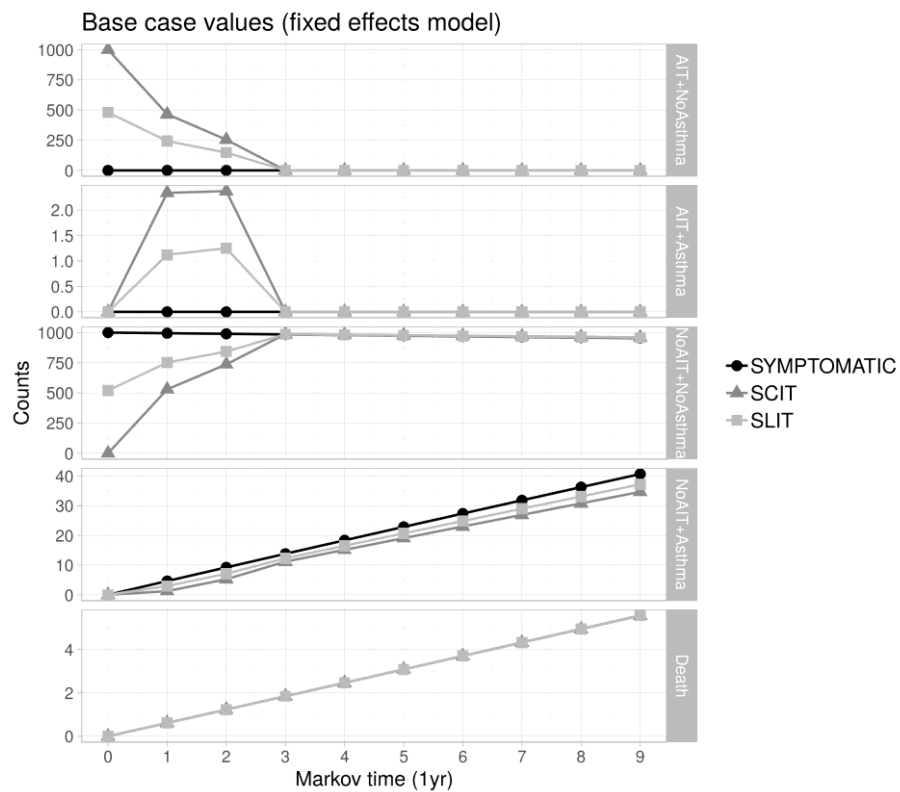
- SCIT

```
> outSCIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0      1000         0         0         0     0
2     1      466.       2.34       530       1.24 0.615
3     2      254.       2.37       737.       5.23 1.23
4     3         0         0       987.      11.2 1.85
5     4         0         0       982.      15.1 2.46
6     5         0         0       978.      19.1 3.08
7     6         0         0       973.      23.0 3.70
8     7         0         0       969.      26.9 4.32
9     8         0         0       964.      30.8 4.94
10    9         0         0       960.      34.6 5.56
```

- SLIT

```
> outSLIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0       480         0       520         0     0
2     1      243.       1.12      752.       2.96 0.615
3     2      147.       1.25      843.       7.10 1.23
4     3         0         0      986.      12.3 1.85
5     4         0         0      981.      16.5 2.46
6     5         0         0      976.      20.7 3.08
7     6         0         0      971.      24.8 3.70
8     7         0         0      967.      29.0 4.32
9     8         0         0      962.      33.1 4.94
10    9         0         0      957.      37.2 5.57
```

We now present the evolution of each of the three arms in a graphical form:



Below, we show the code for calculating the QALY in the three arms:

- SYMPTOMATIC

```
> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(
+     qalyCycleUndsc = (qaly_NoAIT_NoAsthma_SYMPTOMATIC * `No AIT+No Asthma`) +
+       (qaly_NoAIT_Asthma_SYMPTOMATIC * `No AIT+Asthma`) +
+       (0 * Death)
+   )
```

```

There were 48 warnings (use warnings() to see them)
>
> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(qalyCycleDsc =
+                               outSYMPTOMATIC$qalyCycleUndsc / ((1 + 0.035) ^
+                               (0:9)))
> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(qalyCumUndsc = cumsum(outSYMPTOMATIC$qalyCycleUndsc))
> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(qalyCumDsc = cumsum(outSYMPTOMATIC$qalyCycleDsc))
>
> outSYMPTOMATIC_qaly <- outSYMPTOMATIC[, -(1:4)]
> outSYMPTOMATIC_qaly
# A tibble: 10 x 4
   qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
         <dbl>         <dbl>         <dbl>         <dbl>
1             957.           957.           957.           957.
2             954.           922.          1911.          1879.
3             952.           888.          2863.          2767.
4             949.           856.          3812.          3623.
5             947.           825.          4759.          4448.
6             944.           795.          5703.          5243.
7             942.           766.          6645.          6010.
8             940.           738.          7585.          6748.
9             937.           712.          8522.          7460.
10            935.           686.          9456.          8146.

```

The values reported above are discounted at 3.5% per annum, and the four columns indicate, respectively:

- qalyCycleUndsc: QALYs for each Markovian cycle, undiscounted values.
- qalyCycleDsc: QALYs for each Markovian cycle, discounted values.
- qalyCumUndsc: cumulative QALYs, undiscounted values.
- qalyCumDsc: cumulative QALYs, discounted values.

- SCIT

```

> outSCIT_qaly
# A tibble: 10 x 4
   qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
         <dbl>         <dbl>         <dbl>         <dbl>
1             968.           968.           968.           968.
2             966.           933.          1934.          1902.
3             964.           900.          2898.          2801.
4             962.           868.          3860.          3669.
5             960.           837.          4820.          4506.
6             958.           807.          5778.          5312.
7             956.           778.          6734.          6090.
8             954.           750.          7688.          6840.
9             952.           723.          8640.          7563.
10            950.           697.          9590.          8260.

```

- SLIT

```

> outSLIT_qaly
# A tibble: 10 x 4
   qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
         <dbl>         <dbl>         <dbl>         <dbl>

```

1	965.	965.	965.	965.
2	963.	930.	1928.	1895.
3	960.	897.	2888.	2792.
4	958.	864.	3846.	3656.
5	956.	833.	4803.	4489.
6	954.	803.	5756.	5292.
7	952.	774.	6708.	6067.
8	950.	746.	7658.	6813.
9	947.	719.	8605.	7533.
10	945.	694.	9551.	8226.

We also include the code for cost calculations, for each of the three arms:

- SYMPTOMATIC

```
> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(costCycleUndsc =
+                               ((costSeasonalSYMPTOMATIC + costHealthSYMPTOMATIC)
+                                * `No AIT+No Asthma`) +
+                               ((costSeasonalSYMPTOMATIC + costHealthSYMPTOMATIC +
+                                costAsthmaDirect) * `No AIT+Asthma`) +
+                               0 * Death)

> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(costCycleDsc =
+                               outSYMPTOMATIC$costCycleUndsc / ((1 + 0.035) ^ (0:9)))

> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(costCumUndsc = cumsum(outSYMPTOMATIC$costCycleUndsc))

> outSYMPTOMATIC <-
+   outSYMPTOMATIC %>% mutate(costCumDsc = cumsum(outSYMPTOMATIC$costCycleDsc))

> outSYMPTOMATIC[, -(5:8)]
# A tibble: 10 x 8
  Cycle `No AIT+No Asthma` `No AIT+Asthma` Death costCycleUndsc costCycleDsc costCumUndsc costCumDsc
  <int>      <dbl>          <dbl> <dbl>      <dbl>      <dbl>      <dbl>      <dbl>
1     0          1000            0  0        118080.    118080.    118080.    118080.
2     1          995.           4.63 0.615    22387.     21630.    140467.    139710.
3     2          990.           9.23 1.23     25107.     23438.    165574.    163148.
4     3          984.          13.8 1.85     27810.     25083.    193384.    188231.
5     4          979.          18.3 2.47     30497.     26576.    223881.    214807.
6     5          974.          22.9 3.08     33166.     27925.    257048.    242732.
7     6          969.          27.3 3.70     35820.     29139.    292867.    271872.
8     7          964.          31.8 4.33     38456.     30226.    331324.    302098.
9     8          959.          36.2 4.95     41077.     31194.    372400.    333292.
10    9          954.          40.6 5.57     43680.     32050.    416081.    365342.
```

- SCIT

```
> # we create two new columns to take into account the costs that must be charged
> # for a single cycle only, due to immunotherapy dropouts
> outSCIT <-
+   outSCIT %>% mutate(
+     `No AIT+No Asthma_disc` = c(
+       `No AIT+No Asthma`[1],
+       `No AIT+No Asthma`[2] - `No AIT+No Asthma`[1],
+       `No AIT+No Asthma`[3] - `No AIT+No Asthma`[2],
+       rep(0, (n + 1) - 3)
+     )
+   )
>
> outSCIT <-
+   outSCIT %>% mutate(
+     `No AIT+Asthma_disc` = c(
+       `No AIT+Asthma`[1],
+       `No AIT+Asthma`[2] - `No AIT+Asthma`[1],
+       `No AIT+Asthma`[3] - `No AIT+Asthma`[2],
+       rep(0, (n + 1) - 3)
+     )
+   )
```

```

+ )
>
> outSCIT <-
+ outSCIT %>% mutate(
+   costCycleUndsc = (costAitSCIT * `AIT+No Asthma`) +
+   (costAitSCIT * `AIT+Asthma`) +
+   ((0.5 * costAitSCIT) * `No AIT+No Asthma_disc`) +
+   ((0.5 * costAitSCIT) * `No AIT+Asthma_disc`) +
+   ((costAsthmaDirect) * (`AIT+Asthma` + `No AIT+Asthma`)) +
+   ((costHealthSCIT) * (`AIT+No Asthma` + `AIT+Asthma`)) +
+   (1000 - Death) * costSeasonalSCIT +
+   0 * Death
+ )
> outSCIT <-
+ outSCIT %>% mutate(costCycleDsc =
+   outSCIT$costCycleUndsc / ((1 + 0.035) ^ (0:9)))
> outSCIT <-
+ outSCIT %>% mutate(costCumUndsc = cumsum(outSCIT$costCycleUndsc))
> outSCIT <-
+ outSCIT %>% mutate(costCumDsc = cumsum(outSCIT$costCycleDsc))
> outSCIT[,~c(1, 7:10, 13, 15)]
# A tibble: 10 x 9
  `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death `No AIT+No Asthma_disc` `No AIT+Asthma_disc` costCycleDsc costCumDsc
    <dbl>         <dbl>         <dbl>         <dbl>         <dbl> <dbl>         <dbl>         <dbl>         <dbl>
1     1000           0           0           0           0         0           0       796860       796860
2     466.         2.34          530         1.24 0.615         530         1.24 413455.    1210315.
3     254.         2.37          737.         5.23 1.23         207.         3.99 223413.    1433728.
4         0           0           987.         11.2 1.85           0           0       23670.    1457398.
5         0           0           982.         15.1 2.46           0           0       24913.    1482311.
6         0           0           978.         19.1 3.08           0           0       26033.    1508344.
7         0           0           973.         23.0 3.70           0           0       27039.    1535383.
8         0           0           969.         26.9 4.32           0           0       27936.    1563319.
9         0           0           964.         30.8 4.94           0           0       28732.    1592051.
10        0           0           960.         34.6 5.56           0           0       29433.    1621484.

```

For reasons of space, we have reported the discounted costs only.

- SLIT

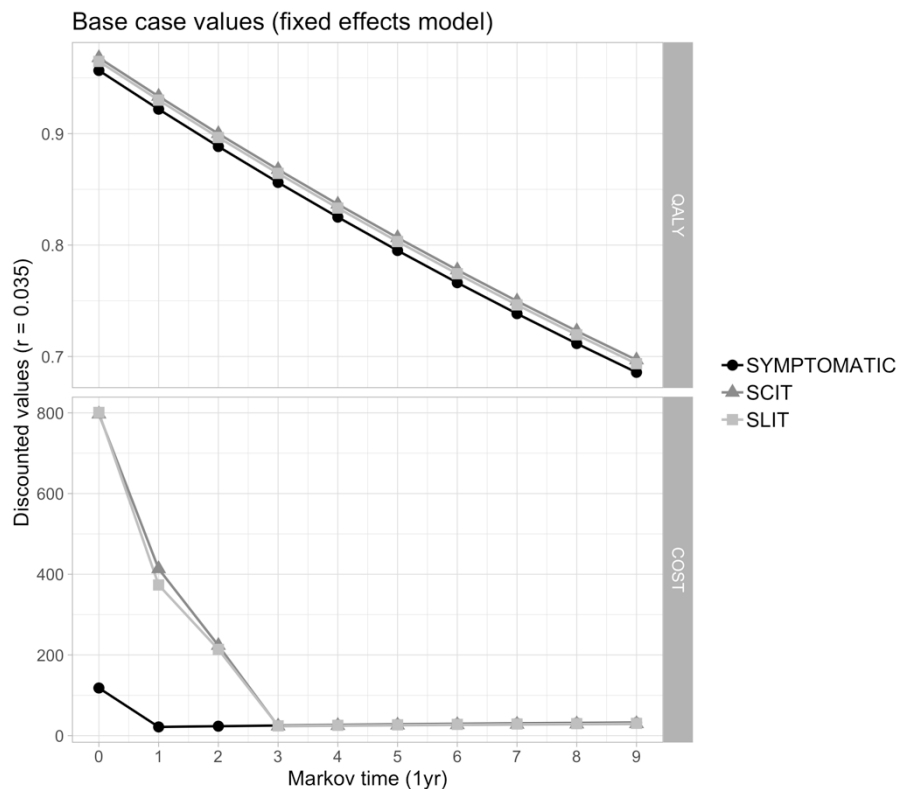
```

> # we create two new columns to take into account the costs that must be charged
> # for a single cycle only, due to immunotherapy dropouts
> outSLIT <-
+ outSLIT %>% mutate(
+   `No AIT+No Asthma_disc` = c(
+     `No AIT+No Asthma`[1],
+     `No AIT+No Asthma`[2] - `No AIT+No Asthma`[1],
+     `No AIT+No Asthma`[3] - `No AIT+No Asthma`[2],
+     rep(0, (n + 1) - 3)
+   )
+ )
>
> outSLIT <-
+ outSLIT %>% mutate(
+   `No AIT+Asthma_disc` = c(
+     `No AIT+Asthma`[1],
+     `No AIT+Asthma`[2] - `No AIT+Asthma`[1],
+     `No AIT+Asthma`[3] - `No AIT+Asthma`[2],
+     rep(0, (n + 1) - 3)
+   )
+ )
>
> outSLIT <-
+ outSLIT %>% mutate(
+   costCycleUndsc = (costAitSLIT * `AIT+No Asthma`) +
+   (costAitSLIT * `AIT+Asthma`) +
+   ((0.5 * costAitSLIT) * `No AIT+No Asthma_disc`) +
+   ((0.5 * costAitSLIT) * `No AIT+Asthma_disc`) +
+   ((costAsthmaDirect) * (`AIT+Asthma` + `No AIT+Asthma`)) +
+   ((costHealthSLIT) * (`AIT+No Asthma` + `AIT+Asthma`)) +
+   (1000 - Death) * costSeasonalSLIT +
+   0 * Death
+ )
>
> outSLIT <-
+ outSLIT %>% mutate(costCycleDsc =
+   outSLIT$costCycleUndsc / ((1 + 0.035) ^ (0:9)))
> outSLIT <-
+ outSLIT %>% mutate(costCumUndsc = cumsum(outSLIT$costCycleUndsc))
> outSLIT <-
+ outSLIT %>% mutate(costCumDsc = cumsum(outSLIT$costCycleDsc))
> outSLIT[,~c(1, 7:10, 13, 15)]

```

```
# A tibble: 10 x 9
  `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death `No AIT+No Asthma_disc` `No AIT+Asthma_disc` costCycleDsc costCumDsc
1      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>
2      480          0          520          0          0          520          0      801124.    801124.
3      243.        1.12        752.        2.96 0.615      232.        2.96      373428.    1174553.
4      147.        1.25        843.        7.10 1.23      90.8        4.14      213779.    1388332.
5          0          0        986.       12.3 1.85          0          0      24276.    1412607.
6          0          0        981.       16.5 2.46          0          0      25622.    1438230.
7          0          0        976.       20.7 3.08          0          0      26838.    1465068.
8          0          0        971.       24.8 3.70          0          0      27931.    1492998.
9          0          0        967.       29.0 4.32          0          0      28907.    1521905.
10         0          0        962.       33.1 4.94          0          0      29775.    1551680.
11         0          0        957.       37.2 5.57          0          0      30540.    1582220.
```

The evolution of both costs and QALYs is shown below:

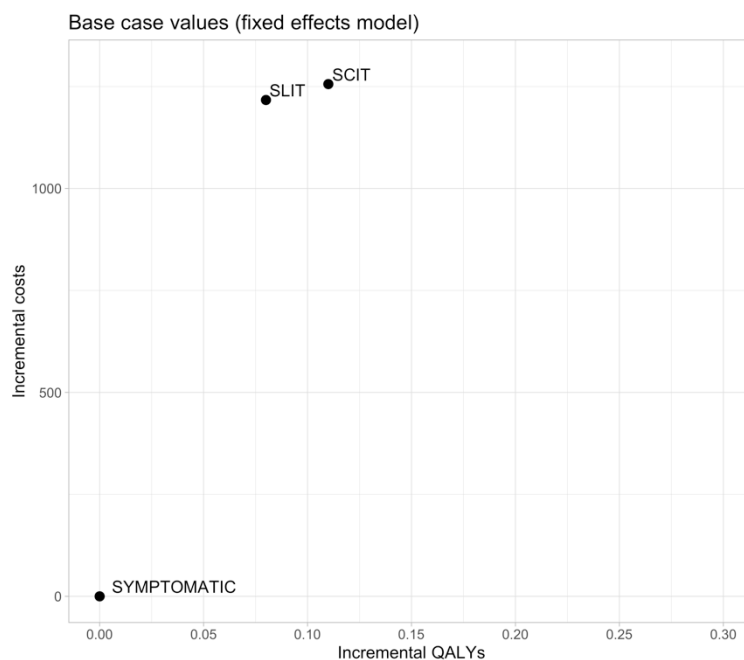


Finally, we represent the total difference in costs and effects (gained QALYs) in the cost-effectiveness plane. We will only use discounted values, and the SYMPTOMATIC strategy is the comparator. We show below the results per patient:

```
> tempICER
      Inc_QALYs Inc_Costs ICERs
SYMPTOMATIC    0.00      0   NaN
SLIT           0.08    1217 15212
SCIT           0.11    1256 11418
```

The first two columns represent the total increase in costs and QALYs gained per patient (over the entire time horizon of the simulation) with respect to the reference strategy (SYMPTOMATIC). It is important to observe that the incremental cost of SCIT is higher than the incremental cost of SLIT. This is mainly due to the higher rate of SLIT therapy dropouts, as a consequence of a lower adherence. However, the incremental gain of SCIT in terms of QALYs is higher, either directly as a

result of the increased effectiveness of this form of immunotherapy, or indirectly as a result of the fewer asthmatic patients observed at the end of the follow-up period. According to the data obtained, SLIT can be considered cost-effective compared to SYMPTOMATIC, if we are willing to pay at least 15200 Eur for each additional QALY gained (over ten years). With SCIT, we must be willing to pay at least 11400 Eur. Below, we report a representation in the cost-effectiveness plane:



1. Scenario: efficacy calculated with the random effect model (REM)

This scenario is conceptually identical to the previous one, with the only difference that the calculations are based on the random effects model. We only report the results.

First of all, we show the QALYs gained per year in each state, for all the three scenarios:

- SYMPTOMATIC

```
> qaly_NoAIT_NoAsthma_SYMPTOMATIC <- (10/12) * 1 + (2/12) *
age_adjusted_utilities[2, 2]
> qaly_NoAIT_NoAsthma_SYMPTOMATIC
[1] 0.9560167
> qaly_NoAIT_Asthma_SYMPTOMATIC <- ageasthma_adjusted_utilities[2, 2]
> qaly_NoAIT_Asthma_SYMPTOMATIC
[1] 0.5431
> qaly_Death <- 0
```

- SCIT

```
> qaly_NoAsthma_SCIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[6, 2],
n + 1)
> qaly_NoAsthma_SCIT
[1] 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395
0.98395
> qaly_Asthma_SCIT <- rep(ageasthma_adjusted_utilities[6, 2], n + 1)
> qaly_Asthma_SCIT
[1] 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668
> # in caso di discontinuazione
> qaly_NoAsthma_NoSCIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[6,
2], n + 1)
> qaly_NoAsthma_NoSCIT
[1] 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395 0.98395
0.98395
> qaly_Asthma_NoSCIT <- rep(ageasthma_adjusted_utilities[6, 2], n + 1)
> qaly_Asthma_NoSCIT
[1] 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668 0.6668
```

- SLIT

```
> qaly_NoAsthma_SLIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[4, 2],
n + 1)
> qaly_NoAsthma_SLIT
[1] 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415
0.96415
> qaly_Asthma_SLIT <- rep(ageasthma_adjusted_utilities[4, 2], n + 1)
> qaly_Asthma_SLIT
[1] 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791
> # in caso di discontinuazione
> qaly_NoAsthma_NoSLIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[4,
2], n + 1)
> qaly_NoAsthma_NoSLIT
[1] 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415 0.96415
0.96415
> qaly_Asthma_NoSLIT <- rep(ageasthma_adjusted_utilities[4, 2], n + 1)
> qaly_Asthma_NoSLIT
[1] 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791 0.5791
```

The evolution of the cohort is absolutely identical to the previous case, since the definition of the matrix of transition probabilities does not include parameters related to utilities. For the evolution of QALYs we have some obvious differences:

- SYMPTOMATIC

```
> outSYMPTOMATIC_qaly
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
    <dbl>         <dbl>         <dbl>         <dbl>
1      956.         956.         956.         956.
2      954.         921.        1910.        1877.
3      951.         888.        2861.        2765.
4      949.         856.        3809.        3621.
5      946.         824.        4755.        4445.
6      944.         795.        5699.        5240.
7      941.         766.        6640.        6005.
```

8	939.	738.	7579.	6743.
9	936.	711.	8515.	7454.
10	934.	685.	9449.	8139.

- SCIT

```
> outSLIT_galy
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1         984.         984.         984.         984.
2         982.         949.        1966.        1933.
3         980.         915.        2946.        2848.
4         979.         883.        3925.        3731.
5         977.         851.        4902.        4582.
6         975.         821.        5877.        5403.
7         973.         792.        6850.        6194.
8         971.         763.        7821.        6958.
9         969.         736.        8790.        7694.
10        967.         710.        9758.        8404.
```

- SLIT

```
> outSLIT_galy
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1         964.         964.         964.         964.
2         962.         929.        1926.        1894.
3         960.         896.        2886.        2790.
4         958.         864.        3844.        3653.
5         955.         833.        4799.        4486.
6         953.         803.        5752.        5288.
7         951.         774.        6703.        6062.
8         949.         746.        7652.        6808.
9         947.         719.        8599.        7527.
10        944.         693.        9543.        8220.
```

As far as the calculation of costs is concerned, there are small differences in the case of SCIT only, due to the fact that the seasonal cost of the symptomatic treatment is inversely related to the amount of the RTSS reduction between the treated and the control group, and therefore the overall cost of symptomatic treatment for patients undergoing SCIT is slightly lower than the previous simulation, based on the fixed effect model (while for SYMPTOMATIC and SLIT we have no differences). The evolution of the total cost for the SCIT arm, in the case of the random effects model, is reported below:

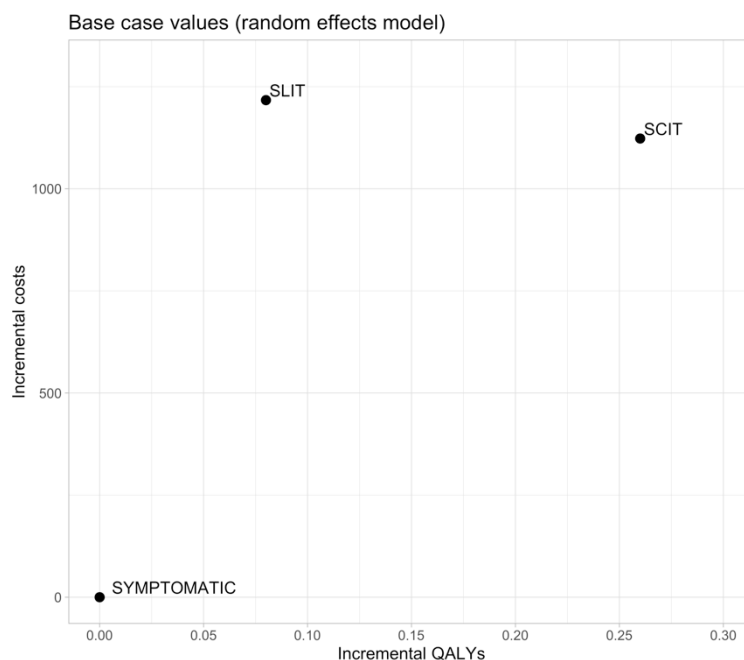
```
> outSCIT_cost
# A tibble: 10 x 4
  costCycleUndsc costCycleDsc costCumUndsc costCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1      781360      781360      781360      781360
2     412435.     398488.     1193795.     1179848.
3     223845.     208962.     1417640.     1388810.
4      10772.       9716.     1428412.     1398526.
5      13126.      11439.     1441539.     1409964.
6      15467.      13023.     1457005.     1422987.
7      17795.      14476.     1474800.     1437463.
```

8	20110.	15806.	1494910.	1453269.
9	22411.	17020.	1517321.	1470289.
10	24700.	18123.	1542022.	1488412.

Finally, here are the ICERs and their representation in the cost-effectiveness plane:

```
> tempICER
```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.08	1217	15212
SCIT	0.26	1123	4319



As we can see, the greater effectiveness of SCIT in the random effects model is immediately reflected in the ICER: in this scenario, we must be willing to pay ‘only’ 4320 Eur per each additional QALY for SCIT to be cost-effective with respect to symptomatic.

2. Scenario: No difference between SCIT and SLIT (fixed effects model)

The sense of this scenario is easily understood: we are assuming that there is no difference in effectiveness between SCIT and SLIT. In this way, based on the fixed effect model, we have the following ICERs:

```
> tempICER
```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.08	1217	15212
SCIT	0.08	1256	15700

In this case, SLIT immunotherapy is slightly more cost-effective as a result of the higher number of dropouts.

3. No clinical benefit after premature discontinuation (fixed effects models)

This scenario is the most unfavourable for immunotherapy, as we hypothesize that the highest level of utility in the two arms SCIT and SLIT (higher than the SYMPTOMATIC arm) is reached only after completing a full cycle of three years of therapy (i.e. from $t = 3$ onwards), while in $t = 0,1,2$ the utilities are at the same level as the SYMPTOMATIC arm, since no significant clinical improvement on symptoms is induced. Moreover, for all patients who discontinue therapy (i.e. before completing a full cycle of three years), the clinical benefit remain at the same level as SYMPTOMATIC for the entire time horizon of the simulation, since a purely symptomatic therapy is never discontinued in any case.

We show below the utilities for the SYMPTOMATIC arms (they are at the same level as the base case):

```
> # SYMPTOMATIC
> qaly_NoAIT_NoAsthma_SYMPTOMATIC <- (10/12) * 1 + (2/12) *
age_adjusted_utilities[1, 2]
> qaly_NoAIT_NoAsthma_SYMPTOMATIC
[1] 0.9567
> qaly_NoAIT_Asthma_SYMPTOMATIC <- ageasthma_adjusted_utilities[1, 2]
> qaly_NoAIT_Asthma_SYMPTOMATIC
[1] 0.5461
> qaly_Death <- 0
```

while for the SCIT arm, according to the assumptions made, we have:

```
> qaly_NoAsthma_SCIT <- c(rep((10/12) * 1 + (2/12) * age_adjusted_utilities[1, 2], 3),
+ (10/12) * 1 + (2/12) * rep(age_adjusted_utilities[5, 2], n - 2))
> qaly_NoAsthma_SCIT
[1] 0.95670 0.95670 0.95670 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805 0.96805
> qaly_Asthma_SCIT <- c(rep(ageasthma_adjusted_utilities[1, 2], 3),
rep(ageasthma_adjusted_utilities[5, 2], n - 2))
> qaly_Asthma_SCIT
[1] 0.5461 0.5461 0.5461 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964
> # in caso di discontinuazione
> qaly_NoAsthma_NoSCIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[1, 2], n + 1)
> qaly_NoAsthma_NoSCIT
[1] 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567
> qaly_Asthma_NoSCIT <- rep(ageasthma_adjusted_utilities[1, 2], n + 1)
> qaly_Asthma_NoSCIT
[1] 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461
```

Similarly, in the SLIT arm we have the following utilities:

```
> qaly_NoAsthma_SLIT <- c(rep((10/12) * 1 + (2/12) * age_adjusted_utilities[1, 2], 3),
+ (10/12) * 1 + (2/12) * rep(age_adjusted_utilities[3, 2], n - 2))
> qaly_NoAsthma_SLIT
[1] 0.95670 0.95670 0.95670 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485 0.96485
> qaly_Asthma_SLIT <- c(rep(ageasthma_adjusted_utilities[1, 2], 3),
rep(ageasthma_adjusted_utilities[3, 2], n - 2))
> qaly_Asthma_SLIT
[1] 0.5461 0.5461 0.5461 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822
> # in caso di discontinuazione
> qaly_NoAsthma_NoSLIT <- rep((10/12) * 1 + (2/12) * age_adjusted_utilities[1, 2], n + 1)
> qaly_NoAsthma_NoSLIT
[1] 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567 0.9567
> qaly_Asthma_NoSLIT <- rep(ageasthma_adjusted_utilities[1, 2], n + 1)
```

```
> qaly_Asthma_NoSLIT
[1] 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461 0.5461
```

The evolution of cohorts along the Markovian cycles is obviously the same as in the base case, and also the trajectory of costs is identical. On the other hand, the evolution of the QALY becomes different, and it is superimposable, both for SCIT and SLIT, to that of the SYMPTOMATIC (due to the high overall rate of discontinuations, which does not allow to obtain a stable utility gain with respect to the SYMPTOMATIC arm):

```
> outSYMPTOMATIC_qaly
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1         957.         957.         957.         957.
2         954.         922.        1911.        1879.
3         952.         888.        2863.        2767.
4         949.         856.        3812.        3623.
5         947.         825.        4759.        4448.
6         944.         795.        5703.        5243.
7         942.         766.        6645.        6010.
8         940.         738.        7585.        6748.
9         937.         712.        8522.        7460.
10        935.         686.        9456.        8146.

> outSCIT_qaly
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1         957.         957.         957.         957.
2         955.         922.        1911.        1879.
3         952.         889.        2864.        2768.
4         950.         857.        3814.        3625.
5         948.         826.        4762.        4452.
6         946.         796.        5708.        5248.
7         944.         768.        6652.        6016.
8         942.         740.        7593.        6756.
9         939.         713.        8533.        7469.
10        937.         688.        9470.        8157.

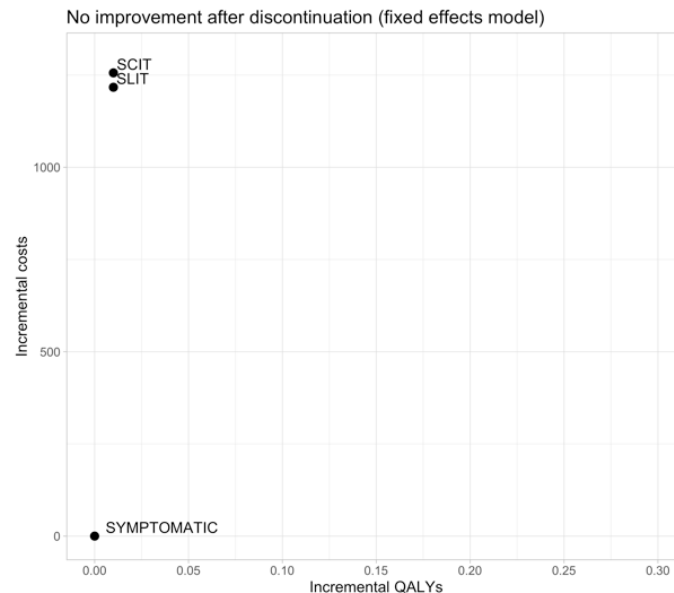
> outSLIT_qaly
# A tibble: 10 x 4
  qalyCycleUndsc qalyCycleDsc qalyCumUndsc qalyCumDsc
      <dbl>         <dbl>         <dbl>         <dbl>
1         957.         957.         957.         957.
2         954.         922.        1911.        1879.
3         952.         889.        2863.        2768.
4         950.         857.        3813.        3624.
5         948.         826.        4761.        4450.
6         945.         796.        5706.        5246.
7         943.         767.        6649.        6013.
8         941.         739.        7590.        6752.
9         938.         713.        8528.        7465.
10        936.         687.        9464.        8152.
```

The fact that the costs remain unchanged, while the incremental utilities increases very little, is immediately reflected in the ICERs:

```
> tempICER
```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.01	1217	121700
SCIT	0.01	1256	125600

Both forms of immunotherapy become impractical: in fact, we should be willing to spend more than 120000 Eur to obtain an average gain of 1 QALY per patient (over the considered time horizon).



4. Scenario: No AIT preventive effects on asthma (fixed effects model)

This scenario is based on the fixed effect model: the only substantial difference is that we are assuming that immunotherapy is not more effective than the purely symptomatic therapy in preventing progression to asthma. This assumption amounts to set:

```
> RRAitAsthma
[1] 1
```

whereas in the previous cases this relative risk was set equal to 0.505 (with a reduction of about 50% of the risk of progression towards asthma). For the SCIT arm, the transition probability that we have calculated at page 12 becomes:

```
> round_preserve_sum(0.74 * prAsthma1yr + 0.26 * (1.000 * prAsthma1yr), 5)
[1] 0.00463
```

and we get the same value for SLIT arm (see the value calculated on page 17 with RR = 0.505):

```
> round_preserve_sum(0.85 * prAsthma1yr + 0.15 * (1.000 * prAsthma1yr), 5)
[1] 0.00463
```

The evolution of the cohorts reflects, for both SCIT and SLIT this increased risk (while for SYMPTOMATIC the evolution is, of course, identical):

- SYMPTOMATIC

```
> outSYMPTOMATIC
# A tibble: 10 x 4
  Cycle `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl> <dbl>
1     0      1000         0     0
2     1       995.       4.63 0.615
3     2       990.       9.23 1.23
4     3       984.      13.8 1.85
5     4       979.      18.3 2.47
6     5       974.      22.9 3.08
7     6       969.      27.3 3.70
8     7       964.      31.8 4.33
9     8       959.      36.2 4.95
10    9       954.      40.6 5.57
```

- SCIT

```
> outSCIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0      1000         0         0         0     0
2     1       462.       4.63       530       2.45 0.615
3     2       251.       4.68       735.       7.95 1.23
4     3         0         0       981.      17.2 1.85
5     4         0         0       976.      21.7 2.47
6     5         0         0       971.      26.2 3.09
7     6         0         0       966.      30.7 3.71
8     7         0         0       961.      35.1 4.33
9     8         0         0       956.      39.5 4.95
10    9         0         0       950.      43.9 5.58
```

- SLIT

```
> outSLIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0       480         0       520         0     0
2     1       241.       2.22       752.       3.50 0.615
3     2       145.       2.47       843.       8.28 1.23
4     3         0         0       983.      15.3 1.85
5     4         0         0       978.      19.8 2.47
6     5         0         0       973.      24.4 3.09
7     6         0         0       967.      28.8 3.71
8     7         0         0       962.      33.3 4.33
9     8         0         0       957.      37.7 4.95
10    9         0         0       952.      42.1 5.57
```

It is worth noting that, apparently paradoxically, at the end of the time horizon of the simulation, both SCIT and SLIT arms will have more asthmatic patients than the SYMPTOMATIC arm. In addition, the number of asthmatic patients of the SCIT arm is slightly higher than that of the SLIT arm. This can be explained on the basis of the following arguments:

- In the SCIT and SLIT arms, the transition to a state of established asthma occurs not only for patients receiving immunotherapy, but also for patients suspending immunotherapy (as a

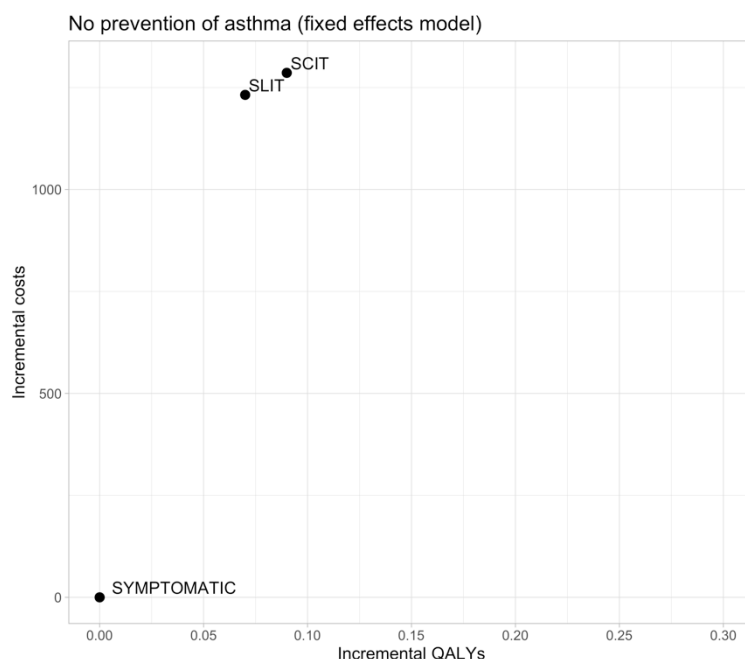
likely consequence of increased instability in the immune system induced by discontinuation of therapy). All this is incorporated in the fact that we have set to a value different from 0 the probability of transition $\Pr(AIT + No\ Asthma \rightarrow No\ AIT + Asthma)$: see the discussion on pag. 9. As long as the effectiveness of immunotherapy in terms of asthma prevention is greater than that of purely symptomatic therapy, this negative effect is hidden by this greater effectiveness: on the contrary, if we suppose that the effectiveness of immunotherapy in terms of prevention of asthma is comparable to that of a purely symptomatic therapy, as long as the immunotherapy is administered we will have a higher quota of asthmatic patients than that we observe when a symptomatic therapy only is administered. For example, up to $t=3$ we have 17.2 asthmatic patients in the SCIT arm and 15.3 in the SLIT arm, versus 13.8 patients in the SYMPTOMATIC arm. From $t=3$ the incidence rate of asthma in SCIT and SLIT returns exactly to the same level as the SYMPTOMATIC arm.

- If the immunotherapy has no superiority with respect to symptomatic therapy in terms of asthma prevention, both SCIT and SLIT becomes more harmful on average, since they induce on average more asthmatic patients than those we would observe with purely symptomatic therapy (although this is a very limited effect). The model, therefore, automatically handles the fact that where we have a lower compliance (in the case of SLIT) we will have on average fewer asthmatic patients.

We go directly to the cost-effectiveness plan and the corresponding ICERs:

```
> tempICER
      Inc_QALYs Inc_Costs ICERs
SYMPTOMATIC      0.00         0   NaN
SLIT              0.07      1232 17600
SCIT              0.09      1286 14289
```

Given the slightly higher costs that have to be borne (given the greater number of asthmatic patients), with SCIT we must be willing to spend about EUR 14300 for each QALY earned over the considered time horizon.



5. Scenario: No asthma prevention by SLIT (fixed effects model)

This scenario is based on the fixed effects model: in this case we are hypothesizing that SCIT only has a greater efficacy than a purely symptomatic therapy in preventing progression towards asthma, while the effectiveness of SLIT is comparable to that of the symptomatic therapy. The following basic input parameters are modified accordingly:

```
> RRAitAsthmaSCIT
[1] 0.505
> RRAitAsthmaSLIT
[1] 1
```

The parameters calculated on page 12 and page 17 will be, respectively:

```
> round_preserve_sum(0.74 * prAsthma1yr + 0.26 * (0.505 * prAsthma1yr), 5)
[1] 0.00403
```

for SCIT, while for SLIT we have:

```
> round_preserve_sum(0.85 * prAsthma1yr + 0.15 * (1.000 * prAsthma1yr), 5)
[1] 0.00463
```

Here is the evolution of the three cohorts (perfectly in line with what we expect):

```
> outSYMPTOMATIC
# A tibble: 10 x 4
  Cycle `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl> <dbl>
1     0      1000         0     0
2     1       995.       4.63 0.615
3     2       990.       9.23 1.23
4     3       984.      13.8 1.85
5     4       979.      18.3 2.47
6     5       974.      22.9 3.08
```

```

7      6      969.      27.3  3.70
8      7      964.      31.8  4.33
9      8      959.      36.2  4.95
10     9      954.      40.6  5.57
> outSCIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0      1000         0         0         0     0
2     1      466.       2.34      530       1.24 0.615
3     2      254.       2.37     737.       5.23 1.23
4     3         0         0     987.      11.2 1.85
5     4         0         0     982.      15.1 2.46
6     5         0         0     978.      19.1 3.08
7     6         0         0     973.      23.0 3.70
8     7         0         0     969.      26.9 4.32
9     8         0         0     964.      30.8 4.94
10    9         0         0     960.      34.6 5.56
> outSLIT
# A tibble: 10 x 6
  Cycle `AIT+No Asthma` `AIT+Asthma` `No AIT+No Asthma` `No AIT+Asthma` Death
  <int>      <dbl>      <dbl>      <dbl>      <dbl> <dbl>
1     0       480         0       520         0     0
2     1      241.       2.22     752.       3.50 0.615
3     2      145.       2.47     843.       8.28 1.23
4     3         0         0     983.      15.3 1.85
5     4         0         0     978.      19.8 2.47
6     5         0         0     973.      24.4 3.09
7     6         0         0     967.      28.8 3.71
8     7         0         0     962.      33.3 4.33
9     8         0         0     957.      37.7 4.95
10    9         0         0     952.      42.1 5.57

```

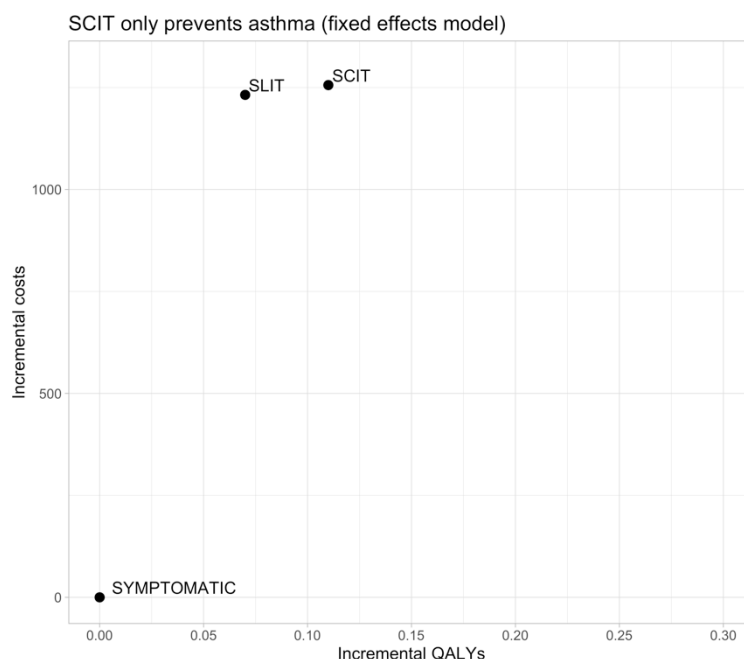
We have the following ICERs:

```

> tempICER
      Inc_QALYs Inc_Costs ICERs
SYMPTOMATIC      0.00         0   NaN
SLIT              0.07      1232 17600
SCIT              0.11      1256 11418

```

The lower costs attributable to asthma and the greater differential increase in QALY earned per patient, make SCIT significantly more cost-effective than the baseline case. We show the cost-effectiveness plane below:



6. Full societal perspective (fixed effects model)

In this scenario, unlike the baseline scenario, the SCIT immunotherapy generates a number of additional costs, namely:

- Indirect non-healthcare costs due to the temporary interruption of work for administering therapy.
- Direct transportation costs.

The evolution of both states and QALYs will be identical to that of the base case. Obviously the evolution of the costs for the SCIT arm changes, as in this case the costs are calculated according to the following function that, as it can be easily verified, includes the two cost components that we have listed above:

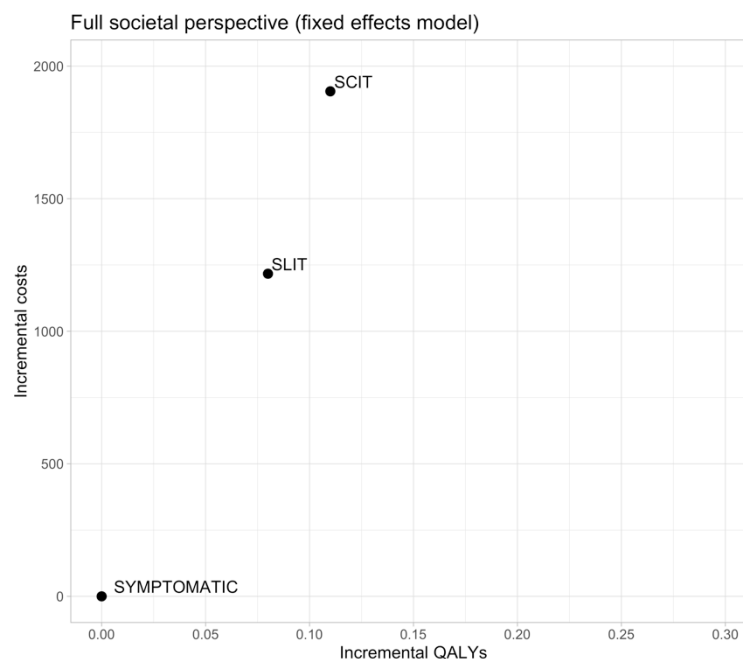
```
> outSCIT <-
+   outSCIT %>% mutate(
+     costCycleUndsc = (costAitSCIT * `AIT+No Asthma`) +
+       (costAitSCIT * `AIT+Asthma`) +
+       ((0.5 * costAitSCIT) * `No AIT+No Asthma_disc`) +
+       ((0.5 * costAitSCIT) * `No AIT+Asthma_disc`) +
+       ((costAsthmaDirect) * (`AIT+Asthma` + `No AIT+Asthma`)) +
+       ((costHealthSCIT) * (`AIT+No Asthma` + `AIT+Asthma`)) +
+       ((costProductivitySCIT) * (`AIT+No Asthma` + `AIT+Asthma`)) +
+       ((costTransportSCIT) * (`AIT+No Asthma` + `AIT+Asthma`)) +
+       (1000 - Death) * costSeasonalSCIT +
+       0 * Death
+   )
```

For this scenario, we have the following ICERs:

```
> tempICER
```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.08	1217	15212
SCIT	0.11	1905	17318

For this scenario the relationship between SCIT and SLIT is reversed: both SCIT and SLIT continue to be cost-effective compared to SYMPTOMATIC, but for this to happen, with SLIT we must be willing to spend about 15200 EUR for 1 additional QALY, while with SCIT we must spend about 17300 EUR.



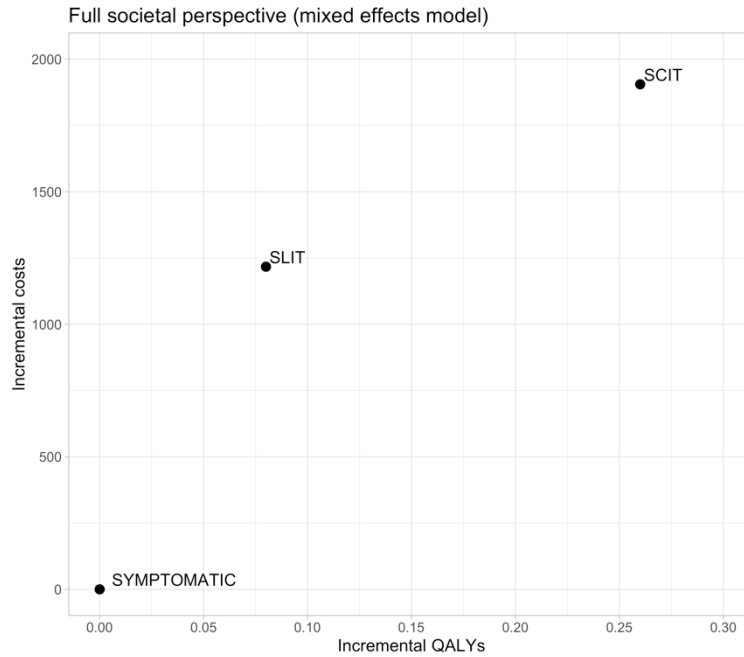
7. Full societal perspective (random effects model)

This scenario coincides with the previous one in terms of costs. The difference lies in the fact that the utilities now calculated on the basis of the random effect model (they are the same as those used for scenario 1). We go directly to the analysis of ICERs:

```
> tempICER
```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.08	1217	15212
SCIT	0.26	1905	7327

The difference in utility level between SCIT and SLIT estimated through the random effects model, makes SCIT cost-effective compared to SLIT, since the additional QALYs gained through SCIT are approximately three times higher than those gained through SLIT. With SCIT, in this scenario, we must be willing to spend about 7300 Eur in order for the therapy to be cost-effective, compared to 15200 that we must be willing to spend with SLIT.



8. Scenario: Symptoms only during the peak of the pollen season (15 days, fixed effects models)

In this scenario, the improvement induced by immunotherapy compared to a purely symptomatic therapy is limited to a 15-day peak of the pollen season. On the other days of the pollen season, the utility of immunotherapy is at the same level as that of the purely symptomatic therapy. If, for example, we refer to the SCIT arm, the QALYs gained per year per patient are calculated as:

$$QALY = \frac{10}{12} \times 1 + \frac{1.5}{12} \text{utility}_{\text{SYMPTOMATIC}} + \frac{0.5}{12} \text{utility}_{\text{SCIT}}$$

Below, we show the QALYs gained per year per patient, for both SCIT and SLIT:

```
# SCIT
> qaly_NoAsthma_SCIT <- rep((10/12) * 1 + (1.5/12) * age_adjusted_utilities[1, 2] +
+ (0.5/12) * age_adjusted_utilities[5, 2], n + 1)
> qaly_NoAsthma_SCIT
[1] 0.9595375 0.9595375 0.9595375 0.9595375 0.9595375 0.9595375 0.9595375 0.9595375 0.9595375
0.9595375 0.9595375
> qaly_Asthma_SCIT <- rep(ageasthma_adjusted_utilities[5, 2], n + 1)
> qaly_Asthma_SCIT
[1] 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964 0.5964
> # in caso di discontinuazione
> qaly_NoAsthma_NoSCIT <- rep((10/12) * 1 + (1.5/12) * age_adjusted_utilities[1, 2] +
+ (0.5/12) * age_adjusted_utilities[5, 2], n + 1)
> qaly_Asthma_NoSCIT <- rep(ageasthma_adjusted_utilities[5, 2], n + 1)

# SLIT
> qaly_NoAsthma_SLIT <- rep((10/12) * 1 + (1.5/12) * age_adjusted_utilities[1, 2] +
+ (0.5/12) * age_adjusted_utilities[3, 2], n + 1)
```

```

> qaly_NoAsthma_SLIT
[1] 0.9587375 0.9587375 0.9587375 0.9587375 0.9587375 0.9587375 0.9587375 0.9587375
0.9587375 0.9587375
> qaly_Asthma_SLIT <- rep(ageasthma_adjusted_utilities[3, 2], n + 1)
> qaly_Asthma_SLIT
[1] 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822 0.5822
> # in caso di discontinuazione
> qaly_NoAsthma_NoSLIT <- rep((10/12) * 1 + (1.5/12) * age_adjusted_utilities[1, 2] +
+ (0.5/12) * age_adjusted_utilities[3, 2], n + 1)
> qaly_Asthma_NoSLIT <- rep(ageasthma_adjusted_utilities[3, 2], n + 1)

```

We report incremental QALYs and costs, and the corresponding ICERs:

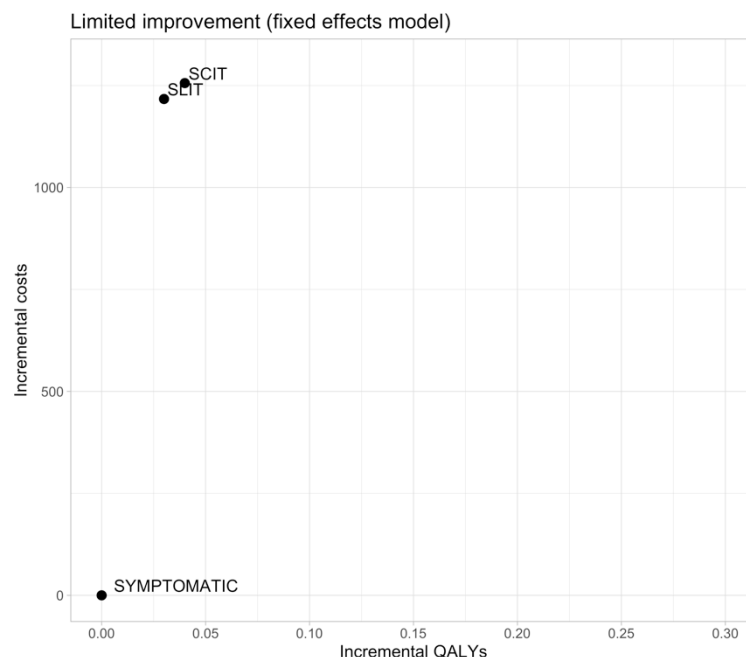
```

> tempICER

```

	Inc_QALYs	Inc_Costs	ICERs
SYMPTOMATIC	0.00	0	NaN
SLIT	0.03	1217	40567
SCIT	0.04	1256	31400

As we expected, ICERs have increased significantly compared to the base case. For SCIT we have to be willing to spend about 31000 Eur to get 1 additional QALY, while for SLIT we have to be willing to spend about 40000 Eur. Even in this clinical scenario, immunotherapy seems to be decidedly impractical from an economic point of view. Here it is the relative cost-effectiveness plan:



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