TECHNOLOGY REVIEW (MINI-HTA)

SUBLINGUAL IMMUNOTHERAPY (SLIT) FOR ATOPY (ALLERGIC RHINITIS, ECZEMA AND ASTHMA)

Malaysian Health Technology Assessment Section (MaHTAS)

Medical Development Division

Ministry of Health Malaysia

003/2022

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Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

eISSN:

SUGGESTED CITATION: Ana Fizalinda AS, Maharita AR, Ku Hasni NH. Sublingual Immunotherapy for atopy (allergic rhinitis, eczema and asthma) Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2021. p. Report No.: 003/2022. eISSN:

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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EXECUTIVE SUMMARY

Background

Atopy refers to the genetic tendency to develop allergic diseases such as allergic rhinitis, asthma and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens and food allergens. The average prevalence of allergic rhinitis was reported as 7.1% in Malaysian adults and 8.7% among both adults and children in an Asia-Pacific study. Meanwhile, the prevalence of asthma in Malaysia according to National Health Morbidity Survey Malaysia 2011 was 6.4%. In Malaysia, according to International Study of Asthma and Allergies in Childhood (ISAAC), the 12-month prevalence of atopic dermatitis (eczema) among Malaysian children has risen from 9.5% in ISAAC-1 (1994 - 1995) to 12.6% in ISAAC-3 (2002 - 2003), with an increase of 0.49% yearly.

Allergen immunotherapy (AIT) is a treatment involving the administration of increasing doses of clinically relevant allergens to patients who have allergic disease. The effect of AIT has been clinically confirmed in the cases of allergic asthma, allergic rhinitis, and hymenoptera hypersensitivity. Allergen-specific immunotherapy can not only reduce allergic symptoms but also induce the clinical remission of patients from IgE-mediated allergic diseases including allergic rhinitis (AR), atopic asthma and venom allergy. It consists of several routes of administration such as subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), and the demand for SLIT is increasing rapidly. Allergen-specific sublingual and subcutaneous immunotherapy is thought to work primarily by inducing T-cell tolerance and promoting regulatory T-cells, which secrete the suppressive cytokines interleukin (IL)-10 and transforming growth factor (TGF)- beta. This in turn leads to production of the non-inflammatory immunoglobulins IgG4 and IgA, thus directing the immune response away from the inflammatory, atopic IgE response. Among the allergens, HDM allergy was shown to be common in Malaysia and the majority of office workers were sensitised to HDM allergens.

In Malaysia, conventional treatment for allergic rhinitis includes oral or topical antihistamines and intranasal corticosteroids as required, with the goal of treatment being symptomatic relief. Due to the advanced technology and recent updates, allergen immunotherapy offers an alternative therapy to provide relief of allergic rhinitis which subsequently will reduce the symptoms of atopy. It claimed induces long term remissions after discontinuation and prevents new sensitization. Hence, this review was conducted upon request by our senior otolaryngologist from Hospital Sultanah Bahiyah, Alor Setar to review the best current scientific evidence SLIT on treatment of atopy.

Objective/aim

To review the best current scientific evidence on effectiveness/efficacy, safety, cost/cost-effectiveness and organisational issues related to sublingual immunotherapy (SLIT) for the treatment of atopy (allergic rhinitis, eczema and asthma).

Results and conclusions

From a total of 722 titles identified through the Ovid and PubMed interfaces, nine studies were included in this review which consisted of seven systematic review of randomised controlled trials (RCTs) which three were from Cochrane reviews, and two economic papers. The included articles were published between 2013 and 2021. Most studies were conducted in United States of America, European countries, United Kingdom, Japan and Korea.

Allergic Rhinitis (AR):

Based on retrievable evidence, there was sufficient good level of evidence retrieved on SLIT for allergic rhinitis. In term of effectiveness (reducing symptoms and medication scores), evidence demonstrated that there was significant reduction in symptoms for SLIT therapy when compared with placebo. Furthermore, when measured by subjective method using total nasal symptom and medication score (TNSMSs) results were found significantly lower in the SLIT group than in the placebo group; which is 30% reduction versus placebo group, suggesting clinically relevant efficacy. A benefit from both subcutaneous immunotherapy (SCIT) and SLIT compared with placebo has been consistently demonstrated and therefore suggesting a moderate effect size in favor of the active treatment, for all patient-centered outcomes. However, a study by Tie K in 2021 found that no significant differences for symptom score between SCIT and SLIT which showed that SCIT and SLIT are comparably effective treatments for adults with allergic rhinitis/ conjunctivitis (AR/C). Recent network meta-analysis (NMA) by Kim JY, showed that from 26 trials for symptom score and 18 for the medication score, a direct pairwise meta-analysis, found a significant reduction of the symptom score was observed for all immunotherapy modalities compared with the placebo but there was no significant difference in the symptom score between SLIT drop and SLIT tablet or SCIT. From this NMA also found that SCIT may be more effective than SLIT drops or tablets in controlling symptoms of allergic rhinitis.

In term of safety, SLIT has been proven to be a safe route of administration. The most common AEs were mouth edema, throat irritation, headache, oral pruritus and ear pruritus and most of the symptoms are mild and required no treatment.

Asthma:

Based on retrievable evidence, there was sufficient good level of evidence retrieved on SLIT for asthma in term of controlling event of exacerbations requiring an emergency department (ED) or hospital visit. The pooled estimate from these studies suggests SLIT may reduce exacerbations compared with placebo or usual care, but the evidence is very uncertain (OR 0.35, 95% (CI) 0.10 to 1.20) due to very low-certainty evidence. In term of asthma symptom and medication scores SLIT showed a trend of SLIT benefit over placebo or usual care. SLIT likely does not increase severe adverse events (SAEs) compared with placebo or usual care and SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm.

Atopic Dermatitis (Eczema) - AE:

Based on retrievable evidence, there was sufficient good level of evidence retrieved on SLIT for AE in term of participant- or parent-reported global assessment of disease severity at the

end of treatment, and the results showed inconclusive (10 trials of house dust mite (HDM). Meanwhile, for participant- or parent-reported specific symptoms of eczema, by subjective measures which includes two trials (n= 184) did not find that the specific immunotherapy (either SCIT or SLIT) improved SCORAD or sleep disturbance when compared to placebo. There is no retrieved evidence on safety SLIT for atopic dermatitis (eczema).

Cost/Cost-effectiveness
A HTA report in 2013 by Meadow A which includes of 14 economic evaluations (EEs) and two reviews of EEs resulted that both SCIT and SLIT were more beneficial than symptomatic treatment (ST), and in some cases also become less costly than ST over time. From this review, there were studies expressed results as incremental cost-effectiveness ratios (ICERs), both SCIT and SLIT were found to be cost-effective at thresholds of £20,000 per quality-adjusted life-year (QALY).

Another economic evaluations paper by Hardin FM in 2021 showed that when compared to SCIT, SLIT is economically favourable and should be considered the financially conscious option for patients with 40% adherence to therapy. By assuming an 80% compliance rate with allergen immunotherapy (AITs) and an estimated efficacy (assumed to be clinically significant improvement in symptoms) of 70% for SLIT and 80% for SCIT, at the 12-month mark, the baseline total cost to the payer of SLIT per successful treatment outcome is USD $1196 while the charge of SCIT per successful treatment outcome is USD $2691.

In our own calculation, based on the cost calculation, the estimated annual cost of allergy immunotherapy HDM SLIT tablet per patient is between MYR 4,823.00 to MYR 5,918.00. To achieve the disease modification, a recommended treatment of three years will incur an estimated cost between MYR13,729.00 to MYR 17,014.00 per patient. Since the recommended indication of this tablet is for those who are not adequately controlled with standard pharmacotherapy, the expected total expenditure will be based on the prevalence of this population.

Organisational:
There was no guideline retrieved which specifically addressed the use of allergen immunotherapy. However, the chronology of SLIT begins in 1998 when WHO recognised that SLIT was a promising alternate mode of immunotherapy and encouraged continued clinical investigation into this form of treatment. Subsequently, in 2001 the ARIA guidelines have documented on SLIT, and have consistently supported the effectiveness and safety of SLIT throughout subsequent updates. Following that in 2009) by their position paper - World Allergy Organization (WAO) published their opinion that the cumulative evidence showed SLIT represented a viable alternative to SCIT and also encouraged continued clinical investigation to characterise optimal techniques .

Methods
Electronic databases were searched through the Ovid interface; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to March 31, 2022. Searches were also run in PubMed, INAHTA and Cochrane Library. Google was used to

search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on March 31, 2022.

Conclusions

Based from the review sublingual immunotherapy (SLIT) showed a significant benefit in term of reducing symptoms and medications used, but inconclusive results when comparing between sub cutaneous (SCIT) and sub lingual in treating patients with AR. Adverse events were common with both SCIT and SLIT and majority were local reactions at the point of administration and resolved spontaneously without treatment.

For patients with asthma, there was uncertain benefit showed for reducing the exacerbations/ hospital ED visits and medications score, but SLIT demonstrated safe option for people with well-controlled mild-to-moderate asthma and rhinitis.

Meanwhile, for patients with AE, the included studies showed inconclusive results to suggest the use of SLIT as an option treatment.

In term of cost effectiveness, the were results SLIT is more economically when compared to placebo and other usual care. Based on the our cost calculation, the estimated annual cost of allergy immunotherapy HDM SLIT tablet per patient is between MYR 4,823.00 to MYR 5,918.00. To achieve the disease modification, a recommended treatment of three years will incur an estimated cost between MYR13,729.00 to MYR 17,014.00 per patient. Since the recommended indication of this tablet is for those who are not adequately controlled with standard pharmacotherapy, the expected total expenditure will be based on the prevalence of this population.

TABLE OF CONTENTS

ABBREVIATION

AEs	Adverse events
AIT	Allergen immunotherapy
AR	Allergic Rhinitis
AD	Atopic dermatitis
AE	Atopic Eczema
AR/C	allergic rhinitis or rhinoconjunctivitis
AASS	Average Adjusted Symptom Score
ARIA	Allergic Rhinitis and its Impact on Asthma
CASP	Critical Appraisal Skills Programme
CPG	Clinical Practice Guideline
CI	Confidence Interval
DBRCTS	double blind randomised controlled trials
EES	economic evaluations
GBD	Global Burden of Disease
GINA	Global Initiative for Asthma
HTA	Health Technology Assessment
HDM	House Dust Mite
INAHTA	The International Network of Agencies for Health Technology Assessment
ISAAC	International Study of Asthma and Allergies in Childhood
JCP	Japanese cedar pollinosis
KSS	Newcastle-Ottawa Scale
NHMS	National Health Morbidity Survey
NICE	The National Institute for Health and Care Excellence
QOL	Quality of Life
RCT	Randomised controlled trial
RoB 2	Cochrane Risk-of-Bias Tool for Randomised Trials
SCORAD	SCORing Atopic Dermatitis
SIT	specific allergen immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SR	Systematic review
TCRS	total combined rhinitis score
TNSMSs	total nasal symptom and medication score
USFDA	United States Food and Drugs Administration
USA	United States of America
UK	United Kingdom
VAS	Visual Analog Score
WHO	World Health Organization

1.0 BACKGROUND

Atopy refers to the genetic tendency to develop allergic diseases such as allergic rhinitis (AR), asthma and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens and food allergens.

Allergen immunotherapy (AIT) is a treatment involving the administration of increasing doses of clinically relevant allergens to patients who have allergic disease with the aim of reducing sensitivity and minimising future symptomatic reaction on natural exposure to the causative agent.[1,2] The effect of AIT has been clinically confirmed in the cases of allergic asthma, allergic rhinitis, and hymenoptera hypersensitivity. Allergen-specific immunotherapy can not only reduce allergic symptoms but also induce the clinical remission of patients from IgE-mediated allergic diseases including AR, asthma and venom allergy.[1] Allergen immunotherapy may be administered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT).[2] Allergen-specific SLIT and SCIT is thought to work primarily by inducing T-cell tolerance and promoting regulatory T-cells, which secrete the suppressive cytokines interleukin (IL)-10 and transforming growth factor (TGF)- beta. This in turn leads to production of the non-inflammatory immunoglobulins IgG4 and IgA, thus directing the immune response away from the inflammatory, atopic IgE response.[2,3,4] Among the allergens, house dust mite (HDM) allergy was shown to be common in Malaysia and the majority of office workers were sensitised to HDM allergens.[5] Sublingual immunotherapy (SLIT) is an alternative way to treat allergies without injections. The sublingual route of administration may offer advantages over the subcutaneous route in terms of acceptability to patients. The oral cavity is a naturally 'tolerogenic environment', as it frequently encounters foreign proteins without the provocation of a local or systemic immune response, and therefore may be an appropriate site for delivery of a treatment intended to produce immune tolerance. Currently, the only forms of SLIT approved by the FDA are tablets for ragweed, northern pasture grasses like timothy and dust mites.[6]

Burden of disease

Estimates of allergy rhinitis (AR) prevalence are as high as 42%, affecting approximately 58 million people in the United States of America (USA). Allergy rhinitis also has a significant economic burden with both direct and indirect costs, including loss of work productivity and nearly twice as many average annual prescriptions for affected patients.[6] Asthma and rhinitis are common respiratory diseases which are increasing globally, especially among the younger population in Asian cities. The prevalence of rhinitis can be up to 45% in children and adolescents in low and middle-income countries in Asia. However, there is a large variation of asthma among adults between Asian countries, the prevalence ranging from 0.7% to 11.9%. One Asia-Pacific study reported that the average prevalence of allergic rhinitis was 8.7% among both children and adults. The prevalence of doctor diagnosed allergic rhinitis among children and adults ranged from 2.5% in Philipines to 12.3% in Vietnam. These large variation indicates that environmental factors could play a role in the occurrence of asthma and rhinitis in Asia.[4]

Sensitization to HDM and cat allergens may cause asthma and rhinitis. House dust mite allergens are a major indoor risk factor for asthma triggering respiratory symptoms in many Asia countries. Most epidemiology studies on HDM and cat allergens are from home environments and few studies are available on allergens levels in office dust.[4] Atopic dermatitis (AD)/eczema is a chronic, relapsing inflammatory skin condition affecting around 20% of children and up to 10% of adults in high-income countries.[7]

The average prevalence of allergic rhinitis was reported as 7.1% in Malaysian adults and 8.7% among both adults and children in an Asia-Pacific study. Meanwhile, the prevalence of asthma in Malaysia according to National Health Morbidity Survey Malaysia 2011 was 6.4%. In Malaysia, according to International Study of Asthma and Allergies in Childhood (ISAAC), the 12-month prevalence of atopic dermatitis (eczema) among Malaysian children has risen from 9.5% in ISAAC-1 (1994 - 1995) to 12.6% in ISAAC-3 (2002 - 2003), with an increase of 0.49% yearly.[8]

In Malaysia, conventional treatment for allergic rhinitis includes oral or topical antihistamines and intranasal corticosteroids as required, with the goal of treatment being symptomatic relief. Due to the advanced technology and recent updates, allergen immunotherapy offers an alternative therapy to provide relief of allergic rhinitis which subsequently will reduce the symptoms of atopy. It claimed induces long term remissions after discontinuation and prevents new sensitisation. Hence, this review was conducted upon request by our senior otolaryngologist from Hospital Sultanah Bahiyah, Alor Setar to review the best current scientific evidence SLIT on treatment of atopy.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of to assess the effectiveness, safety and cost-effectiveness of sublingual immunotherapy for atopy (allergic rhinitis, eczema and asthma).

3.0 TECHNICAL FEATURES

Figure 1: Examples of sublingual immunotherapy

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – March 2022
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2022
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to March 2022
- EBM Reviews – Health Technology Assessment – 1st Quarter 2022
- EBM Reviews - NHS Economic Evaluation Database - 1st Quarter 2022

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA

General databases such as Google was used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on humans. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 31 March 2022.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with allergic rhinitis, asthma, atopic dermatitis (eczema) House Dust Mite allergens
Interventions	Sublingual immunotherapy
Comparators	Subcutaneous immunotherapy Placebo Usual care/ standard treatment
Outcomes	Effectiveness: symptom reduction, medication score, combination symptom and medications, SCORAD, exacerbation Adverse effects, complications, safety issues, Cost-effectiveness, cost-utility, cost-minimisation, cost-analysis and economic evaluation

	Organisational –guidelines, recommendations
Study design	Health Technology Assessment (HTA), Systematic reviews (SR), Randomised control trials (RCTs), observational studies
Type of publication	English, full text articles

Exclusion criteria

Study design	Case report, survey, anecdotal, animal studies
Type of publication	Non-English

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 722 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2022), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2022), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2022), EBM Reviews-Health Technology Assessment (1st Quarter 2022), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2022) and PubMed. The last search was run on 31 March 2022. Additional articles were identified from reviewing the references of retrieved articles.

Twenty-five articles were identified from references of retrieved articles. After removal of 75 duplicates, 321 titles were screened. A total of 122 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 92 abstracts were found to be irrelevant. Twenty-one potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 21 full text articles, eight full text articles were included and 13 full text articles were excluded. (Figure 1). The review included eight studies which were consisted of six systematic review (three from Cochrane Library), one double blind RCTs with network meta-analysi, one RCT, one Health Technology Assessment (HTA) report and two studies were included for economic implication.

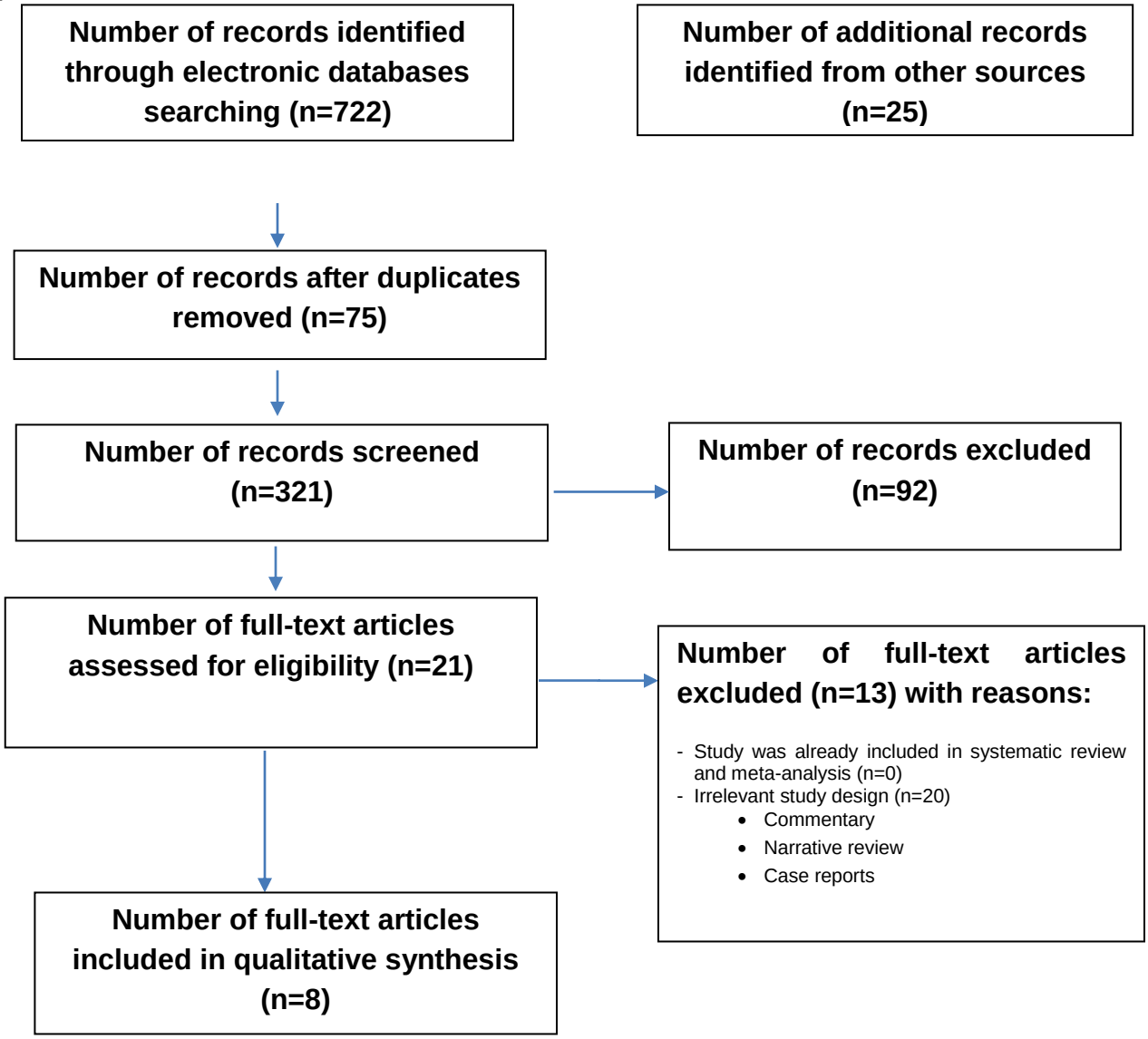
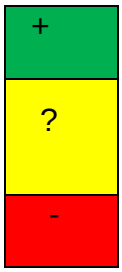


Figure 1: Flow chart of study selection

The included articles were published between 2010 and 2022. Most studies were conducted in European countries, USA, Japan and Korea.

5.1 Assessment of risk of bias in included studies

Risk of bias was assessed using Risk of Bias in Systematic reviews (ROBIS) for systematic review and meta-analysis and Cochrane Risk of Bias (ROB) 2.0 for RCT. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.



Indicates low risk of bias

indicates unclear risk of bias / some concerns

Indicates high risk of bias

Risk of bias assessment for included systematic review and meta-analysis

Three systematic review from Cochrane Library (Radulovic S, Fortescue R and Tam H) were rated to have an overall low risk of bias. All three studies had prespecified its clinical question and inclusion criteria for study eligibility. No language restriction were applied.

Table 3: Summary of risk of bias assessment for systematic review and meta-analysis using ROBIS

REVIEW	D1	D2	D3	D4	OVERALL
Radulovic S et al	+	+	+	+	+
Fortescue R et al	+	+	+	+	+
Tam H et al	+	+	+	+	+
Tie K et al	+	-	+	?	?
Kim JY et al	+	-	+	+	?

There was some concern regarding the method used to identify and select the studies. While the search terms were mentioned in the article, the full search strategy was not reported. However, the inclusion assessment, appraisal and data collection process were reported to have been conducted independently by at least two reviewers. The quantitative synthesis

(network meta-analysis) undertaken was considered appropriate. No detail was provided on statistical heterogeneity. The authors also did not state whether sensitivity analyses were used to assess the robustness of their findings. However, the included studies were reported to have comparative patients' demographic and baseline data.

Risk of bias assessment for included RCT

There is only one RCT study was assessed for the risk of bias. Masuyama S et al. was rated to have an overall low risk of bias. Random sequence generation and allocation concealment were performed adequately. There was some concern with the blinding process as it was not possible to blind the urologists who performing the treatment procedure or the sham procedure. This could introduce performance bias. Participants were reportedly blinded so there was low risk of bias for subjective measurements (urologic symptom scores, QoL, erectile function, ejaculatory function, minor adverse events). Blinding was considered not relevant for objective measurements (major adverse events, retreatment, acute urinary retention). Outcomes were analysed using intention to treat analysis. Nevertheless, the sexual function outcomes (erectile function and ejaculatory function) were measured in a limited subset of participants who were sexually active at baseline and during the follow-up period. Selective reporting was considered to have a low risk of bias as all prespecified outcomes were reported and analysed.

REVIEW	D1	D2	D3	D4	D5	OVERALL
Masuyama R et al.	+	+	+	+	+	+

Figure 2: Assessment of risk of bias of RCT (RoB2)

5.2 Effectiveness:

There were eight studies retrieved on the effectiveness of sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis, asthma and atopic dermatitis (eczema). Of the eight studies, three systematic review from Cochrane Library, one Health technology Assessment (HTA) report, one network meta-analysis, one systematic review with meta-analysis and one randomised controlled trials (RCTs). Five studies were related to the effectiveness sublingual immunotherapy while one study for asthma and atopic dermatitis each.

5.2.1 Sublingual immunotherapy for treatment allergic rhinitis

A systematic review of RCTs with meta-analysis by Tie K et al in in USA to determine whether SCIT or SLIT better in improving patient outcomes and quality of life (QOL) for adults with allergic rhinitis or rhinoconjunctivitis (AR/C) with or without mild to moderate asthma. Forty-six RCTs over 39 studies were included for the adjusted indirect comparisons, of which 13 RCTs analysed SCIT versus placebo, and 33 RCTs analysed SLIT versus placebo. The 46 RCTs were published between 2001 and 2019 and included single-center and multicenter studies that collected data from sites in Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Russia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, and USA. The most commonly documented allergens included birch, grass pollen, house dust mites, and ragweed pollen.[8]

In this review, they conducted two main statistical analyses for each outcome measure i.e.:

(i) a head-to-head comparison of SCIT versus SLIT (from RCTs directly comparing SCIT versus SLIT) and

(ii) (ii) an adjusted indirect comparison (from RCTs comparing SCIT versus placebo against RCTs comparing SLIT versus placebo)

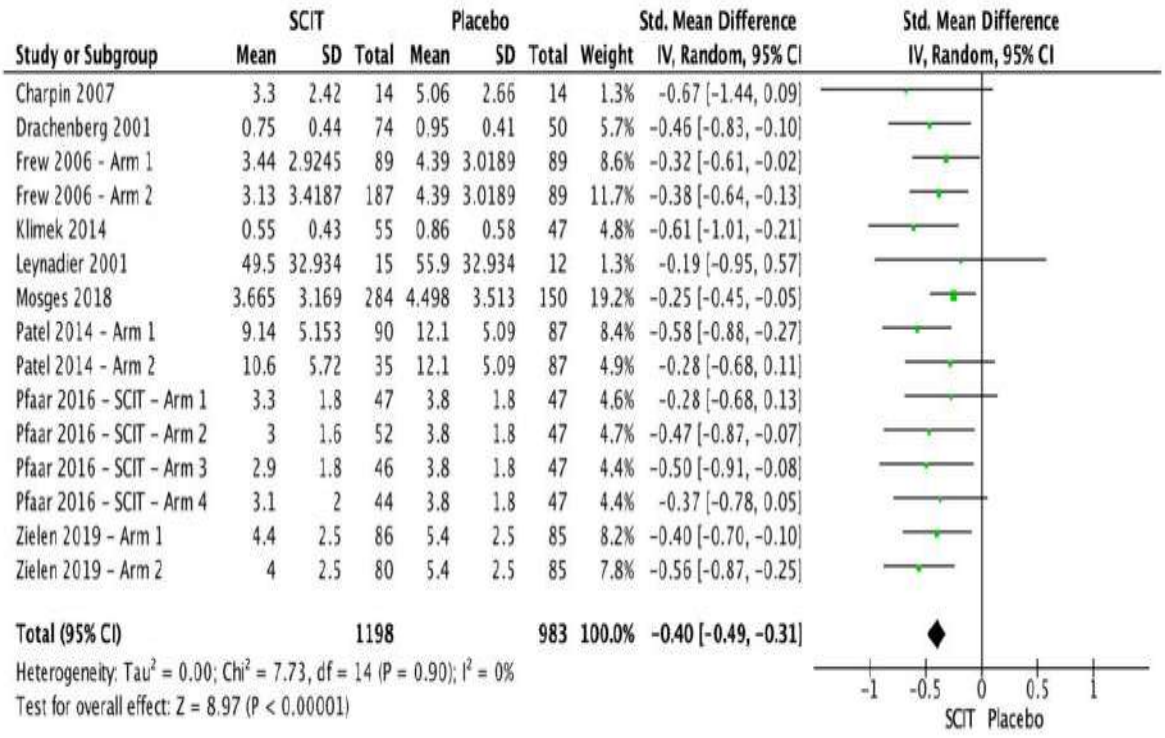
A meta-analysis with head-to-head comparison between SCIT versus SLIT which combined a total of seven head-to-head SCIT versus SLIT RCTs met qualitative synthesis criteria. There were not enough studies to carry out a direct head-to-head comparison meta-analysis for any outcome measure. None of the seven studies reported significant differences between SCIT and SLIT for any of their measured outcomes. By using adjusted indirect comparison between the pooled SCIT versus placebo demonstrated SMDs and MDs are reported as absolute values (positive favours SCIT) along with their associated CIs. Statistically significant results favouring SCIT were found for: **(see Figure 2)**[8, level- I]

- symptom score (SS) (SMD: 0.40; 95% CI: 0.31 to 0.49; 15 arms across nine studies; SCIT n = 1,198, placebo n = 983)
- medication score (MS) (SMD: 0.26; 95% CI: 0.14 to 0.39; seven arms across six studies; SCIT n = 656, placebo n = 409)
- combined symptom medication score (CSMS) (SMD: 0.42; 95% CI: 0.17 to 0.67; nine arms across seven studies; SCIT n = 1,004, placebo n = 781), and

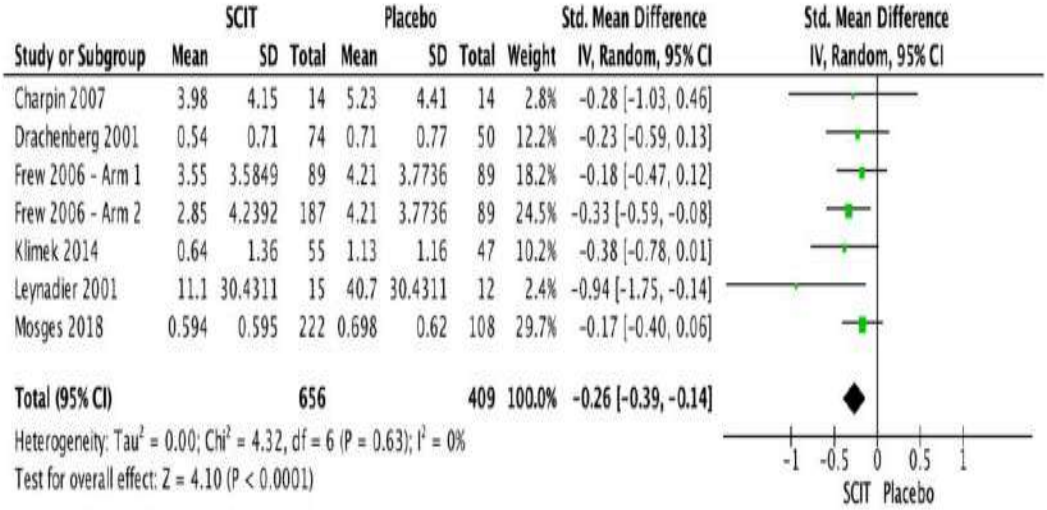
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score (MD: 0.24; 95% CI: 0.04 to 0.44; one arm across one study; SCIT n = 332, placebo n = 170).

Heterogeneity among studies varied for SS, MS, and CSMS. Because there was only one arm from one study for the RQLQ, no meta-analysis was performed, so heterogeneity is not applicable. [8, level- I]

A Symptom Score



B Medication Score



C Combined Symptom Medication Score

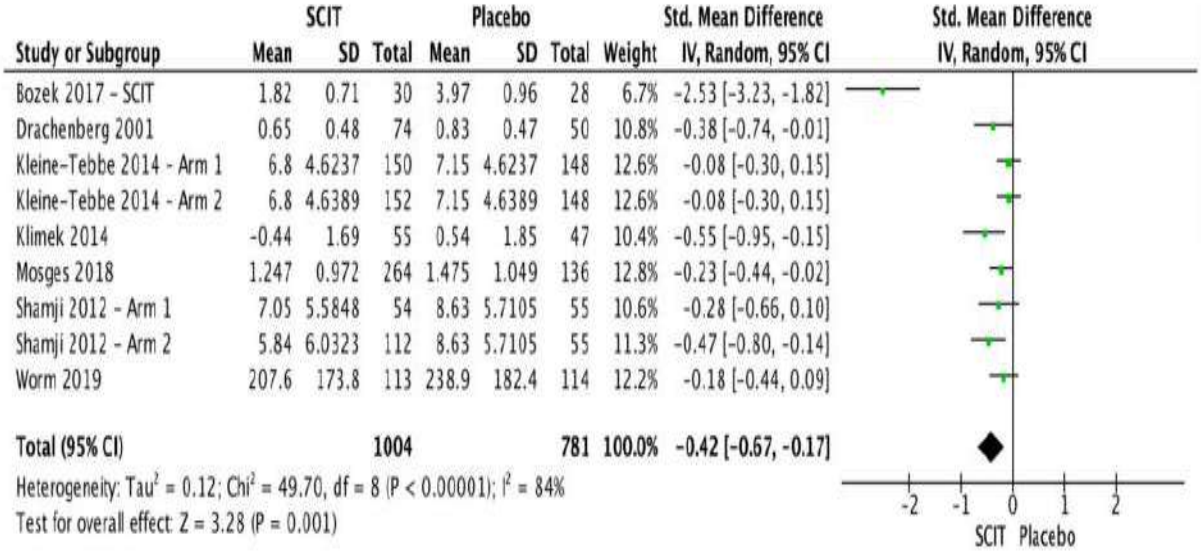


Figure 2: Forest plots for RCTs comparing SCIT vs placebo for symptom score (A), medication score (B), and combined symptom medication score (C). The standardised mean difference (SMD) is reported for symptom score, medication score, and combined symptom medication score. The overall SMD is represented by the black diamond. Heterogeneity and statistical significance are displayed at the bottom.

For adjusted indirect comparison between pooled SLIT versus placebo, the following SMDs and MDs are reported as absolute values (positive favours SLIT) along with their associated CIs. Statistically significant results favouring SLIT were found for:

- SS (SMD: 0.42; 95% CI: 0.32 to 0.53; 41 arms across 25 studies; SLIT n= 4,750, placebo n = 4,830)
- MS (SMD: 0.40; 95% CI: 0.28 to 0.53; 29 arms across 19 studies; SLIT n = 3,823, placebo n = 3,869)
- CSMS (SMD: 0.37; 95% CI: 0.29 to 0.45; 25 arms across 16 studies; SLIT n = 3,726, placebo n = 3,893), and
- RQLQ (MD: 0.32; 95% CI: 0.20 to 0.43; 10 arms across eight studies; SLIT n= 1,700, placebo n = 1,747).

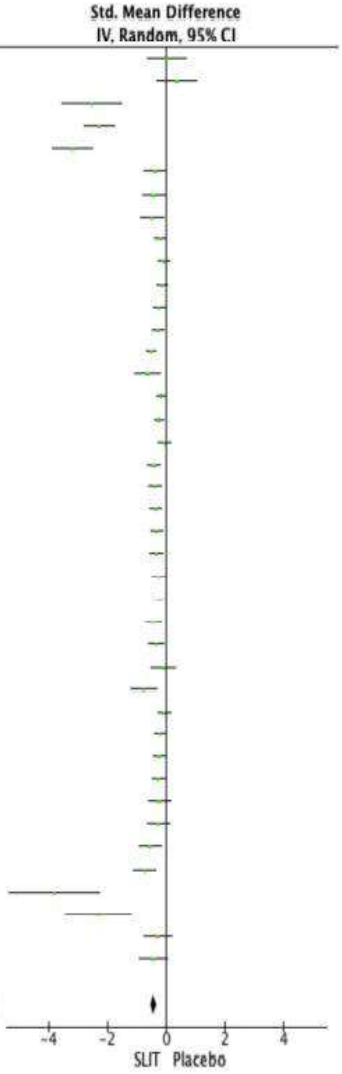
There was significant heterogeneity among studies for SS, MS, CSMS, and RQLQ as **seen in Figure 3**).

A Symptom Score

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amar 2009 - Arm 1	4	4.1495	19	3.9	3.8899	17	1.5%	0.02 [-0.63, 0.68]
Amar 2009 - Arm 2	5.4	4.0844	17	3.9	3.8899	17	1.4%	0.37 [-0.31, 1.05]
Ariano 2005	4.95	2.16	20	10.4	1.96	10	0.8%	-2.53 [-3.55, -1.50]
Bozek 2013	2.656	0.634	47	3.975	0.501	48	1.8%	-2.29 [-2.81, -1.77]
Bozek 2014	2.106	0.822	41	5.023	0.991	37	1.4%	-3.19 [-3.87, -2.51]
Couroux 2019 - Arm 1	5.66	3.8074	52	7.1	3.8469	54	2.3%	-0.37 [-0.76, 0.01]
Couroux 2019 - Arm 2	5.42	3.9949	48	7.1	3.8469	54	2.3%	-0.43 [-0.82, -0.03]
Couroux 2019 - Arm 3	5.29	3.6368	46	7.1	3.8469	54	2.3%	-0.48 [-0.88, -0.08]
Cox 2012	3.21	4.543	208	4.16	4.5148	228	3.1%	-0.21 [-0.40, -0.02]
Creticos 2013 - Arm 1	5.11	3.5491	197	5.37	3.5491	198	3.0%	-0.07 [-0.27, 0.12]
Creticos 2013 - Arm 2	4.87	3.5906	195	5.37	3.5906	198	3.0%	-0.14 [-0.34, 0.06]
Creticos 2013 - Arm 3	4.43	3.6869	194	5.37	3.6869	198	3.0%	-0.25 [-0.45, -0.06]
Creticos 2014	0.79	1.56	196	1.37	2.29	193	3.0%	-0.30 [-0.50, -0.10]
Dahl 2006 - 1	2.4	1.6	282	3.4	2.2	286	3.1%	-0.52 [-0.69, -0.35]
Dahl 2006 - 2	2.1	1.7	61	3.3	2.2	32	2.1%	-0.63 [-1.07, -0.19]
Demoly 2016 - Arm 1	2.9	2.3027	297	3.3	2.3027	298	3.1%	-0.17 [-0.33, -0.01]
Demoly 2016 - Arm 2	2.76	2.1534	284	3.3	2.1534	298	3.1%	-0.25 [-0.41, -0.09]
Didier 2009 - Arm 1	0.79	0.52	142	0.82	0.54	148	2.9%	-0.06 [-0.29, 0.17]
Didier 2009 - Arm 2	0.6	0.5	136	0.82	0.54	148	2.9%	-0.42 [-0.66, -0.19]
Didier 2009 - Arm 3	0.62	0.52	143	0.82	0.54	148	2.9%	-0.38 [-0.61, -0.14]
Didier 2011 - Arm 1	2.56	4.2094	188	4.03	4.1379	205	3.0%	-0.35 [-0.55, -0.15]
Didier 2011 - Arm 2	2.67	4.0723	188	4.03	4.1379	205	3.0%	-0.33 [-0.53, -0.13]
Didier 2013 - Arm 1	2.8	3.2197	137	3.89	3.2197	155	2.9%	-0.34 [-0.57, -0.11]
Didier 2013 - Arm 2	3.07	3.2122	143	3.89	3.2122	155	2.9%	-0.25 [-0.48, -0.03]
Durham 2006	2.474	2.1374	141	2.935	2.0991	136	2.9%	-0.22 [-0.45, 0.02]
Durham 2010	2.68	2.2369	142	3.63	2.2369	115	2.8%	-0.42 [-0.67, -0.17]
Durham 2012	2.6	2.3538	137	3.4	2.3538	104	2.8%	-0.34 [-0.60, -0.08]
Ellis 2018	4.2	4.5491	43	4.6	4.2759	44	2.2%	-0.09 [-0.51, 0.33]
Horak 2009	4.85	1.967	45	6.87	3.114	44	2.1%	-0.77 [-1.20, -0.34]
Murphy 2013	5.69	4.9792	163	6.06	5.1536	166	3.0%	-0.07 [-0.29, 0.14]
Nelson 2011	3.83	4.0694	184	4.69	4.3162	207	3.0%	-0.20 [-0.40, -0.01]
Nolte 2013 - Arm 1	4.81	3.4322	150	5.59	3.4322	164	2.9%	-0.23 [-0.45, -0.00]
Nolte 2013 - Arm 2	4.65	3.4841	159	5.59	3.4841	164	2.9%	-0.27 [-0.49, -0.05]
Pfaar 2016 - SLIT - Arm 1	3.63	1.95	54	4.1	2.18	52	2.3%	-0.23 [-0.61, 0.16]
Pfaar 2016 - SLIT - Arm 2	3.56	1.69	56	4.1	2.18	52	2.3%	-0.28 [-0.66, 0.10]
Pfaar 2016 - SLIT - Arm 3	3.03	1.71	53	4.1	2.18	52	2.3%	-0.54 [-0.93, -0.15]
Pfaar 2016 - SLIT - Arm 4	2.59	1.89	54	4.1	2.18	52	2.3%	-0.74 [-1.13, -0.34]
Quercia 2011 - Arm 1	6.6	2.41	10	20.27	4.15	11	0.4%	-3.82 [-5.36, -2.28]
Quercia 2011 - Arm 2	9.18	5.06	11	20.27	4.15	11	0.7%	-2.31 [-3.43, -1.18]
Skoner 2010 - Arm 1	0.46	1.4	34	1	2.3	36	2.0%	-0.28 [-0.75, 0.19]
Skoner 2010 - Arm 2	0.19	1.16	33	1	2.3	36	2.0%	-0.43 [-0.91, 0.04]
Total (95% CI)			**4750**			**4830**	**100.0%**	**-0.42 [-0.53, -0.32]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 227.45$, df = 40 ($P < 0.00001$); $I^2 = 82\%$

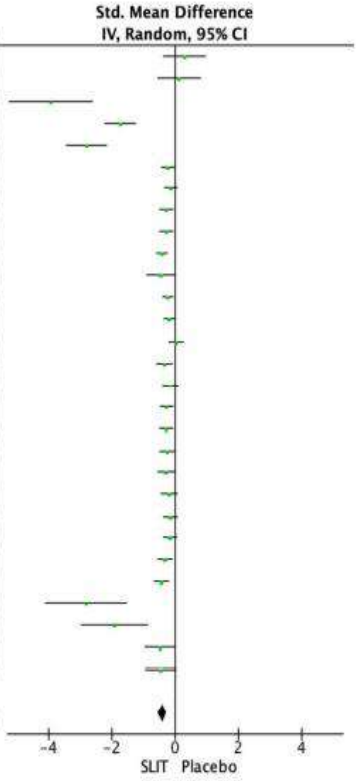
Test for overall effect: $Z = 7.90$ ($P < 0.00001$)



B Medication Score

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amar 2009 - Arm 1	0.1	0.166	19	0.05	0.1556	17	2.0%	0.30 [-0.36, 0.96]
Amar 2009 - Arm 2	0.07	0.1556	17	0.05	0.1556	17	2.0%	0.13 [-0.55, 0.80]
Ariano 2005	3	1.03	20	7.2	1.06	10	0.8%	-3.93 [-5.24, -2.62]
Bozek 2013	0.345	0.076	47	0.467	0.063	48	2.8%	-1.74 [-2.21, -1.26]
Bozek 2014	0.429	0.115	41	0.885	0.201	37	2.1%	-2.79 [-3.43, -2.16]
Cox 2012	0.11	0.3894	208	0.2	0.3926	228	4.3%	-0.23 [-0.42, -0.04]
Creticos 2013 - Arm 1	2.58	3.8026	197	3.09	3.8026	198	4.3%	-0.13 [-0.33, 0.06]
Creticos 2013 - Arm 2	2.01	3.8434	195	3.09	3.8434	198	4.2%	-0.28 [-0.48, -0.08]
Creticos 2013 - Arm 3	1.99	3.99	194	3.09	3.99	198	4.2%	-0.28 [-0.47, -0.08]
Dahl 2006 - 1	1.5	1.9	282	2.4	2.5	286	4.4%	-0.40 [-0.57, -0.24]
Dahl 2006 - 2	2.4	3.9	61	4.2	4.1	32	3.0%	-0.45 [-0.88, -0.02]
Demoly 2016 - Arm 1	2.13	3.1114	297	2.83	3.1114	298	4.4%	-0.22 [-0.39, -0.06]
Demoly 2016 - Arm 2	2.22	3.1993	284	2.83	3.1993	298	4.4%	-0.19 [-0.35, -0.03]
Didier 2009 - Arm 1	0.45	0.59	142	0.43	0.49	148	4.1%	0.04 [-0.19, 0.27]
Didier 2009 - Arm 2	0.28	0.39	136	0.43	0.49	148	4.1%	-0.34 [-0.57, -0.10]
Didier 2009 - Arm 3	0.36	0.47	143	0.43	0.49	148	4.1%	-0.15 [-0.38, 0.08]
Didier 2011 - Arm 1	0.31	0.5896	188	0.47	0.587	205	4.2%	-0.27 [-0.47, -0.07]
Didier 2011 - Arm 2	0.31	0.5759	188	0.47	0.587	205	4.2%	-0.27 [-0.47, -0.08]
Durham 2006	1.463	2.4342	141	2.046	2.4024	136	4.1%	-0.24 [-0.48, -0.00]
Durham 2010	2.32	3.213	142	3.25	3.213	115	4.0%	-0.29 [-0.54, -0.04]
Durham 2012	2.4	3.1384	137	3	3.1384	104	4.0%	-0.19 [-0.45, 0.06]
Murphy 2013	1.07	2.5534	163	1.47	2.8345	166	4.2%	-0.15 [-0.36, 0.07]
Nelson 2011	1.25	2.7129	184	1.7	2.8775	207	4.2%	-0.16 [-0.36, 0.04]
Nolte 2013 - Arm 1	1.89	3.0257	150	2.87	3.0257	164	4.1%	-0.32 [-0.55, -0.10]
Nolte 2013 - Arm 2	1.57	2.9798	159	2.87	2.9798	164	4.1%	-0.44 [-0.66, -0.21]
Quercia 2011 - Arm 1	1.4	1.07	10	9.82	3.82	11	0.8%	-2.82 [-4.09, -1.54]
Quercia 2011 - Arm 2	2.45	3.56	11	9.82	3.82	11	1.1%	-1.92 [-2.96, -0.88]
Skoner 2010 - Arm 1	0.16	0.92	34	0.63	1.06	36	2.8%	-0.47 [-0.94, 0.01]
Skoner 2010 - Arm 2	0.0003	1.64	33	0.63	1.06	36	2.8%	-0.46 [-0.93, 0.02]
Total (95% CI)			**3823**			**3869**	**100.0%**	**-0.40 [-0.53, -0.28]**

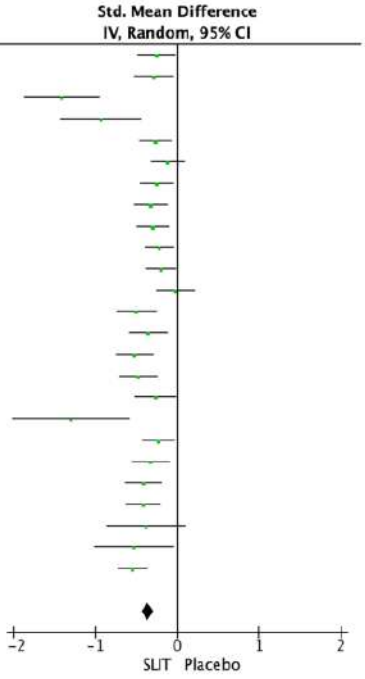
Heterogeneity: Tau² = 0.08; Chi² = 177.90, df = 28 (P < 0.00001); I² = 84%
Test for overall effect: Z = 6.34 (P < 0.00001)



C Combined Symptom Medication Score

Study or Subgroup	SLIT Mean	SLIT SD	SLIT Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bergmann 2014 - Arm 1	3.18	2.6599	141	3.87	2.6841	153	4.3%	-0.26 [-0.49, -0.03]
Bergmann 2014 - Arm 2	3.09	2.6822	136	3.87	2.6841	153	4.3%	-0.29 [-0.52, -0.06]
Bozek 2017 - SLIT	1.85	0.93	47	6.03	4.02	48	2.1%	-1.41 [-1.87, -0.96]
Bozek 2018	3.64	3.6986	38	6.44	1.7493	34	1.9%	-0.94 [-1.43, -0.45]
Cox 2012	0.32	0.4759	208	0.45	0.4832	228	4.9%	-0.27 [-0.46, -0.08]
Creticos 2013 - Arm 1	7.7	6.1856	197	8.46	6.1856	198	4.7%	-0.12 [-0.32, 0.07]
Creticos 2013 - Arm 2	6.88	6.1697	195	8.46	6.1697	198	4.7%	-0.26 [-0.45, -0.06]
Creticos 2013 - Arm 3	6.41	6.3132	194	8.46	6.3132	198	4.7%	-0.32 [-0.52, -0.12]
Creticos 2014	0.82	1.64	218	1.44	2.4	211	4.8%	-0.30 [-0.49, -0.11]
Demoly 2016 - Arm 1	7.74	6.1825	256	9.12	6.1825	257	5.1%	-0.22 [-0.40, -0.05]
Demoly 2016 - Arm 2	7.91	6.0883	241	9.12	6.0883	257	5.0%	-0.20 [-0.37, -0.02]
Didier 2009 - Arm 1	0.62	0.45	142	0.63	0.39	148	4.3%	-0.02 [-0.25, 0.21]
Didier 2009 - Arm 2	0.44	0.36	136	0.63	0.39	148	4.2%	-0.50 [-0.74, -0.27]
Didier 2009 - Arm 3	0.49	0.39	143	0.63	0.39	148	4.3%	-0.36 [-0.59, -0.13]
Didier 2011 - Arm 1	3.38	3.21	147	5.28	3.942	165	4.3%	-0.52 [-0.75, -0.30]
Didier 2011 - Arm 2	3.46	3.625	149	5.28	3.942	165	4.4%	-0.48 [-0.70, -0.25]
Didier 2015	0.27	0.4112	127	0.38	0.4112	133	4.1%	-0.27 [-0.51, -0.02]
Marogna 2013	58.8	50.7376	19	158.1	92.4087	19	1.1%	-1.30 [-2.01, -0.60]
Nelson 2011	5.08	5.4259	184	6.39	5.755	207	4.7%	-0.23 [-0.43, -0.03]
Nolte 2013 - Arm 1	6.7	5.374	150	8.46	5.374	164	4.4%	-0.33 [-0.55, -0.10]
Nolte 2013 - Arm 2	6.22	5.3636	159	8.46	5.3636	164	4.4%	-0.42 [-0.64, -0.20]
Pfaar 2019	1	1.0703	179	1.45	1.0673	178	4.6%	-0.42 [-0.63, -0.21]
Skoner 2010 - Arm 1	0.63	2.02	34	1.63	2.99	36	2.0%	-0.39 [-0.86, 0.09]
Skoner 2010 - Arm 2	0.19	2.32	33	1.63	2.99	36	1.9%	-0.53 [-1.01, -0.05]
Worm 2014	4.66	3.7076	253	6.7	3.7076	247	5.0%	-0.55 [-0.73, -0.37]
Total (95% CI)			**3726**			**3893**	**100.0%**	**-0.37 [-0.45, -0.29]**

Heterogeneity: Tau² = 0.02; Chi² = 67.11, df = 24 (P < 0.00001); I² = 64%
Test for overall effect: Z = 9.09 (P < 0.00001)



D Rhinoconjunctivitis Quality of Life Questionnaire

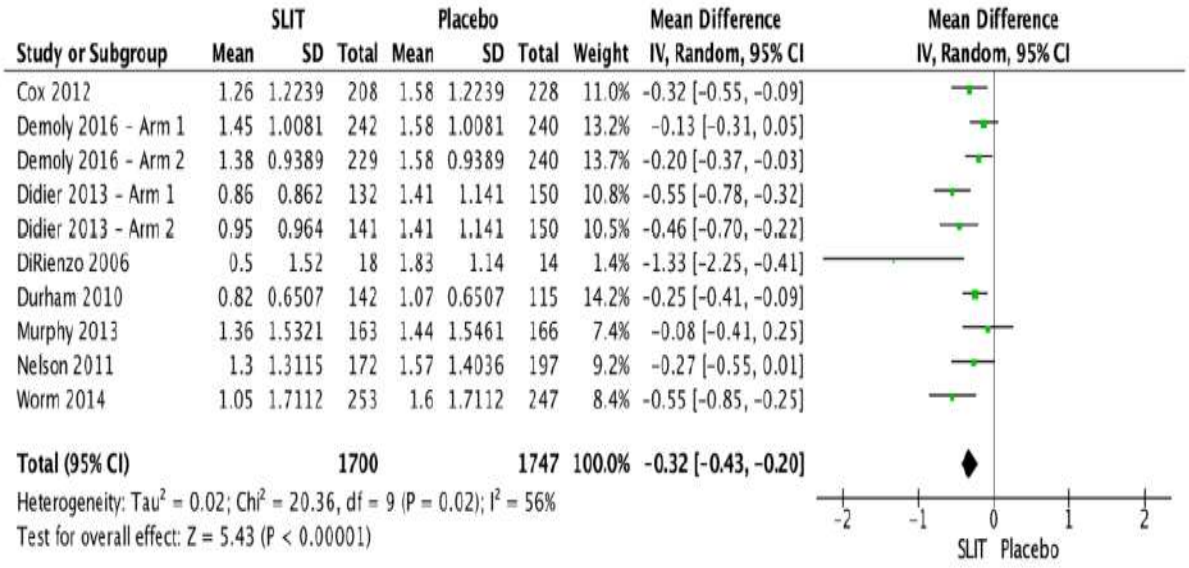


Figure 3: Forest plots for RCTs comparing SLIT to placebo for symptom score (A), medication score (B), combined symptom medication score (C), and Rhinoconjunctivitis Quality of Life Questionnaire (D). The standardised mean difference (SMD) is reported for symptom score, medication score, and combined symptom medication score, whereas the mean difference (MD) is reported for RQLQ. The overall SMD or MD is represented by the black diamond. Heterogeneity and statistical significance are displayed at the bottom.

For adjusted indirect comparison between pooled SCIT versus placebo against pooled SLIT versus placebo showed that the following reported SMDs and MDs, positive values favuor SCIT, whereas negative values favour SLIT. However, upon comparing pooled data, no significant differences were found between SCIT and SLIT for SS (SMD: -0.02; 95% CI: -0.15 to 0.11), MS (SMD: -0.14; 95% CI: -0.31 to 0.03), CSMS (SMD: 0.05; 95% CI: -0.21 to 0.31), or RQLQ (MD: -0.08; 95% CI: -0.31 to 0.15; as **seen in Table 2**

Table 2: Adjusted Indirect Comparison – Subcutaneous Versus Sublingual Immunotherapy

Adjusted Indirect Comparison – Subcutaneous Versus Sublingual Immunotherapy.

	SMD* (95% CI)	*P* value
SS	−0.02 (−0.15, 0.11)	.77
MS	−0.14 (−0.31, 0.03)	.11
CSMS	0.05 (−0.21, 0.31)	.71
RQLQ	−0.08 (−0.31, 0.15)	.50

*Positive favors SCIT; negative favors SLIT. Standardized mean difference reported for SS, MS, and CSMS; mean difference reported for RQLQ.

CI = confidence interval; CSMS = combined symptom medication score; MS = medication score; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SMD = standardized mean difference; SS = symptom score.

A network meta-analysis (NMA) by Kim JY et al in 2021 in Korea to compare the efficacy of SLIT drops, SLIT tablets, and SCIT in patients with perennial allergic rhinitis through network analysis. All studies included in the NMA included double blind randomized controlled trials (DBRCTS) of AIT for the treatment of HDM-induced perennial AR with the primary outcome was the nasal symptom score, and the secondary outcome was the medication score. (**as seen in Figure 4**) This NMA included 26 DBRCTs for meta-analysis with consist of 12 studies with 766 patients for SLIT drop, with 5744 patients for SLIT tablet, six with 233 patients for SCIT, and two studies including both SLIT drop and SCIT. A total of 3331 patients treated with immunotherapy and 3412 controls who received placebo. Of the 26 studies, both the symptom and medication scores were evaluated in 18 studies, and the symptom scores alone were evaluated in eight studies. Thirteen studies were performed in Europe, nine in Asia, one in North America, one in Africa, one in Oceania, and one in multiple continents. Twelve of 26 studies (three of 12 in SLIT drop and nine of 10 in SLIT tablet) were conducted in multiple centers, whereas the rest were conducted in single centers. Immunotherapy with HDM extract was performed in all except for two studies in which allergoid was used for immunotherapy. The duration of AIT ranged from 6 months to 3 years.[11, level-I]

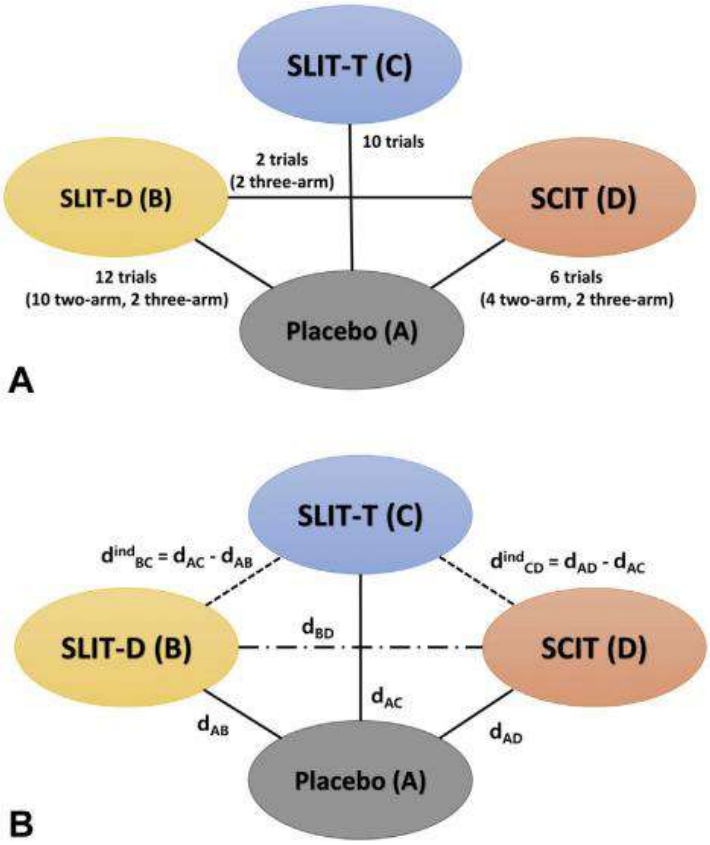


Figure 4: Schematic of practical approach for network meta-analysis (NMA). (A) Available trials for direct comparison. (B) Network diagram. The solid line indicates a weighted average of direct and indirect estimates with direct evidence dominantly contributing to NMA estimates. Dotted and solid line indicates a weighted average of direct and indirect estimates with indirect evidence dominantly contributing to NMA estimates. Dotted line indicates indirect estimates. Relative treatment effects compared with the placebo were used to calculate indirect comparisons (dindBC and dindCD). Other NMA estimates (dAB, dAC, dAD, and dBD) were calculated from weighted averages of direct and indirect estimates. D, drops; T, tablets; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

Direct pairwise meta-analysis

The clinical efficacy of HDM immunotherapy for the symptom score is shown in **Figure 5.** Direct pairwise meta-analysis revealed a significant reduction in the symptom score (SS) in each immunotherapy group relative to the placebo group, with pooled SMDs of -0.461 (95% CI, -0.795 to -0.127) for SLIT drop, -0.329 (95% CI, -0.426 to -0.231) for SLIT tablet, and -1.669 (95% CI, -2.753 to - 0.585) for SCIT. Severe heterogeneity was in SLIT drop and SCIT studies (I^2= 77% and 91%, respectively), and high heterogeneity was found in SLIT tablet studies (I^2 = 64%).[11, level-I]

When they restricted the pooled analysis to studies with a low risk of bias, it included five studies with 374 patients for SLIT drop, six studies with 3825 patients for SLIT tablet, and four studies with 175 patients for SCIT. Whereas sensitivity analysis of studies with a low risk of bias revealed a significant reduction in SS for SLIT tablet relative to the placebo by direct pairwise comparison, no significant differences were observed for SLIT drop and SCIT with pooled SMDs of -0.156 (95% CI, -0.472 to 0.159) for SLIT drop, -0.302 (95% CI, -0.366 to -0.238) for SLIT tablet, and -0.990 (95% CI, -2.076 to 0.097) for SCIT. Because the sensitivity analysis included only studies with a low risk of bias, heterogeneity among SLIT drop and SLIT tablet studies was moderate and low, respectively (I^2 = 38% and 0%, respectively), whereas that among SCIT studies was still severe (I^2 = 90%).[11, level-I]

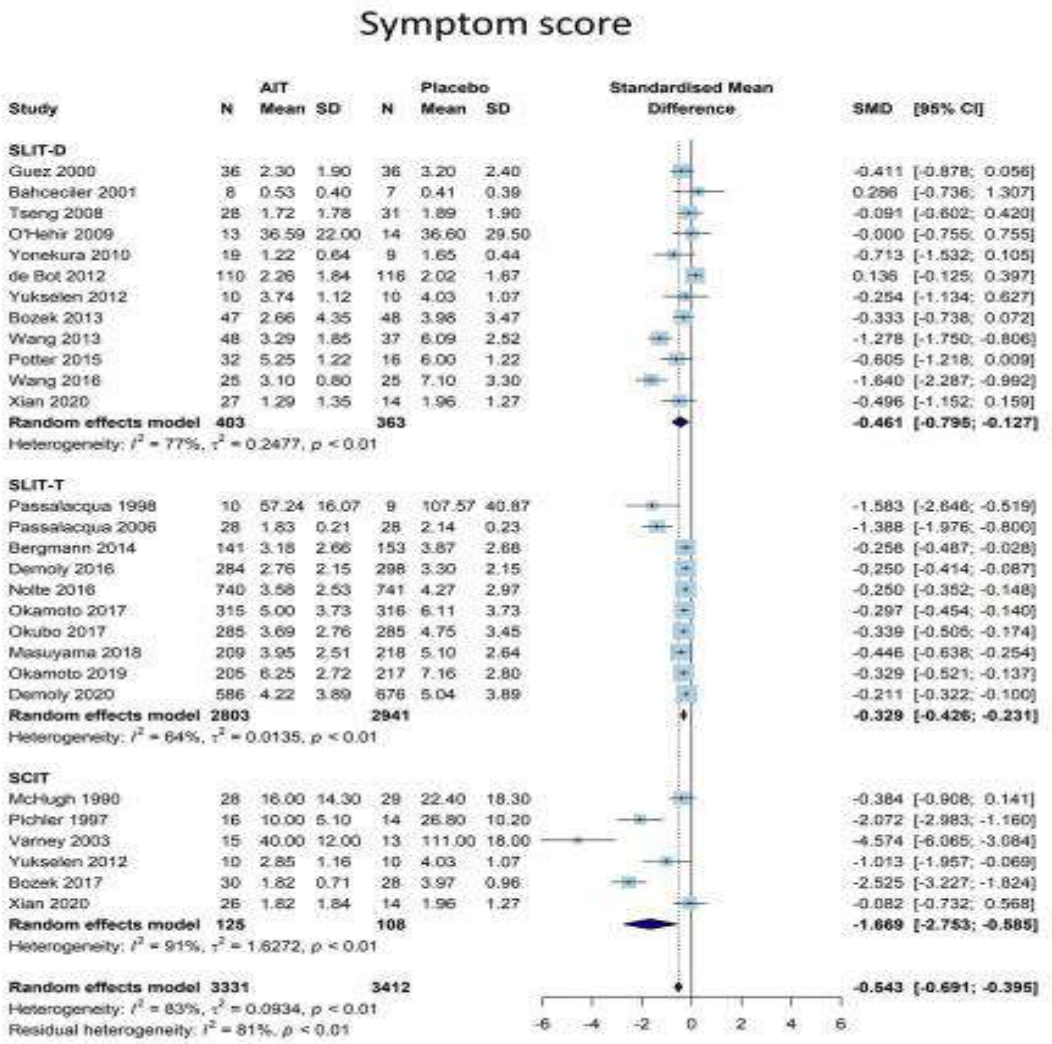


Figure 5: Direct pairwise comparison for symptom scores (SS) of immunotherapy modalities versus placebo. AIT, allergen-specific immunotherapy; CI, confidence interval; D, drops; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMD, standardised mean difference; T, tablets

The clinical efficacy of HDM immunotherapy based on the medication score (MS). Among the 26 studies, 18 evaluated the medication score. A significant reduction in MS for each immunotherapy group relative to the placebo group was identified by direct pairwise meta-analysis: pooled SMDs of -0.546 (95% CI, -0.860 to -0.232) for SLIT drop, -0.227 (95% CI, -0.371 to -0.083) for SLIT tablet, and -0.697 (95% CI, -1.039 to -0.355) for SCIT **(Figure 6)**. The degree of heterogeneity was moderate, severe, and low among SLIT drop, SLIT tablet, and SCIT studies, respectively (I^2 = 47%, 85%, and 0%, respectively).[11, level-I]

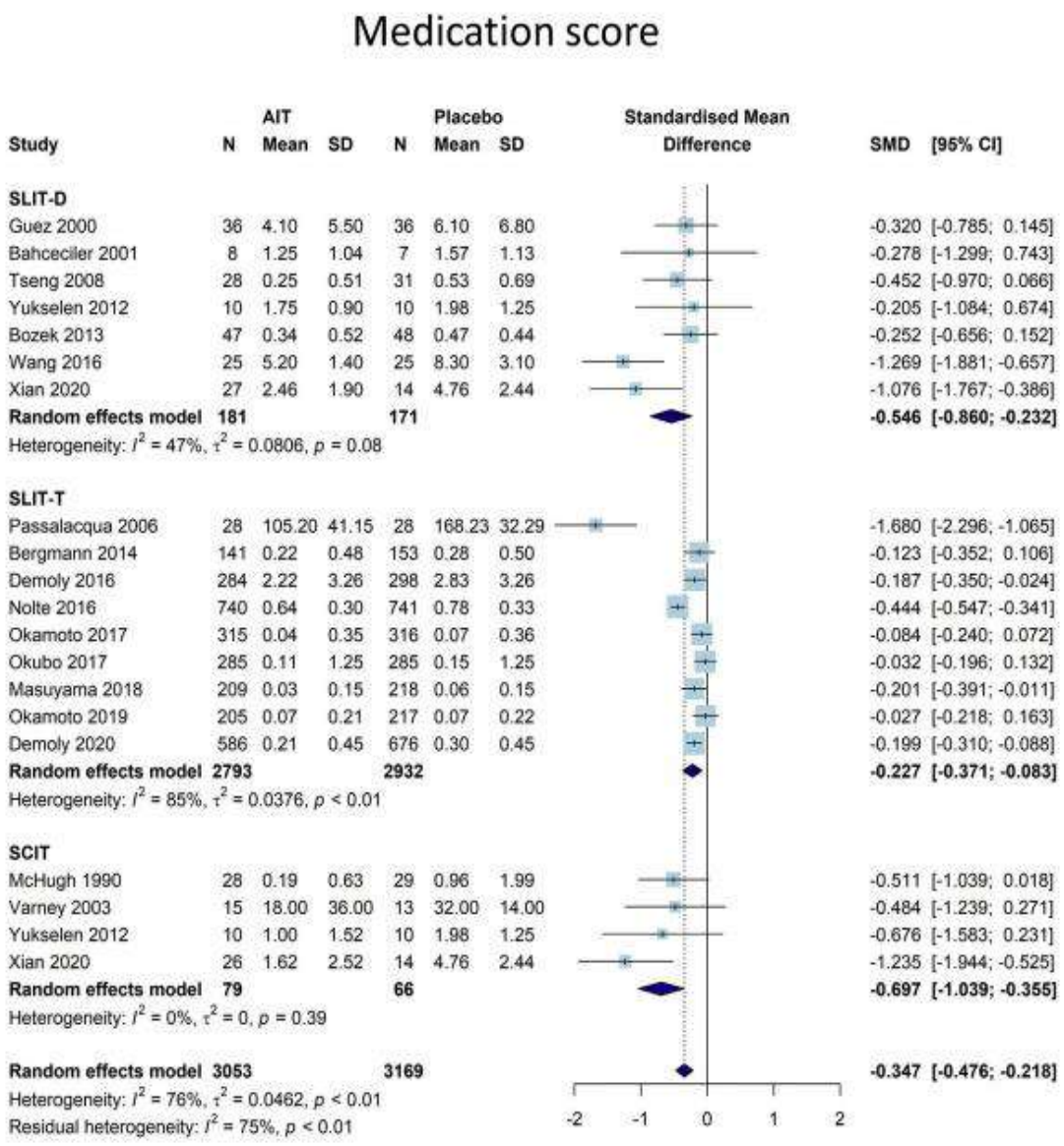


Figure 6: Direct pairwise comparison for medication scores (MS) of immunotherapy modalities versus placebo. AIT, allergen-specific immunotherapy; CI, confidence interval; D, drops; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMD, standardised mean difference; T, tablets.

When performing the NMA, there was no significant difference in symptom score between SLIT drop and SLIT tablet (SMD, -0.123; 95% CI, -0.428 to 0.182) (**Figure 7, A).** The SCIT had greater clinical efficacy in the symptom score compared with SLIT drop or SLIT tablet (SMD: -0.697, 95% CI, -1.105 to -0.288; and SMD: -0.819, 95% CI, -1.242 to -0.397). Direct comparison estimated by NMA indicated that all AIT modalities had significant clinical efficacy based on the symptom score compared with the placebo, which was in agreement with pairwise comparisons. The sensitivity analysis of studies with a low risk of bias revealed no significant difference in the symptom score between SLIT drop and SLIT tablet (SMD, 0.070; 95% CI, -0.283 to 0.424)[11, level-I]

The medication score was not significantly different between studies with SLIT drop and SLIT tablet (SMD, -0.254; 95% CI, -0.552 to 0.044) **(Figure 7, B)**. The improvement in medication score was greater for SCIT than for SLIT tablet (SMD, -0.517; 95% CI, -0.914 to -0.121) but not significantly different than that for SLIT drop (SMD, -0.263; 95% CI, 0.664 to 0.137). Direct comparisons estimated by NMA demonstrated that all AIT modalities had significant clinical efficacy based on the medication score compared with the placebo, which was in agreement with pairwise comparisons.[11, level-I]

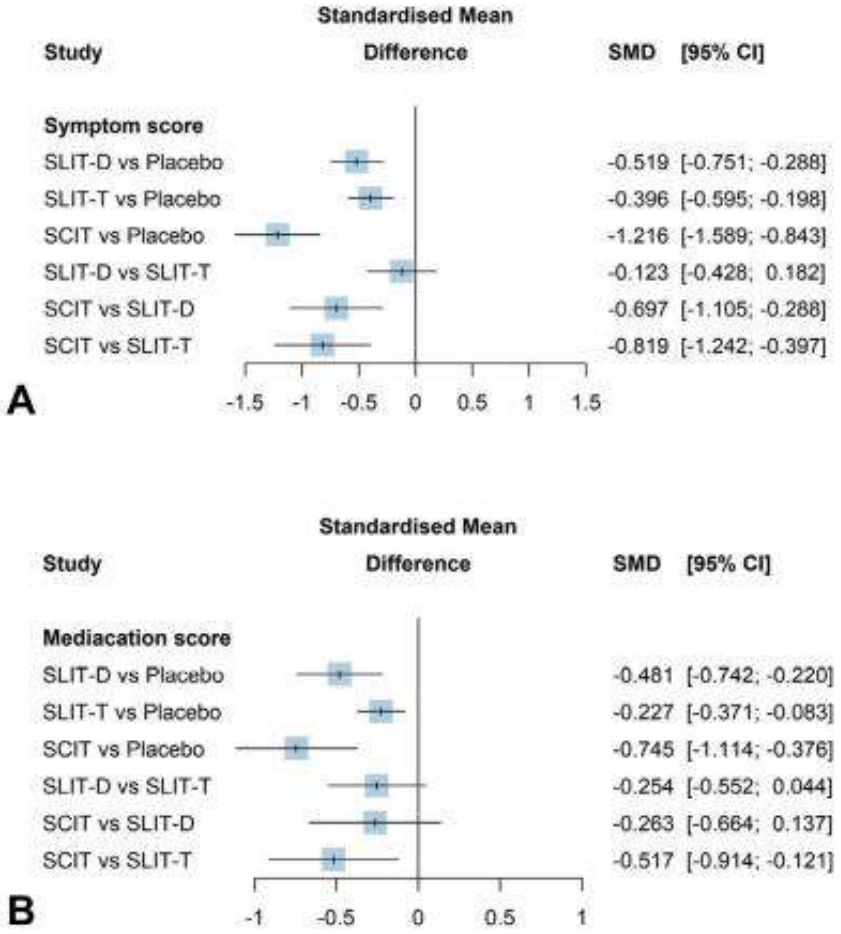


Figure 7: Results of network meta-analysis. Direct and indirect comparison of (A) the symptom score and (B) the medication score. CI, confidence interval; D, drops; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMD, standardised mean difference; T, tablets.

Masuyama K et al conducted a review in 2018 of all double blind RCTs to discuss AIT, especially the current status of SLIT in Japan. From this review, the authors highlighted three types of SLIT to manage HDM as allergens in Japan (Cedartolen®, Miticure® and Actair®). In particular, the prevalence of Japanese cedar pollinosis (JCP) has increased more than other forms of AR caused by HDM or pollinosis other than JCP, and continues to rise. Hence, in this review, the studied the effectiveness of these SLIT drop or tablets in the treatment of AR.

Five hundred and thirty-one patients (N=531) with JCP, aged 12 - 64 years, who had had symptoms of JCP for the previous 2 years and JCP-specific IgE levels of class 3 or higher, were randomised into a Cedartolen® group and a placebo group. Treatments were given for an average of 18 months from October 2010 to April 2012. Treatment began before the start of the pollen season in 2011 and continued to the end of the pollen season in 2012 ~one year). The primary endpoint was the total nasal symptom and medication score (TNSMSs) during the peak symptom period in the second season. The results showed that TNSMSs during the peak symptom period were significantly lower in the SLIT group than in the placebo group **(Fig. 8).**

The study demonstrated of 30% reduction compared with the placebo group in TNSMSs, thus suggesting clinically relevant efficacy.[12, level-I]

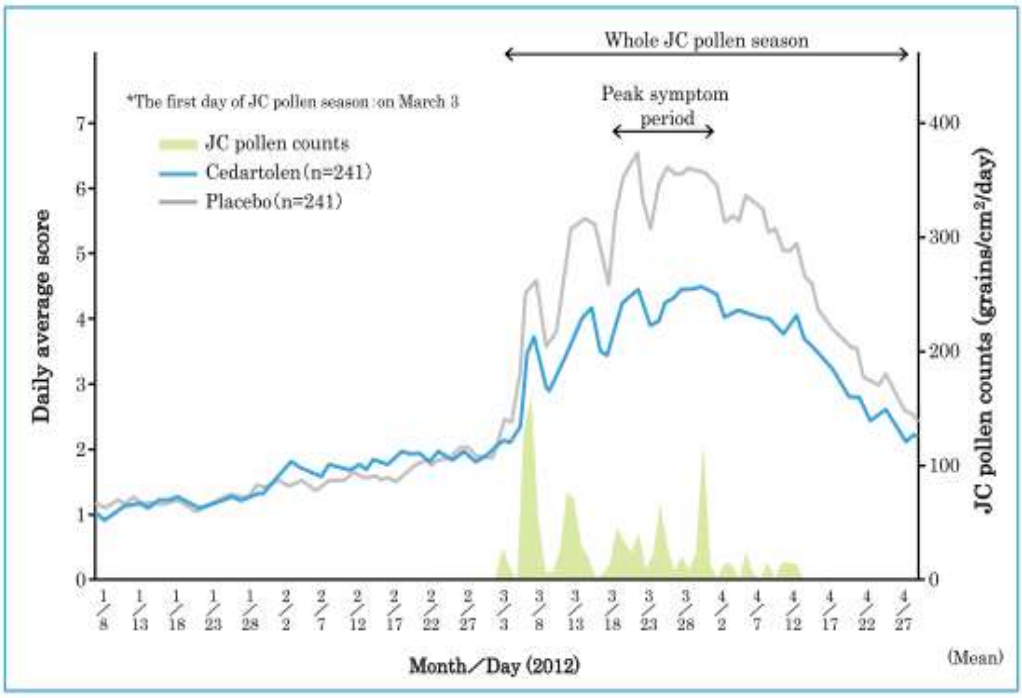


Figure 8: Total Nasal Symptom Medication Score (TNSMS) in 2012. The placebo group is represented by the grey line, the SLIT group by the blue line, the JCP count by green shading.

Another DBRCTs conducted to seek the efficacy of HDM tablet Miticure® in Japanese patients with HDM-induced AR. In this study a total of 946 subjects (N=946) were randomly assigned to receive daily treatment with a SQ HDM SLIT tablet at a dose of 20,000 JAU (12 SQ) or 10,000 JAU (6 SQ) or a placebo (a nominal strength of 10,000 JAU has the same potency as 6 SQ-HDM- the unit used in Europe and the United States). Before reaching the maintenance dose, an up-dosing of one or two weeks was chosen. The participants received treatment for 12 months. The primary endpoint was the total combined rhinitis score (TCRS), i.e., the sum of the rhinitis symptom and medication score during the last eight weeks of the treatment period. The primary endpoint was the TCRS during the last 8 weeks of the treatment period. The absolute differences in adjusted means TCRS to the placebo were 1.15 ($p < 0.001$) in the 10,000 JAU group and 0.09 ($p < 0.001$) in the 20,000 JAU group, respectively **(Table 3)**. The relative differences to the placebo group were 22% and 19% in the 10,000 and 20,000 JAU groups, with 95% CI upper limits of 13% and 10%, respectively.[12, level-I]

Table 3: Analytic results on the primary end point (TCRS)

Analysis set	Treatment group	No.	Adjusted mean	Absolute difference from placebo (95% CI)	*P* value	Relative difference to placebo (95% CI)
FAS (LME)	Global null hypothesis (placebo = 10,000 JAU = 20,000 JAU)				<.001	–
	Placebo	285	5.14	–	–	–
	10,000 JAU	285	3.99	1.15 (0.64 to 1.65)	<.001	22% (13% to 31%)
	20,000 JAU	281	4.14	0.99 (0.48 to 1.50)	<.001	19% (10% to 28%)
	All active treatment	566	4.07	1.07 (0.62 to 1.52)	<.001	21% (13% to 28%)
ITT (MMRM)	**Placebo**	317	5.15	–	–	–
	10,000 JAU	304	3.95	1.19 (0.70 to 1.69)	<.001	23% (14% to 31%)
	20,000 JAU	307	4.14	1.00 (0.51 to 1.49)	<.001	19% (10% to 28%)
	All active treatment	611	4.05	1.10 (0.68 to 1.52)	<.001	21% (14% to 28%)
PPS (LME)	**Placebo**	276	5.12	–	–	–
	10,000 JAU	279	3.98	1.15 (0.64 to 1.65)	<.001	22% (13% to 31%)
	20,000 JAU	274	4.16	0.96 (0.45 to 1.48)	<.001	19% (9% to 27%)
	All active treatment	553	4.07	1.06 (0.61 to 1.51)	<.001	21% (13% to 28%)

The third SLIT tablet study using a DBRCTs on tablet Actair® for patients with HDM-induced AR in Japan with a total of 968 (N=968) participants subjects were randomised to receive 300 IR (the same potency as 57,000 JAU), 500 IR (95,000 JAU), or placebo groups. Before reaching the maintenance dose, an up-dosing of two weeks was chosen. The participant received treatment for 52 weeks (~one year). The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS) during the last 8 weeks of the treatment period. The AASSs over week 44e52 in both active groups significantly improved compared with that in the placebo group. The mean absolute and relative differences in the AASSs (vs placebo) were 1.11 (18.2%) for the 300 IR group and 0.80 (13.1%) for the 500 IR group. The differences between the 300 IR and 500 IR groups was not statistically significant. The AASS in the 300 IR group was significantly improved at week 8 -10, and this improvement was maintained until the end of the treatment.[12, level-I]

From this review, the authors reported that when comparing the two RCT trials, it seems likely that the efficacy of Miticure® and Actair® is the same, although the strengths of the two HDM SLIT tablets were quite different according to the JAUs (10,000 and 57,000, respectively). Also, before initiate a treatment using SLIT, it is concerned to have a correct diagnosis of JCP-or HDM-induced AR is necessary, and the appropriate indication for SLIT must be considered carefully.[12, level-I]

A Cochrane review in 2010 by Radulovic was conducted to evaluate the efficacy and safety of SLIT for allergic rhinitis in adults and children. This review was a randomised, double-blind, placebo-controlled trials of SLIT therapy in adults or children. The primary outcome measures were symptom and medication scores.

A total of 60 randomised controlled trials in the review. Forty-nine were suitable for pooling in meta-analyses (N= 2333 SLIT, N= 2256 placebo participants). Overall, it showed a significant reduction in symptoms (SMD = -0.49; 95% CI -0.64 to -0.34, $p <$ 0.00001) and medication requirements (SMD= -0.32; 95% CI -0.43 to -0.21, $p <$

0.00001) in participants receiving SLIT compared to placebo. **(as seen in Figure 9)**[13], level- I

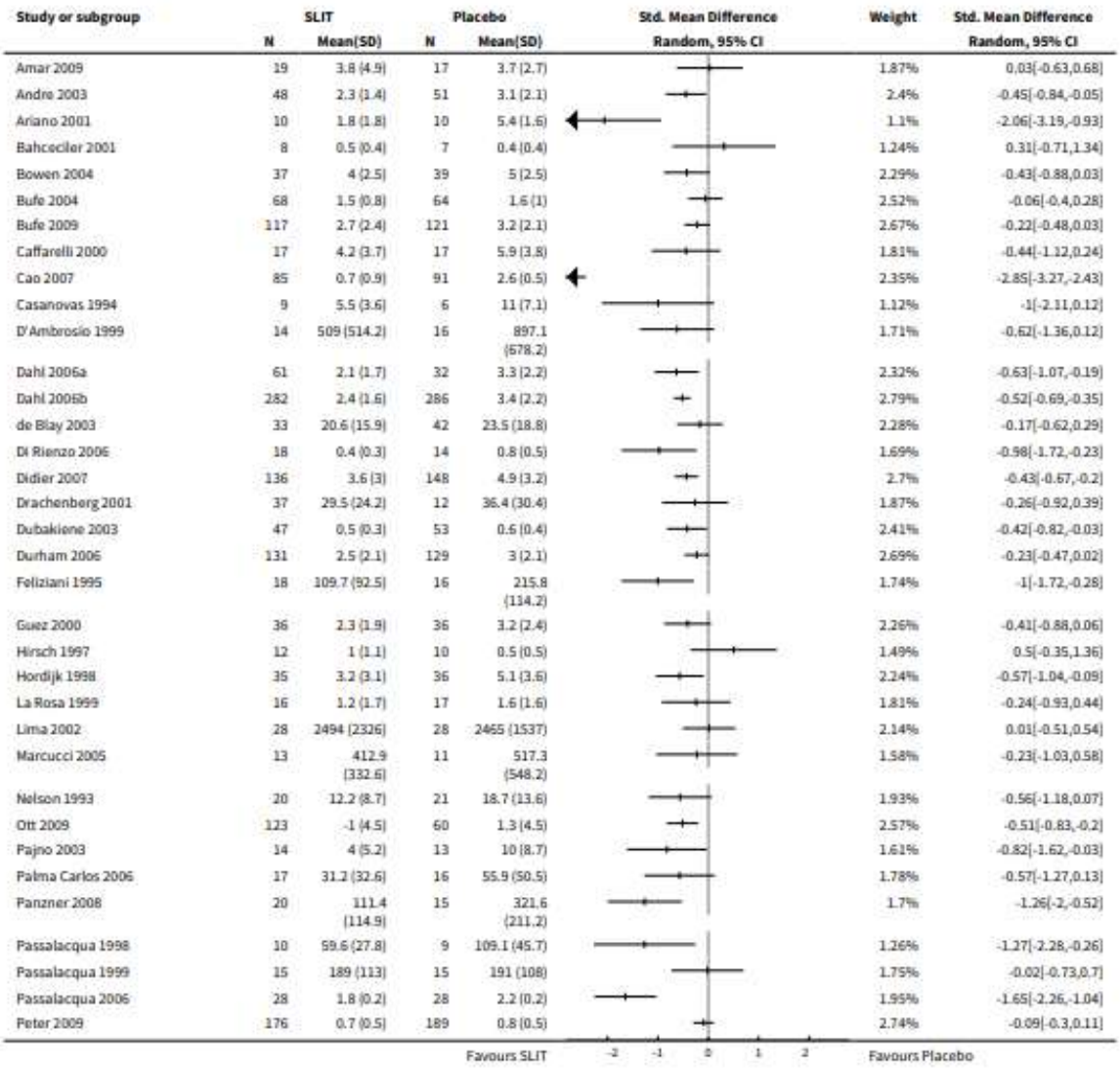


Figure 9: Analysis comparison 1 SLITversus placebo - all, Outcome 1 Allergic rhinitis symptom scores

5.2.2 Sublingual immunotherapy for asthma

A Cochrane review updated in 2020 by Fortescue R which formerly done in 2015 was conducted to assess the efficacy and safety of SLIT compared with placebo or standard care for adults and children with asthma. In this review, its included parallel randomised controlled trials (RCTs), blinded and unblinded, of any duration that evaluated SLIT versus placebo or as an add-on to standard medical management of

asthma. No cross over trials were included in this review due to long term effects of management. The review will demonstrated the primary outcomes as following:[12, level-I]

i. Exacerbation requiring emergency department (ED) visit or hospitalisation (participants with at least one)
ii. Quality of life (measured on a validated scale, e.g. Asthma Quality of Life Questionnaire)
iii. Serious adverse events (all-cause)

Meanwhile the secondary outcomes are as follows:

i. Asthma symptom scores (measured on a validated scale, e.g. Asthma Control Questionnaire)
ii. Exacerbations requiring systemic corticosteroids (participants with at least one).
iii. Response to provocation tests
iv. Required dose of ICS

In this review, the authors included 52 individual studies (74 records) in the original version of the review, screened the titles and abstracts of 401 records after removal of duplicates, at then excluded 177 records and reviewed the full texts of 224 records. In addition to the 52 included studies, they listed seven as ongoing, 12 as awaiting classification, and 111 as excluded studies. The update for the review included a total of three update searches conducted on 25 July 2017, 27 November 2018, and 29 October 2019, returning a total of 148 records after deduplication. The process then excluded 75 records after reviewing titles and abstracts, and reviewed the full texts of the remaining 73. A further 31 records were excluded on the basis of full-text assessment. The remaining 42 records met the inclusion criteria, of which 22 records were references to 15 new studies, and 12 records were linked to studies already included in the review. Two records were listed as two new ongoing studies. In the end,the review update includes a total of 66 studies, of which 15 are new included studies since the last version of the review.[12, level-I]

Sixty-six studies met the inclusion criteria of the review. These studies included a total of 8846 participants with asthma, and 7944 were randomly assigned to comparisons of interest in this review (representing 2917 more participants than were included in the original review). The largest included study randomly assigned 1482 participants, and the smallest just 15. The median total number of participants across all 66 studies was 60. All included trials were RCTs with parallel design and compared SLIT versus placebo plus conventional therapy (n = 49) or conventional pharmacotherapy alone (n = 17). Trial duration varied, with the shortest lasting just one day and the longest 156 weeks. The median duration of all included studies was 52 weeks (interquartile range 18.4 to 78 weeks). Twenty-three studies recruited only teenagers and adults, and 31 studies recruited children only; three studies included mixed populations of adults and children. In nine studies the age range of participants was not reported and no specific the ethnicity of participants. Most of the included studies (n = 47) targeted HDM allergy.[12, level-I]

Results:

Outcomes were reported inconsistently across studies, and validated scales were rarely used. Most included studies reported asthma symptoms and medication scores, and many studies also reported outcomes not specified in our protocol, including lung function (e.g. peak expiratory flow rate (PEFR) (n = 32)) and laboratory immunological outcomes (e.g. serum allergen-specific IgE and IgG levels (n = 32)). Due to insufficient studies contributing data to the primary analyses, thus unable to complete the planned sensitivity and subgroup analyses.[12, level-I]

Results from the primary outcomes of exacerbations requiring ED or hospital admission, included only two studies. One short study involved 43 participants and four different SLIT dosing arms by Calderon in 2006 and reported no events during the four-week treatment period or during the five- to six-week follow-up period. The second study included 61 participants, and reported that five participants in the SLIT group and 10 in the control group either attended ED or was admitted to hospital over 52 weeks of treatment; (OR = 0.35, 95% CI 0.10 to 1.20; participants = 108; studies = 2; heterogeneity of $I^2 = 0$; with very low-certainty evidence. (**See Figure 8**)[12, level-I]

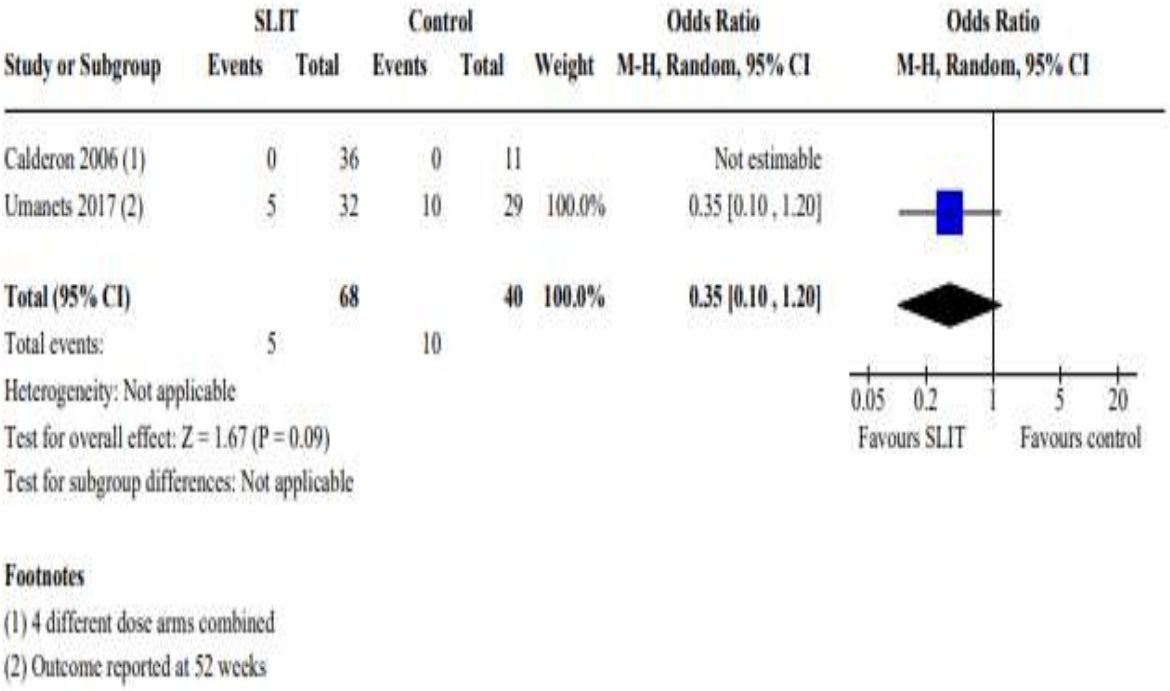


Figure 8: Forest plot of comparison: 1 Sublingual immunotherapy versus control, outcome: 1.1 Exacerbation requiring ED or hospital visit.

5.2.3 Sublingual immunotherapy for atopic dermatitis (eczema)

A systematic review from Cochrane by Tam H et al. in 2016 consisted of RCTs to assess the effects of SIT, including subcutaneous, sublingual, intradermal, and oralroutes, comparedvwith placebo or a standard treatment in people with atopic eczema. In this review, they included any high-dose immunotherapy with standardised allergen extracts for single allergen or mixed allergens administered by the sublingual (under the tongue), subcutaneous (under the skin), intradermal (into the skin), or oral route compared with placebo or a standard treatment, such as emollients, topical corticosteroids, or topical calcineurin inhibitors in all clinical trials registered up to 3 August 2015 using the terms 'immunotherapy and (eczema or dermatitis)'. This review included any outcome measures as listed for primary outcomes:[13, level-I]

i. Participant- or parent-reported global assessment of disease severity at the end of treatment, i.e. the proportion with good or excellent improvement at this time as reported in the trials (whether treatment was given for one, two, or three years, or other duration).
ii. Participant- or parent-reported specific symptoms of eczema, by subjective measures such as itch or sleep disturbance (SCORing Atopic Dermatitis (SCORAD) part C).
iii. Adverse events, such as acute episodes of asthma or anaphylaxis.

Meanwhile, the listed outcome for secondary outcomes are:

i. Investigator- or physician-rated global assessment of disease severity at the end of treatment, i.e. the proportion with good or excellent improvement at this time as reported in the trials (whether treatment was given for one, two, or three years, or other duration).
ii. Parent- or participant-rated eczema severity assessed using a published scale (e.g. Patient Oriented Eczema Measure (POEM)).
iii. Investigator- or physician-rated eczema severity assessed using a published scale (e.g. SCORAD).
iv. Use of other medication for treatment of eczema during the intervention period (e.g. topical/systemic corticosteroids, calcineurin inhibitors, or oral antihistamines).
v. Validated eczema-related quality of life scores (e.g. Dermatitis Family Impact Questionnaire, Children's Dermatology Life Quality Index).

From the systematic search identified 1550 references from electronic databases and six additional reports from other sources, which gave a total of 1556 records. They excluded 1465 references based on titles and abstracts, selected 91 records for which they screened the full text and finally excluded 64 records and listed one as an ongoing study. Overall, 26 reports of 12 separate studies met the inclusion criteria with a total of 733 participants. (N=733) Six trials studied SCIT, four studied SLIT, one studied intradermal immunotherapy and one studied oral immunotherapy. Eight trials compared the intervention with a placebo and four compared the intervention with a standard treatment. The duration of treatment was less than a year in one trial, and at least a year for others.[13, level-I]

Results:

Primary outcomes: Participant- or parent-reported global assessment of disease severity at the end of treatment

There is only one study by Warner in 1978, measured this outcome as whether the eczema was improved, no change, or it was worse as rated by the participants or parents and the data were only available for 20 participants at the end of the treatment (nine active, 11 placebo), with improvement in 7/9 (78%) of the immunotherapy group and 3/11 (27%) in the placebo group (RR= 2.85, 95% CI 1.02 to 7.96). Another study, by Glover 1992, measured this outcome as whether the eczema was better, the same, or worse as rated by parents. And data only available for 24 participants, with improvement in 8/13 (62%) of those in the active treatment group (immunotherapy) and 9/11 (81%) in the placebo group (RR= 0.75, 95% CI 0.45 to 1.26). No meta-analysis were performed due to high heterogeneity between the two studies (I^2 = 83%). The quality of the evidence was low.[13, level-I]

Primary outcomes: Participant- or parent-reported specific symptoms of eczema, by subjective measures

Two studies were included to calculate SCORing Atopic Dermatitis (SCORAD) part C scores at the end of treatment, and the components of SCORAD part C, which are itch measured by Visual Analogue Scales (VAS) and sleep disturbance measured by VAS each on a scale from 0 to 10. A meta-analysis, with a total of 184 participants, showed no significant difference in SCORAD part C (mean difference (MD= -0.74, 95% CI -1.98 to 0.50; I^2 = 0%; or severity of sleep disturbance (MD= -0.49, 95% CI -1.03 to 0.06; I^2 = 0%. An original data that showed subjective symptom scores at the end of the treatment on a scale of 0 to 100, where higher scores meant more symptoms, and a component of the symptom score, which measured itching severity on a scale of 0 to 10, where higher scores also mean more symptoms. These data were available for 60 participants at the end of the treatment (31 active, 29 placebo), with a mean overall severity score (SS= 37.3; 95% CI 32.4 to 42.1) in the immunotherapy group and (SS= 80.8; 95% CI 75.8 to 85.7) in the control group (p < 0.001) and a mean itch severity score of (SS= 3.2; 95% CI 2.3 to 4.0) in the immunotherapy group versus (SS= 7.5; 95% CI 6.9 to 8.0) in the control group (p < 0.001). The dfference between groups in change in itch severity score from baseline was also statistically significant (MD= -4.20; 95% CI -3.69 to -4.71). One study by Glover 1992, reported symptoms in the form of itch score presented graphically that showed no significant difference between the active and placebo groups. One study, Leroy 1993, reported a mean itch score of 2.2 (or 33% reduction from baseline) after immunotherapy compared with 2.6 (or 19% reduction from baseline) in the control group.[13, level-I]

Secondary outcomes: 'Investigator- or physician-rated global assessment of disease severity

Six studies reported investigator- or physician-rated global assessment of disease severity with 262 participants, showed significant improvement in disease severity (RR= 1.48; 95% CI 1.16 to 1.88; I^2 = 19%). Only one study (Leroy 1993) with 24 participants,reported improvement in 70% of all of the participants that used an

investigator-rated index of disease severity at a threshold of 50% improvement. This was significant between the treatment and the placebo group ($p < 0.003$), but there were no separate data for the treatment and placebo group, hence not included in a meta-analysis.[13, level-I]

Secondary outcomes: Parent- or participant-rated eczema severity assessed using a published scale

None of the studies reported participant- or parent-rated eczema severity using a published scale, except for two studies by Di Rienzo 2014 and Novak 2012 with (n=184), which recorded SCORAD part C (MD= -0.74; 95% CI -1.98 to 0.50; I^2 = 0%).[13, level-I]

From this review, the authors were reported a generally inconclusive in results due to the small number of studies thus were unable to determine by subgroup analyses a particular type of allergen or a particular age or level of disease severity where allergen immunotherapy was more successful. Also were unable to determine whether SLIT was associated with more local adverse reactions compared with SCIT.

5.3 SAFETY

There were two RCTs study retrieved on safety of SLIT for AR, meanwhile, there were one Cochrane on the safety of SLIT for asthma and none study retrieved for SLIT for AD (eczema).

In general, SLIT appears to be better tolerated than SCIT. SLIT should only be prescribed by physicians with appropriate allergy training and expertise. Specific instructions should be provided to patients regarding the management of adverse reactions, unplanned interruptions in treatment, and situations when SLIT should be withheld. The majority of SLIT adverse events are local reactions (e.g., oromucosal pruritus) that occur during the beginning of treatment and resolve within a few days or weeks without any medical intervention (e.g., dose adjustment, medication). Only a few cases of SLIT-related anaphylaxis have been reported but there have been no fatalities.

5.3.1 Safety: Sublingual immunotherapy (SLIT) for allergy rhinitis (AR)

From Tie KJ systematic review and meta-analysis, reported that adverse events (AEs) were reported in 11 of the 13 SCIT versus placebo RCTs and 29 of the 33 SLIT versus placebo RCTs. The vast majority of AEs from SCIT were injection site reactions (e.g., pruritus, swelling, edema, erythema, and wheal formation), whereas less common AEs included headaches, fatigue, nasopharyngitis, and tonsillitis. One study reported mild systemic anaphylactic reaction. The majority of AEs from SLIT were local reactions (e.g., oral pruritus, oral swelling, mouth oedema, facial flushing, throat irritation, and lip paresthesia), whereas less common AEs included headaches, fatigue, nasopharyngitis, pyrexia, angioedema, generalised pruritus, and abdominal cramps.

In the review by Kim KJ, the occurrence of serious adverse events (SAEs) was a reported outcome for 29 included studies involving 4810 participants, but only seven studies observed any events. Although events were infrequent, analysis using risk differences (RDs) suggests that no more than 1 in 100 are likely to suffer an SAE as a result of treatment with SLIT (RD −0.0004, 95% CI −0.0072 to 0.0064; **Figure 9**; Analysis 1.3; moderate-certainty evidence)

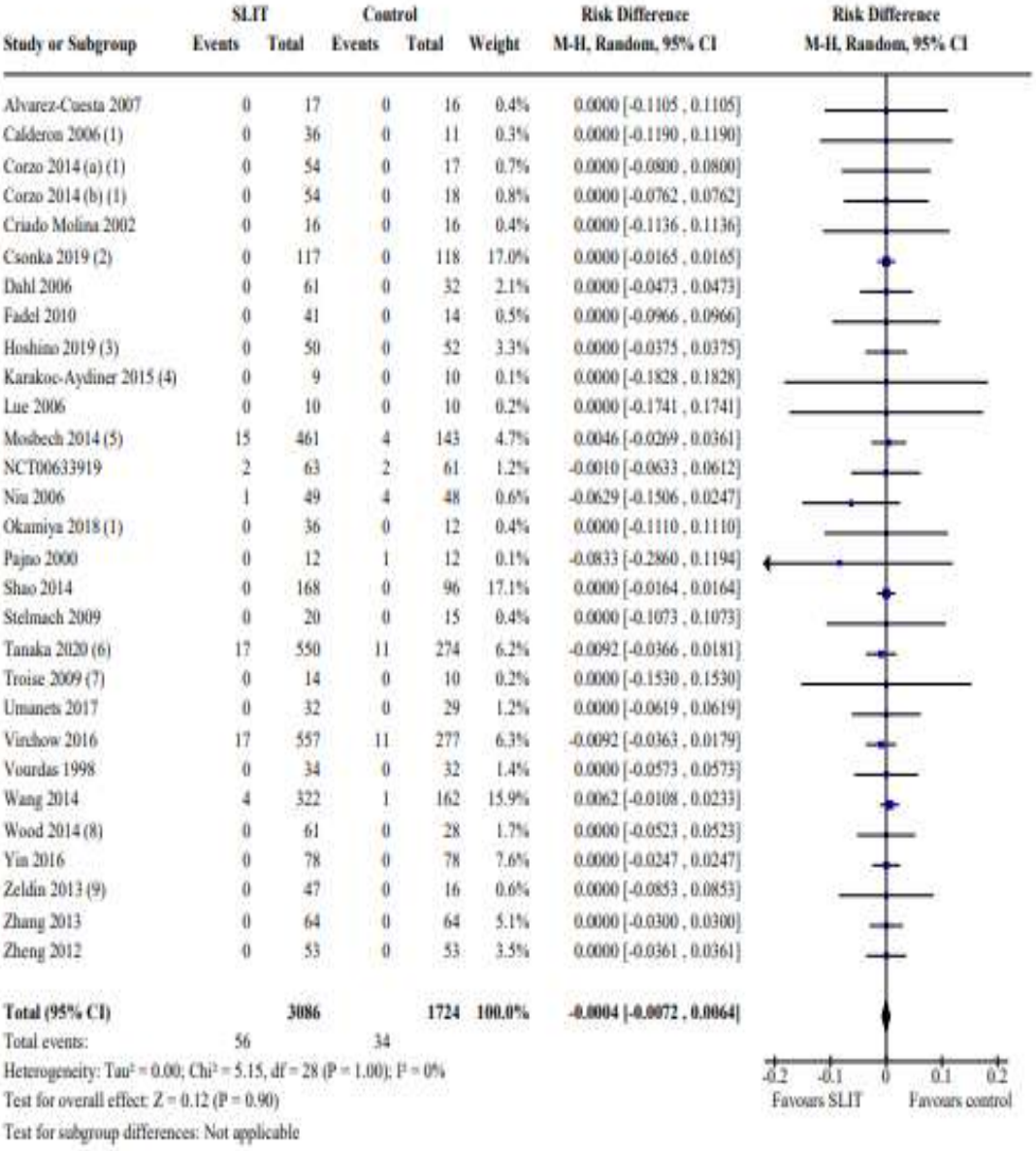


Figure 9: Forest plot of comparison: 1 Sublingual immunotherapy versus control, outcome: 1.3 Serious adverse events.

5.3.2 Safety: Sublingual immunotherapy (SLIT) for asthma

From Cochrane review by Fortescue R et al., the occurrence of serious adverse events (SAEs) was a reported outcome for 29 included studies (SLIT vs placebo) involving 4810 participants, but only seven studies observed any events. Although events were infrequent, analysis using risk differences (RDs) suggests that no more than 1 in 100 are likely to suffer an SAE as a result of treatment with SLIT (RD −0.0004, 95% CI −0.0072 to 0.0064; **as seen in Figure 10**; Analysis 1.3; moderate-certainty evidence)

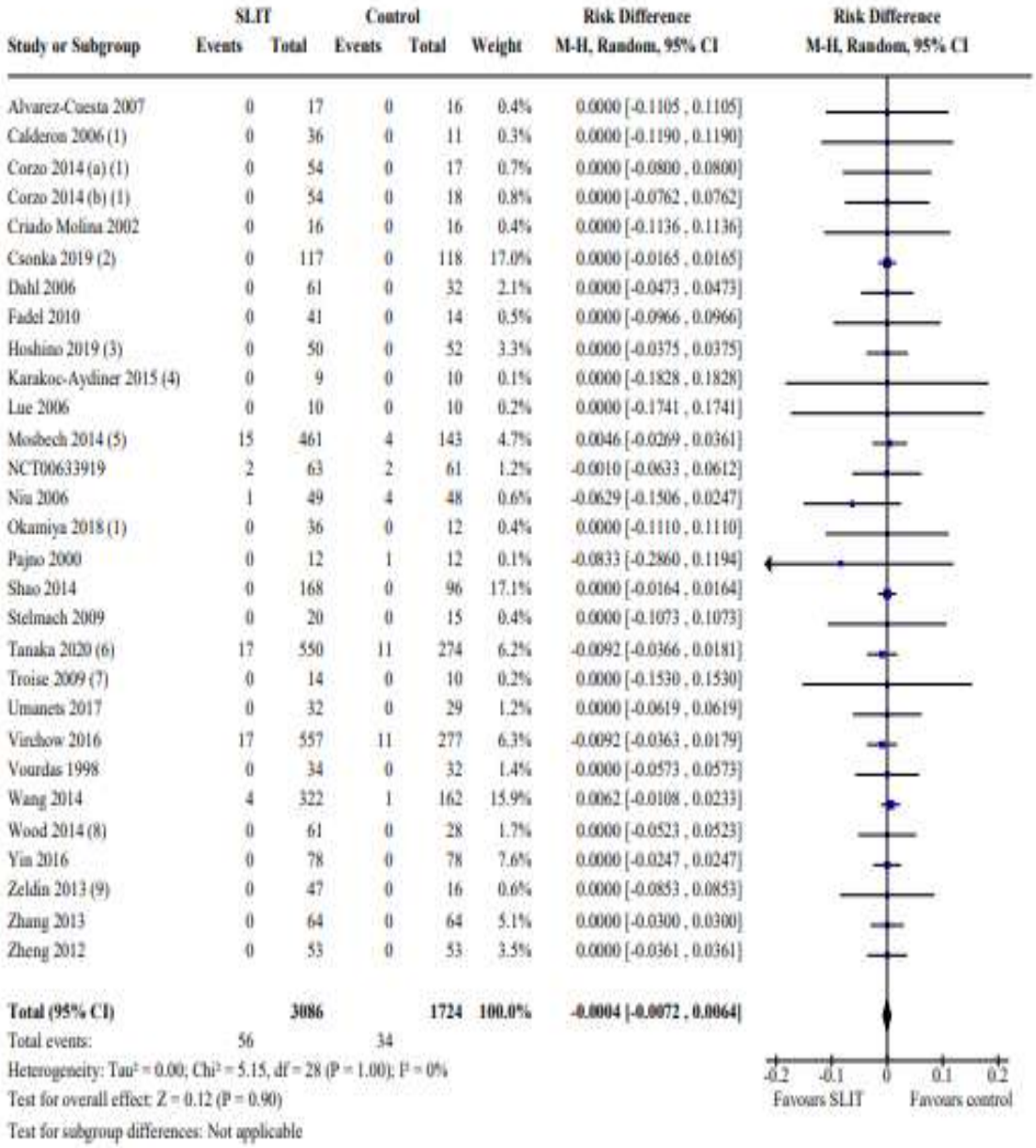


Figure 10: Forest plot of comparison: 1 Sublingual immunotherapy versus control, outcome: 1.3 Serious adverse events.

Adverse events were reported by just over half of the included studies, but often not in a way that could be combined in a meta-analysis; where this was the case, results of the quantitative synthesis are supplemented by narrative summaries of data that could not be included. Outcomes less frequently reported included skin prick tests (n = 16), bronchial provocation tests (n = 11), quality of life (n = 7), exacerbations (n = 7), and ICS dose reduction (n = 3). Despite the large number of outcomes reported in the included studies, meta-analysis was to some degree hampered by the wide range of non-validated measures used;two of ourthree primary outcomes of interest were rarely reported (exacerbations and quality of life)

5.3.3 Safety: Sublingual immunotherapy (SLIT) for atopic dermatitis (eczema)

There is no retrieved evidence regarding safety of SLIT for atopic dermatitis.

5.4 COST / COST-EFFECTIVENESS ANALYSIS

A HTA report by Meadows A et al in 2013 was conducted to determine the comparative cost-effectiveness of SCIT and SLIT for seasonal AR itis in adults and children. In this report, all published economic evaluations (EEs) which evaluating the costs and benefits of SCIT and/or SLIT compared with standard care / symptomatic treatment or of SCIT compared with SLIT. Thus, the purpose of the systematic review was to gain an overview of existing evidence in this area and to identify any suitable data (e.g. costs, utilities, transition probabilities) with which to populate a new Markov model.

Therefore, its identified 406 potentially relevant publications, of which 330 were excluded at the title/abstract stage. Of the 76 publications that were potentially relevant, full texts could not be obtained for eight. Full-text copies of 68 papers were examined, of which 52 were excluded. Sixteen publications were included. Of these, 14 were primary EEs and two were reviews of EE studies. In addition, three studies were identified that reported utility-based outcomes for seasonal AR. Five studies compared SCIT with standard care, six studies compared SLIT with standard care and two studies compared both SCIT and SLIT with standard care. One study compared different forms of SCIT (short and long term and with an adjuvant) to SLIT and standard care. Six studies were undertaken from a purely societal perspective, and two were from a health insurer perspective. Five studies considered a combination of cost perspectives: two considered societal, health service and patient perspectives, one used societal and NHS (Italy) perspectives, one used societal and third-party payer points of view, and one used societal, NHS (Germany) and health insurer perspectives.[2, level-I]

Results:

Seven studies compared SLIT with standard care, and all found that SLIT was more cost-effective. Studies reporting results of EEs based on data from randomised studies seemed to have been the most robust. Four studies reported cost per QALY all were

based on the same multinational trial (GT–0893) and included populations from different European countries in the respective analyses. All found that Grazax was cost-effective (below a threshold of £20,000), providing that annual costs of Grazax remain below £2200. The current annual cost in the UK is £814 (at £2.23 per tablet). Six studies compared SCIT with standard treatment and all found that SCIT was associated with better outcomes and/or lower long-term costs. Two studies calculated a cost per QALY for SCIT and found a low ICER, but the robustness of this result is uncertain. The evaluation by Keiding and Jørgensen found that SCIT either dominated ST or was associated with very low ICERs. When SCIT and SLIT were directly compared against each other, SCIT was found to be both more effective and more cost-effective over the long term, however, small sample size for this results (n=64), and therefore more studies based on larger samples are needed.[2, level-I]

From this HTA report, the authors consistently found that where either SCIT or SLIT was compared with standard therapy, it was more effective or, in some cases, both more effective and cost-effective. The most robust studies found that SLIT is likely to be cost-effective at thresholds of £20,000. In addition, although SCIT was also found to be cost-effective at a threshold of £20,000 (based on two studies), however, these results were associated with slightly greater uncertainty. Only two studies looked at the cost-effectiveness of SCIT compared with SLIT. Although suggestive of greater cost-effectiveness for SCIT, both studies had some methodological concerns associated with them and neither presented combined cost-effectiveness measures.[2, level-I]

A recent EEs study from Haydin FM et al in 2021, aims to compare the cost effectiveness of SCIT and SLIT as treatment modalities for adult patients with AR and conjunctivitis who undergo testing and qualify for AIT. A cost-effectiveness sensitivity analysis was then performed using a decision tree model to compare the modalities. A sensitivity and threshold analysis was then performed to assess the strength of recommendations after identifying results at baseline. **(see Figure 11)**[16]

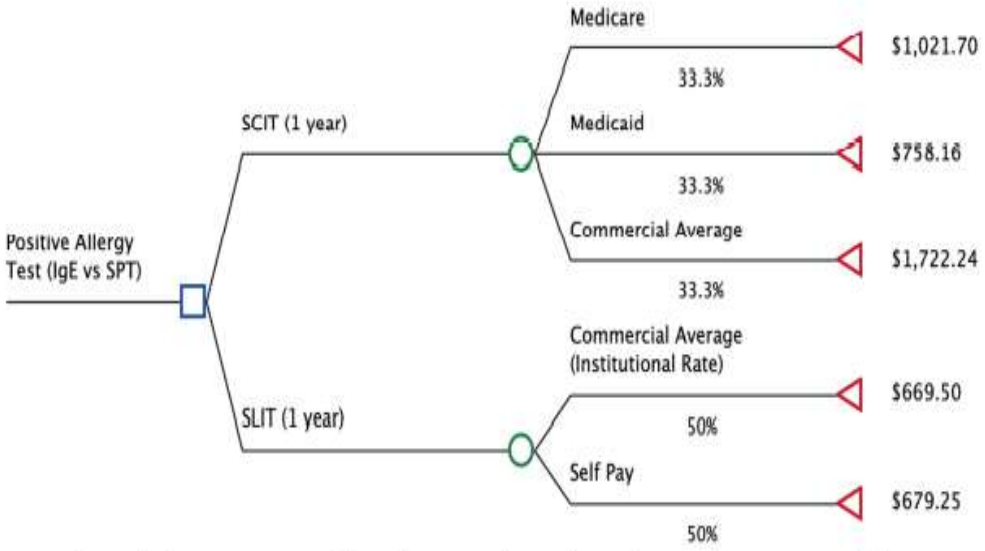


Figure 11: Cost-effective analysis of subcutaneous vs sublingual immunotherapy from the payor's perspective. A decision tree illustrating the fundamental components of this cost-effective analysis. Squares represent decisions (binary), circles represent chance (probabilities), and the triangles represent terminal payoffs. SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin pinprick test.

Results:

Table 4: Parameters Used in Decision Tree Analysis

Parameter	Baseline value	Range	References
Charge of SCIT to payer, per 12 months of therapy	1722.24	NA	NA
Charge of SLIT to payer, per 12 months of therapy	669.50	NA	NA
Adherence to SCIT	80	10-90	9
Adherence to SLIT	80	10-90	9
Effectiveness of SCIT	80	60-90	11, 12, 13
Effectiveness of SLIT	70	60-90	14, 15

Abbreviations: NA, Not applicable; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

The results of the analysis are highlighted in **Table 4**, which illustrates that for an assumed 80% efficacy of SCIT compared to 70% efficacy for SLIT, at all adherence rates, SLIT is the more cost-effective option per successful outcome to the payor. SCIT only becomes the more cost-effective option if, for instance, adherence rate is <40% to SLIT and the patient is >90% adherent to the SCIT treatment plan. When comparing head-to-head 80% adherence to either therapy, for a range of efficacy levels (60%-90% effective for each, as these values vary in the literature), SLIT is the more cost-effective modality.[16]

The authors concluded that the results of this study indicated that for the insurance payor, cost of SLIT per successful outcome, as determined by clinically significant

reduction in AR symptoms, is favourable when compared to cost of SCIT per successful outcome per 1 year of immunotherapy treatment. This EEs demonstrated that payor coverage of SLIT may be the economically for cost reduction in the AR adult patient population. SCIT becomes the more cost-effective option in certain scenarios, for instance, if a patient is at least >90% adherent to SCIT and less than <40% adherent to SLIT therapy.[16]

PART II: ECONOMIC IMPLICATION

Cost implication

The average prevalence of allergic rhinitis was reported as 7.1% in Malaysian adults and 8.7% among both adults and children in an Asia-Pacific study.[1,2,3] Meanwhile, the prevalence of asthma in Malaysia according to National Health Morbidity Survey Malaysia 2011 was 6.4%.[4] Among the allergens, HDM allergy was shown to be common in Malaysia and the majority of office workers were sensitized to HDM allergens.[1] Hence, the cost implication of an allergy immunotherapy HDM SLIT tablet was calculated in this analysis. As an example, HDM SLIT tablet (ACARIZAX®) is registered in Malaysia and are reported to be available in private hospitals.[5] This tablet is indicated for adults (18-64 years) and adolescence (12-17 years).[5] However, the retail price of this tablet in Malaysia is irretrievable from open sources. Thus, the cost estimation was based on the published literatures and was adjusted to the year 2021.[6,7,8,9]

The international treatment guidelines refer to a treatment period of 3 years for allergy immunotherapy to achieve disease modification.[5] In this analysis, the range of cost was calculated based on the recommended dose of one sublingual tablet daily for a minimum duration of one year as there is no indication for continuing treatment if no improvement is observed during the first year of treatment [5,8] The estimated cost of allergen test from private healthcare facilities was included in this analysis as this tablet is only indicated for those with a positive test of house dust mite sensitisation (skin prick test and/or specific IgE).[10] However, cost of pharmacotherapy was not included in this analysis. In addition, no difference in routine clinic visits associated with the initiation of this treatment is simulated in this analysis. The summary of the cost inputs is illustrated as **Table 6.**

Table 6: Summary of cost inputs

Resource	Unit cost	Sources
HDM SLIT tablet	MYR 12.20 to MYR 15.20*	8,9
Allergen test	MYR 370	10

*unit cost after foreign currency conversion

Based on the cost calculation, the estimated annual cost of allergy immunotherapy HDM SLIT tablet per patient is between MYR 4,823.00 to MYR 5,918.00. To achieve the disease modification, a recommended treatment of three years will incur an estimated cost between MYR13,729.00 to MYR 17,014.00 per patient. Since the recommended indication of this tablet is for those who are not adequately controlled with standard pharmacotherapy, the expected total expenditure will be based on the prevalence of this population.

5.5 ORGANISATIONAL

5.5.1 Guidelines

There was no guideline retrieved which specifically addressed the use of allergen immunotherapy. The chronology of SLIT treatment as follows:

In 1998, WHO recognised that SLIT was a promising alternate mode of immunotherapy and encouraged continued clinical investigation into this form of treatment. Subsequently, in 2001 the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines documented SLIT, and have consistently supported the effectiveness and safety of SLIT throughout subsequent updates. Continously, in 2009 from the position paper of World Allergy Organization (WAO) have published their opinion that the cumulative evidence showed SLIT represented a viable alternative to SCIT and encouraged continued clinical investigation to characterise optimal techniques.

The position of both SCIT and SLIT as potential therapeutic options for asthma has yet to be clearly established within international asthma guidelines. The Global Initiative for Asthma Guidelines (GINA) state that the efficacy of allergen immunotherapy for asthma is limited, and that potential benefits of immunotherapy must be weighed against the risk of adverse reactions, cost and duration of treatment- (GINA 2019). The UK guidance adopts a similar position and does not routinely recommend immunotherapy for asthma in adults or children. Furthermore, The National Institute for Health and Care Excellence (NICE), which advises the National Health Service (NHS) in the UK on cost-elective treatments, currently does not provide guidance on the use of SCIT or SLIT for asthma. The United States adult asthma management guidelines (Expert Panel Report 3) and The 2020 Focused Updates to the Asthma Management Guidelines state that SCIT should be considered for allergic asthma (approximately

equivalent to mild-to-moderate persistent asthma) of the six treatment steps. The European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend HDM-SCIT as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-sensitized-allergic asthma.

5.5.2 Sublingual immunotherapy registration

The U.S. Food and Drug Administration (FDA) approved four allergy tablets products. Two are directed at different kinds of grass pollen, one is for dust mites and one is for short ragweed. The two grass pollen allergy tablets are Oralair® (Stallergenes-Greer), which has five kinds of northern grass pollen, and Grastek® (ALK Inc.), which has timothy grass pollen. The short ragweed allergy tablet is called Ragwitek® (ALK Inc.). The dust mite tablet is called Odactra® (ALK Inc.). These four allergy tablets provide an additional option for the treatment of allergic rhinitis/rhinoconjunctivitis triggered by dust mite, ragweed or timothy/northern grasses.

In Japan, a standardised JCP extract for SLIT, Cedartolen® has been available since October 2014. After a large scale of clinical trials on SLIT tablets, the Ministry of Health, Labour and Welfare approved two different SLIT tablets namely Miticure® and Actair®. They have been available since June 2015. Consequently, one SLIT extract Cedartolen® for JCP and two SLIT tablets Miticure® and Actair® are available for HDM-induced allergic rhinitis.

In Malaysia, SLIT named Acarizax® is readily marketed which consist of standardised allergen extract from the house dust mites 12 SQ-HDM* per oral lyophilisate: 6 SQ-HDM *Dermatophagoides pteronyssinus*, 6 SQ-HDM *Dermatophagoides farina* (*SQ-HDM is the dose unit for Acarizax®. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract.

5.6 LIMITATION

Our review has several limitations and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles and further limited the study numbers. Few RCTs studies included in this review had small sample size which limit the generalisability of the findings.

6.0 CONCLUSION

Based from the review sublingual immunotherapy (SLIT) showed a significant benefit in term of reducing symptoms and medications used when compared with placebo, but inconclusive results when comparing between subcutaneous (SCIT) in treating patients with AR. Adverse events were common with both SCIT and SLIT and majority were local reactions at the point of administration and resolved spontaneously without treatment.

For patients with asthma, there was uncertain benefit showed for reducing the exacerbations/ hospital ED visits and medications score, but SLIT demonstrated safe option for people with well-controlled mild-to-moderate asthma and rhinitis.

For patients with AE, the included studies showed inconclusive results to suggest the use of SLIT as an option treatment.

In term of cost effectiveness, there were results SLIT is more economically when compared to placebo and other usual care. Based on the our cost calculation, the estimated annual cost of allergy immunotherapy HDM SLIT tablet per patient is between MYR 4,823.00 to MYR 5,918.00. To achieve the disease modification, a recommended treatment of three years will incur an estimated cost between MYR13,729.00 to MYR 17,014.00 per patient. Since the recommended indication of this tablet is for those who are not adequately controlled with standard pharmacotherapy, the expected total expenditure will be based on the prevalence of this population.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1. RHINITIS, ALLERGIC/
2. allergic rhiniti*.tw.
3. ECZEMA/
4. eczema*.tw.
5. eczematous dermatiti*.tw.
6. ECZEMA, DYSHIDROTIC/
7. dyshydrotic eczema*.tw.
8. pompholyx*.tw.
9. vesicular palmoplantar eczema*.tw.
10. ASTHMA/
11. asthma*.tw.
12. bronchial asthma*.tw.
13. DERMATITIS, ATOPIC/
14. (atopic adj1 (dermatiti* or eczema)).tw.
15. atopic neurodermatiti*.tw.
16. disseminated neurodermati*.tw.
17. infantile eczema*.tw.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. SUBLINGUAL IMMUNOTHERAPY/
20. sublingual immunotherap*.tw.
21. 19 or 20
22. 18 and 21
23.

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

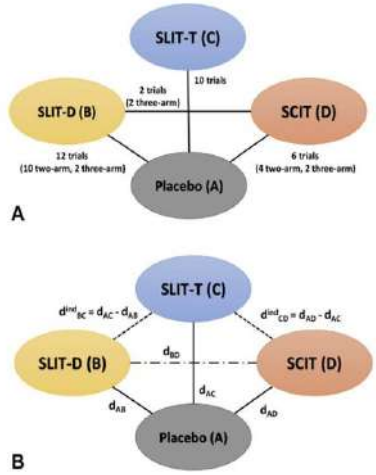
Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Allergy Rhinitis (AR)?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Tie K, Miller C, Zanation AM, et al. Subcutaneous Versus Sublingual Immunotherapy for Adults with Allergic Rhinitis: A Systematic Review with Meta-Analyses**. Laryngoscope. 2022 Mar;132(3):499-508**	SR + MA Aim: To determine whether subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) better improves patient outcomes and quality of life for adults with allergic rhinitis or rhinoconjunctivitis (AR/C) with or without mild to moderate asthma. Methods: Study selection: 4 databases (PubMed, Cochrane Library, EMBASE, & Web of Science) were queried from inception to July 30, 2020 for" RCTs of SCIT versus placebo, SLIT versus placebo, or SCIT versus SLIT Eligible studies: were RCTs that included only adults with	I	46 RCTs over 39 studies were included for the adjusted indirect comparisons, of which: 13 RCTs analysed SCIT vs placebo, and 33 RCTs analysed SLITvs placebo -published between 2001 and 2019 in Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Russia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, and United States	1.A head-to-head comparison of: SCIT vs SLIT; directly comparing SCIT vs SLIT) 2. An adjusted indirect comparison comparing SCIT vs placebo against RCTs comparing SLIT vs placebo)	Placebo SCIT		Effectiveness Outcomes: - symptom score (SS) - medication score (MS) - combined symptom medication score (CSMS) or - Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score Results: MA: Head-to-Head Comparison: SCIT vs SLIT: 7 RCTs - None of the seven studies reported significant differences between SCIT and SLIT for any of their measured outcomes Adjusted Indirect Comparison: Pooled SCIT vs Placebo (positive favors SCIT) Statistically significant results favoring SCIT for: SS (SMD: 0.40; 95% CI: 0.31–0.49; 15 arms across 9 studies; SCIT n = 1,198, placebo n = 983), MS (SMD: 0.26; 95% CI: 0.14–0.39; 7 arms across 6 studies; SCIT n = 656, placebo n = 409), CSMS (SMD: 0.42; 95% CI: 0.17–0.67; 9 arms across 7 studies; SCIT n = 1,004, placebo n = 781) RQLQ (MD: 0.24; 95% CI: 0.04–0.44;	ROB 2.0

	AR/C with or without mild to moderate asthma						1 arm across 1 study; SCIT n = 332, placebo n = 170). Adjusted Indirect Comparison: Pooled SLIT vs Placebo (positive favors SLIT) Statistically significant results favoring SLIT: <u>SS</u> (SMD: 0.42; 95% CI: 0.32–0.53; 41 arms across 25 studies; SLIT n = 4,750, placebo n = 4,830), MS (SMD: 0.40; 95% CI: 0.28–0.53; 29 arms across 19 studies; SLIT n = 3,823, placebo n = 3,869), <u>CSMS</u> (SMD: 0.37; 95% CI: 0.29–0.45; 25 arms across 16 studies; SLIT n = 3,726, placebo n = 3,893), and <u>RQLQ</u> (MD: 0.32; 95% CI: 0.20–0.43; 10 arms across 8 studies; SLIT n = 1,700, placebo n = 1,747). -significant heterogeneity among studies for SS, MS, CSMS, and RQLQ Adjusted Indirect Comparison: Pooled SCIT vs Placebo Against Pooled SLIT vs Placebo (positive values favor SCIT, whereas negative values favor SLIT) - no significant differences were found between SCIT and SLIT for SS, MS, CSMS or RQLQ <u>Safety</u> (AEs) were reported in 11 of the 13 SCIT vs placebo RCTs and 29 of the 33 SLIT vs placebo RCTs. Majority of <u>AEs from SCIT</u> were injection site reactions (e.g., pruritus, swelling, edema, erythema, and wheal	

							formation), whereas less common AEs included headaches, fatigue, nasopharyngitis, and tonsillitis Majority of AEs from SLIT were local reaction (e.g., oral pruritus, oral swelling, mouth edema, facial flushing, throat irritation, and lip paresthesia), whereas less common AEs included headaches, fatigue, nasopharyngitis, pyrexia, angioedema, generalized pruritus, and abdominal cramps. Author's Conclusion: Both SCIT and SLIT are effective treatment options for adults with pharmacotherapy-refractory AR/C with or without mild to moderate asthma. Based on results from an adjusted indirect comparison, treatment with either SCIT or SLIT results in comparable patient outcomes, so the decision for choosing between the two may be guided by other considerations, such as availability, cost, and patient preference. More future head-on RCTs analyzing SCIT vs SLIT are needed to directly compare the two.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Allergy Rhinitis (AR)?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2.Kim JY, Jang MJ, Kim DY, et al. Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis-Based Comparison**. J Allergy Clin Immunol Pract. 2021 Dec;9(12):4450-4458.e6.**	NMA Aims: aim of this study was to compare SLIT drop, SLIT tablet, and SCIT efficacy in patients with HDM associated perennial AR	I	26 DBRCTs for meta-analysis 12 studies with 766 patients (SLIT drop); 5744 patients (SLIT tablet) 6 studies with 233 patients (SCIT) and 2 studies including both SLIT drop & SCIT) Total of N= 3331 (immunotherapy) vs N= 3412 (placebo)	SLIT SCIT	placebo		The primary outcome was the nasal symptom score, & the secondary outcome was the medication score.  Reducing Symptom Score (SS) PMA (Direct pairwise): -revealed a significant reduction in the SS in each immunotherapy group relative to the placebo group, with pooled: SMDs of -0.461 (95% CI, -0.795 to -0.127) for SLIT drop -0.329 (95% CI, -0.426 to -0.231) for SLIT tablet, and -1.669 (95% CI, -2.753 to -0.585) for SCIT	**ROB 2.0**

							Severe heterogeneity was in SLIT drop and SCIT studies (I^2 = 77% and 91%, respectively), and SLIT tablet studies (I^2= 64%). sensitivity analysis of studies with a low risk of bias revealed a significant reduction in SS for SLIT tablet relative to the placebo by direct pairwise comparison: no significant differences were observed for SLIT drop and SCIT with pooled SMDs of -0.156 (95% CI, -0.472 to 0.159) for SLIT drop, -0.302 (95% CI, -0.366 to -0.238) for SLIT tablet, and -0.990 (95% CI, -2.076 to 0.097) for SCIT sensitivity analysis included only studies with a low risk of bias, heterogeneity among SLIT drop and SLIT tablet studies was moderate & low, respectively (I^2=38% and 0%, while among SCIT studies was still severe (I^2=90%). NMA: In NMA, there was no significant difference in SS between SLIT drop and SLIT tablet (SMD,-0.123; 95% CI, -0.428 to 0.182) The SCIT had greater clinical efficacy in the SS compared with SLIT drop or SLIT tablet (SMD: -0.697, 95% CI, -1.105 to -0.288; and SMD: -0.819, 95% CI, -1.242 to -0.397) Direct comparisons estimated by NMA indicated that all AIT modalities had significant clinical efficacy based on the SS compared with the placebo, which was in agreement with pairwise	

							comparisons. The sensitivity analysis of studies with a low risk of bias revealed no significant difference in the symptom score between SLIT drop and SLIT tablet (SMD, 0.070; 95% CI, -0.283 to 0.424) <u>Reduction in Medication Score (MS)</u> Direct PMA: In 18/26 studies, showed a significant reduction MS for each immunotherapy group relative to the placebo group was identified by pooled SMDs of -0.546 (95% CI, -0.860 to -0.232) for SLIT drop, -0.227 (95% CI, -0.371 to -0.083) for SLIT tablet, and -0.697 (95% CI, -1.039 to -0.355) for SCIT. heterogeneity was moderate, severe, and low among SLIT drop, SLIT tablet, and SCIT studies, respectively (I^2= 47%, 85%, and 0%, respectively). <u>Author's Conclusion:</u> This study demonstrated the clinical efficacy of all HDM immunotherapy modalities & suggests that SCIT may be more effective than SLIT drops or tablets in controlling symptoms of allergic rhinitis.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Allergy Rhinitis (AR)?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Masuyama K, Matsuoka T, Kamijo A. Current status of sublingual immunotherapy for allergic rhinitis in Japan. Allergol Int. 2018 Jul;67(3):320-325.	Aim: This review article will discuss AIT, especially the current status of SLIT in Japan. RCTs	I	Cedartolen®: N=531 with Japanese cedar pollinosis (JCP); Age: 12 – 64 yrs who had had symptoms of JCP for the previous 2 years and JCP-specific IgE levels (ImmunoCAP) of class 3 or higher Treatment began before the start of the pollen season in 2011 & continued to the end of the pollen season in 2012 SQ HDM Tablet Miticure®: N=946 8 weeks of the treatment period. Actair® N= 968 subjects vs placebo last 8 weeks of the treatment period.	1. Cedartolen® (1st product for SLIT in Japan. It was approved in 2014 2. HDM tablet Miticure® 3. Actair®	Placebo	18 months from Oct 2010 to April 2012	1. Cedartolen®: The primary endpoint was the total nasal symptom and medication score (TNSMSs) during the peak symptom period in the second season. As a result, the TNSMSs during the peak symptom period were signif icantly lower in the SLIT group than in the placebo group Results: Effectiveness 30% reduction compared with the placebo group, suggesting clinically relevant efficacy. At least one adverse event (AE) occurred in 212 of the 266 subjects (79.7%) in the SLIT group and in 189 of the 265 subjects (71.3%) in the placebo group. Results: Safety The most common AEs were mouth oedema, throat irritation, headache, oral pruritis and ear pruritus, and most of the AEs were mild and required no treatment. No anaphylactic reactions and no deaths occurred. Treatment-related AEs occurred in 36 subjects (13.5%) in the SLIT group vs 14 (5.3%) in the placebo group 2. SQ HDM tablet Miticure® in Japanese patients with HDM-induced AR. A total of 946 subjects were randomly assigned to receive daily treatment with a SQ HDM SLIT tablet at a dose of	

							20,000 JAU (12 SQ) or 10,000 JAU (6 SQ) or a placebo. Before reaching the maintenance dose, an up-dosing of 1 or 2 weeks was chosen. The subjects received treatment for 12 months. The primary endpoint was the total combined rhinitis score (TCRS), i.e., the sum of the rhinitis symptom and medication score during the last 8 weeks of the treatment period. Results: Effectiveness The absolute differences in adjusted means TCRS to the placebo were 1.15 ($p < 0.001$) in the 10,000 JAU group and 0.09 ($p < 0.001$) in the 20,000 JAU group, respectively. The relative differences to the placebo group were 22% and 19% in the 10,000 and 20,000 JAU groups, with 95% CI upper limits of 13% and 10%, respectively. Results: Safety Adverse drug reactions (ADRs) were observed in 63.6% of the subjects in the active treatment groups. No marked differences were seen between the two active treatment groups. 3. Actair® The primary efficacy endpoint was the Average Adjusted Symptom Score (AASS) during the last 8 weeks of the treatment period. Results: Effectiveness The AASSs over week 44-52 in both active groups significantly improved compared with that in the placebo group. The mean absolute and relative	

							differences in the AASSs (vs placebo) were 1.11 (18.2%) for the 300 IR group and 0.80 (13.1%) for the 500 IR group. The differences between the 300 IR and 500 IR groups was not statistically significant. The AASS in the 300 IR group was significantly improved at week 8-10, and this improvement was maintained until the end of the treatment. <u>Results: Safety</u> Adverse drug reactions (ADRs) were observed in 66.8% of the 300 IR group, 73.1% of the 500 IR group, and 18.6% of the placebo group. No marked differences were seen between the two active treatment groups. The incidence of ADRs leading to withdrawal was higher in the active group than in the placebo, and most of the ADRs were mild in severity. The most frequent ADRs were throat irritation, mouth edema, and oral and ear pruritis. No cases of anaphylactic shock were reported. <u>Author's Conclusion:</u> Before introducing SLIT, a correct diagnosis of JCP-or HDM-induced AR is necessary, and the appropriate indication for SLIT must be considered carefully. Adequate informed consent from patients with regard to the administration schedule of SLIT and local AE frequently observed during the early time of the introduction of SLIT is also required. Doctors need to prepare for AEs when necessary even if they are few and mild. This could improve both patient adherence and the efficacy of SLIT.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Allergy Rhinitis (AR)?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Meadows A, Kaambwa B, Novielli N et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess 2013;17(27).	HTA DBRCTs of SCIT or SLIT, or of SCIT compared with SLIT, and economic evaluations were included. Meta-analysis and indirect comparison meta-analysis and meta-regression were carried out. A new economic model was constructed to estimate cost–utility. Aim: To determine the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal AR in adults and children	I	For the review of clinical effectiveness, analyses were limited to 4 patient-centred outcomes – -symptom scores (SSs) -medication scores (MSs) -combined symptom and medication scores (SMS), and -QoL adverse events (AEs)	SCIT/SLIT	Usual care Placebo		<u>Results: Effectiveness</u> 17 new RCTs of SCIT vs placebo and 11 of SLIT vs placebo One small head-to-head trial of SCIT compared with SLIT was found. From 17 newly identified RCTs of SCIT (vs placebo) and 11 newly identified RCTs of SLIT (vs placebo), only five trials of each type of intervention reported data in a form suitable for meta-analysis. <u>meta-analysis</u>: Statistically significant results were found for both SCIT and SLIT, suggesting a moderate effect size in favour of the active treatment for all patient-centred outcomes (SS, MS, SMS, and QoL). A large amount of variability in how outcomes were scored meant that results had to be presented as standardised mean differences (SMD). Interpretation of these is difficult and the clinical significance of the results is uncertain. There is less evidence for children, particularly for SCIT. One small SCIT trial found significantly lower SSs	ROB; Low risk of bias

							and MSs, and improved QoL, in the actively treated group (after 3 years of treatment). For SLIT, statistically significant results (based on 9 studies) were found for SSs but not for MSs. The one study including a QOL measure found a statistically significant difference in favour of SLIT. Indirect comparisons of SCIT with SLIT were suggestive of SCIT being more beneficial for SSs and MSs, but this was associated with substantial residual heterogeneity. No statistically significant difference was found between the 2 interventions for combined SMSs or QoL, which could arguably be deemed more clinically useful outcomes. <u>Results: Safety</u> Adverse events (AEs) were common with both SCIT and SLIT, but the majority were local reactions at the point of administration and resolved spontaneously without treatment. Systemic reactions were less common, occurring in approximately 4.4% of injections for SCIT, and most were graded as mild or moderate in severity. However, 19% of systemic reactions following SCIT treatment were considered to be severe, compared with only 2% of systemic reactions following SLIT. Discontinuations due to AEs were similar between the interventions – 3% and 3.4% for SCIT and SLIT, respectively. No fatalities occurred in any of the trials.	

							<u>Author's Conclusion:</u> Based on a substantial number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than ST only, and this remains the case for the vast majority of subgroup analyses based on differences in population and treatment protocol. It is uncertain to what extent this statistical significance translates to clinically significant differences across the different types of outcome measures used. An indirect comparison is suggestive of SCIT being more beneficial than SLIT based on SSs and MSs, but no such difference could be shown for combined SMSs or QoL, and firm conclusions cannot be drawn.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Allergy Rhinitis (AR)?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Radulovic S, Calderon MA, Wilson D, et al. Sublingual immunotherapy for allergic rhinitis. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD002893.	SR with MA (Cochrane) Aim: To evaluate the efficacy and safety of SLIT for allergic rhinitis in adults and children. Inclusion/Exclusion Criteria: Randomised, double-blind, placebo-controlled trials of SLIT in adults or children.	I	60 RCTs Randomised, double-blind, placebo-controlled clinical trials. 49 pooled in MA (N=2333 – SLIT vs 2256 – placebo) excluded trials dealing with asthma only from the review	SLIT	placebo	Treatment lasted for < 6 mo in 17 studies; 6-12 mo in in 16 studies and > 12 mo in 16 studies	Primary outcome measures were symptom and medication scores. <u>Results: Effectiveness</u> <u>SLIT vs placebo</u> significant reduction in symptoms from 49 studies (SMD -0.49; 95% CI -0.64 to -0.34, *p*< 0.00001) and There was significant heterogeneity between the studies (Chi^2 = 256.76, *p* < 0.00001, I^2 = 81%) Medication scores 38 trials reported medication score results, with a total of 1737 patients in the SLIT group and 1642 in the placebo group. The combined SMD was -0.32 (95% CI -0.43 to -0.21, P < 0.00001). Significant heterogeneity was indicated (Chi^2 = 73.32, P = 0.0003, I^2= 50%) <u>Results: Safety</u> None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none ofthe systemic reactions reported required the use of adrenaline. <u>Author's Conclusion:</u> SLIT is effective for allergic rhinitis and has been proven to be a safe route of administration	JADAD scale Original from 2003 For the 2010 update, for ROB using the Cochrane Collaboration 'Risk of bias' tool as guided by The Cochrane Handbook for Systematic Reviews of Interventions

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for asthma?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Fortescue R, Kew KM, Leung MShiu Tsun. Sublingual immunotherapy for asthma. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD011293. D	SR (Cochrane) Aims: To assess the elicacy and safety of SLIT vs placebo or standard care for adults and children with asthma. most recent search for trials for the current update was conducted on 29 October 2019 Inclusion/Exclusion Criteria: parallel randomised controlled trials, irrespective of blinding or duration, that evaluated SLIT versus placebo or as an add-on to standard asthma management.	I	66 studies met the inclusion criteria for this update, including 52 studies from the original review. double-blind and placebo-controlled, varied in duration from 1D – 3 yrs and recruited participants with mild or intermittent asthma, often with comorbid allergic rhinitis. 23 studies recruited adults and teenagers; 31 recruited only children; 3 recruited both; and 9 did not specify	SLIT	Placebo/ Usual or standard care tx	1D – 3 years	The primary outcome: (mostly asthma or rhinitis symptoms), and only 2 small studies reported our primary outcome of: - exacerbations requiring an ED or hospital visit; <u>Results: Effectiveness</u> Pooled estimate : suggests SLIT may reduce exacerbations compared with placebo or usual care, but the evidence is very uncertain (OR 0.35, 95 (CI) 0.10 to 1.20; n = 108; very low-certainty evidence). 9 studies reporting quality of life could not be combined in a meta-analysis and, whilst the direction of elect mostly favoured SLIT, the elects were often uncertain and small. <u>Results: Safety</u> SLIT likely does not increase SAEs compared with placebo or usual care, and analysis by risk dilerence suggests no more than 1 in 100 people taking SLIT will have a serious adverse event (RD −0.0004, 95% CI −0.0072 to 0.0064; participants = 4810; studies = 29; moderate-certainty evidence). Secondary outcome asthma symptom and medication scores were mostly measured with non-	

							validated scales, which precluded meaningful meta-analysis or interpretation, but there was a general trend of SLIT benefit over placebo. Changes in ICS use (MD −17.13 µg/d, 95% CI −61.19 to 26.93; low-certainty evidence), exacerbations requiring oral steroids (studies = 2; no events), and Bronchial provocation (SMD 0.99, 95% CI 0.17 to 1.82; low-certainty evidence) were not oJen reported. Results were imprecise and included the possibility of important benefit or little elect and, in some cases, potential harm from SLIT. More people taking SLIT had adverse events of any kind compared with control (OR 1.99, 95% CI 1.49 to 2.67; high-certainty evidence; participants = 4251; studies = 27), but events were usually reported to be transient and mild. <u>Author;s Conclusion:</u> Trials mostly recruited mixed populations with mild and intermittent asthma and/or rhinitis and focused on non-validated symptom and medication scores. The review findings suggest that SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm, but the role of SLIT for people with uncontrolled asthma requires further evaluation.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for atopic eczema?

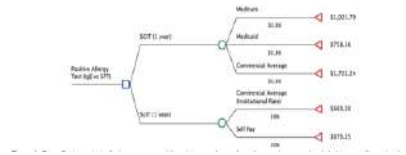
Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. Tam H, Calderon MA, Manikam L, et al. Specific allergen immunotherapy for the treatment of atopic eczema. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD008774.	SR (RCTs) (Cochrane) Aim: To assess the effects of specific allergen immunotherapy (SIT), including subcutaneous, sublingual, intradermal, and oralroutes, compared with placebo or a standard treatment in people with atopic eczema. Inclusion/Excusion Criteria RCTs of SIT that used standardised allergen extracts in people with AE	I	12 RCTs the total number of participants N=733. grass pollen, or other inhalant allergens (two trials). They were administered subcutaneously (six trials), sublingually (four trials), orally, or intradermally (two trials). Overall, the risk of bias was moderate, with high loss to follow up and lack of blinding as the main methodological concern.	SIT: (SCIT & SLIT) HDM (10 trials) Others: grass pollen, or other inhalant allergens (2 trials). They were administered SCIT (6 trials), SLIT (4 trials), orally, or intradermally (2 trials)	Usual care placebo	nil	primary outcomes: 'Participant- or parent-reported global assessment of disease severity at the end of treatment'; 'Participants or parent-reported specific symptoms of eczema, by subjective measures'; and 'Adverse events, such as acute episodes of asthma or anaphylaxis'. SCORing Atopic Dermatitis (SCORAD) is a means of measuring the eLect of atopic dermatitis by area (A); intensity (B); and subjective measures (C), such as itch and sleeplessness, which we used. For 'Participant- or parent-reported global assessment of disease severity at the end of treatment', one trial (20 participants) found improvement in 7/9 participants (78%) treated with the SIT compared with 3/11 (27%) treated with the placebo (risk ratio (RR) 2.85, 95% confidence interval (CI) 1.02 to 7.96; P = 0.04). Another study (24 participants) found no difference: global disease severity improved in 8/13 participants (62%) treated with the SIT compared with 9/11 (81%) treated with the placebo (RR 0.75, 95% CI 0.45 to 1.26; P = 0.38). For 'Participant- or parent-reported	no meta-analysis because of high heterogeneity The quality of the evidence was low. small number of studies

							specific symptoms of eczema, by subjective measures', two trials (184 participants) did not find that the SIT improved SCORAD part C (mean difference (MD) -0.74, 95% CI -1.98 to 0.50) or sleep disturbance (MD -0.49, 95% CI -1.03 to 0.06) more than placebo. For SCORAD part C itch severity, these two trials (184 participants) did not find that the SIT improved itch (MD -0.24, 95% CI -1.00 to 0.52).One other non-blinded study (60 participants) found thatthe SIT reduced itch compared with no treatment(MD -4.20, 95% CI -3.69 to -4.71) and reduced the participants' overall symptoms (P < 0.01), 7 trials reported systemic adverse reactions: 18/282 participants (6.4%) treated with the SIT had a systemic reaction compared with 15/210 (7.1%) with no treatment (RR 0.78, 95% CI 0.41 to 1.49; the quality of the evidence was moderate). The same 7 trials reported local adverse reactions: 90/280 participants (32.1%) treated with the SIT had a local reaction compared with 44/204 (21.6%) in the no treatment group (RR 1.27, 95% CI 0.89 to 1.81). As these had the same study limitations, we deemed the quality of the evidence to also be moderate. <u>secondary outcomes:</u> there was a significant improvement in 'Investigator- or physician-rated global assessment of disease severity at the end of treatment' 6 trials, 262	

							participants; RR 1.48, 95% CI 1.16 to 1.88). None of the studies reported our secondary outcome 'Parent- or participant-rated eczema severity assessed using a published scale', but two studies (n = 184), which have been mentioned above, used SCORAD part C, which we included as our primary outcome 'Participant- or parent-reported specific symptoms of eczema, by subjective measures' <u>Author's Conclusion:</u> Limited evidence that SIT may be an effective treatment for people with AE. The treatments used in these trials were not associated with an increased risk of local or systemic reactions. Future studies should use high quality allergen formulations with a proven track record in other allergic conditions and should include participant-reported outcome measures.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Ar/asthma/atopic eczema? (Economic)

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Hardin FM, Eskander PN, Franzese C. Cost-effective Analysis of Subcutaneous vs Sublingual Immunotherapy From the Payor's Perspective. OTO Open. 2021 Oct 25;5(4):2473974X 211052955 (Economic)	Economic (CEA) Payor's perspective Aim: Compare the CE of (SCIT) and aqueous (SLIT) as treatment modalities for adult patients with AR and conjunctivitis who undergo testing and qualify for allergen immunotherapy (AIT) Assumption: 80% compliance rate with AIT and an estimated efficacy (assumed to be clinically significant improvement in symptoms) of 70% for SLIT & 80% for SCIT, at the 12-month mark	-	The decision tree was constructed via TreeAge Pro Healthcare Version 2021 R2.0.	SCIT	SLIT	-	Decision tree model -constructed following recently published technique guidelines to study the cost-effectiveness of the 2 modalities in a population of 100 theoretical patients with clinical diagnoses of allergic rhinitis The hypothetical patients had positive allergy test results, whether in vitro specific IgE testing or skin prick testing, with appropriate controls and skin prick results considered positive if they were 3 mm or greater than the negative control. The decision would then be made to treat only the positive test allergens that correlated with patient symptoms. One treatment vial was created per 10 weeks of SCIT treatment, with SCIT patients receiving 5 vials per year for their therapy. In contrast, for SLIT patients, there would be 3 vials mixed annually. This model was produced and manipulated to determine the relative charge per successful outcome of SCIT vs aqueous SLIT. A cost-effectiveness sensitivity analysis was then performed using a decision tree model to compare the modalities. A sensitivity and threshold analysis was then performed to assess the strength of recommendations after identifying results at baseline.	**USA**

							 Results: illustrates that for an assumed 80% efficacy of SCIT compared to 70% efficacy for SLIT, at all adherence rates, SLIT is the more cost-effective option per successful outcome to the payor. SCIT only becomes the more cost-effective option if, for instance, adherence rate is <40% to SLIT and the patient is >90% adherent to the SCIT treatment plan. When comparing head-to-head 80% adherence to either therapy, for a range of efficacy levels (60%-90% effective for each, as these values vary in the literature), SLIT is the more cost-effective modality. The baseline total cost to the payor of SLIT per successful treatment outcome is USD$1196 while the charge of SCIT per successful treatment outcome is USD$2691. - favours SLIT as the more cost-effective modality per successful outcome.	

Evidence Table : Effectiveness/Safety
Question : Is sublingual immunotherapy effective and safe for Ar/asthma/atopic eczema? (Economic)

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Meadows A, Kaambwa B, Novielli N et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess 2013;17(27). (ECONOMIC)	HTA DBRCTs of SCIT or SLIT, or of SCIT compared with SLIT, and economic evaluations were included. Meta-analysis and indirect comparison meta-analysis and meta-regression were carried out. A new economic model was constructed to estimate cost–utility. Aim: To determine the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal AR in adults and children	I	For the review of clinical effectiveness, analyses were limited to 4 patient-centred outcomes – -symptom scores (SSs) -medication scores (MSs) -combined symptom and medication scores (SMS), and -QoL adverse events (AEs)	SCIT/SLIT	Usual care Placebo		Searches for EEs identified 14 EEs and two reviews of EEs. Overall, the studies found that both SCIT and SLIT were more beneficial than symptomatic treatment (ST), and in some cases also become less costly than ST over time. Where studies expressed results as incremental cost-effectiveness ratios (ICERs), both SCIT and SLIT were found to be cost-effective at thresholds of £20,000 per quality-adjusted life-year (QALY). An alternative, simpler, model was therefore constructed, which used data on quality-of-life improvement based on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) from the direct and indirect comparison meta-analyses. Using a number of assumptions, changes in RQLQ were mapped to changes in European Quality of Life-5 Dimensions (EQ-5D), in order to express results as cost per QALY. Based on a threshold of £20,000–30,000 per QALY, results showed that immunotherapy compared with ST became cost-effective after around 6 years from the start of treatment (NHS and patient perspective; 7 years for NHS perspective only).	**EUROPE**

							SCIT was found to be cost-effective compared with SLIT after around 5 years, based on the same threshold. This is based on SCIT being both more effective and more costly than SLIT. Results overall should be seen as indicative because they are based on a very simple analysis. Sensitivity analyses were restricted to varying the time horizon and using upper and lower confidence limits for RQLQ improvement. Author's Conclusion: CEAs suggest that both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per QALY from around 6 years. However, these estimates were based on limited data and the use of a number of assumptions. Potential cost savings resulting from future cases of asthma avoided were not included in the analysis, but would likely lead to an increase in cost-effectiveness.	