A report on treatment options in allergic rhinoconjuctivitis for Universitätsklinikum Schleswig-Holstein/Campus Kiel

Kleijnen Systematic Reviews Ltd

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Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD
United Kingdom
Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: robert@systematic-reviews.com
Website: www.systematic-reviews.com

Pawel Posadzki
Charlotte Ahmadu
Lisa Stirk
Jos Kleijnen
Robert Wolff

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
AC	Allergic conjunctivitis
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARC	Allergic rhinoconjuctivitis
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
DARE	Database of Abstracts of Reviews of Effects
FAQ	Frequently asked question
GIN	Guidelines International Network
HRQoL	Health-related quality of life
HTA	Health technology assessment
KSR	Kleijnen Systematic Reviews
MD	Mean difference
NICE	National Institute for Health and Care Excellence (UK)
NMA	network meta-analyses
NR	Not reported
PICOS	Participants, intervention, comparators, outcomes, and study design
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SDM	Shared decision making
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
SR	Systematic review
SSD	Standardised score difference
UK	United Kingdom
UKSH	Universitätsklinikum Schleswig-Holstein

1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the relevant treatment options for allergic rhinoconjunctivitis with/-out allergic bronchial asthma.

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed with clinical experts at Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. These questions reflect the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Systematic reviews (SRs) and health technology assessments (HTAs) evaluated herein aim to inform clinicians, patients, researchers, and health policy makers on relevant evidence pertaining to the aetiology as well as the management of allergic rhinoconjunctivitis with or without asthma.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients* with allergic conditions (allergic rhinoconjunctivitis with/-out allergic bronchial asthma)	Patients with uncontrolled asthma; severe autoimmune diseases/inflammation of organs; intake of immunosuppressive drugs (e.g. methotrexate, except for biologics); active malignant neoplastic diseases; severe cardio–vascular diseases (New York Heart Association Grade III or IV)
Intervention/ comparator	1. Subcutaneous immunotherapy 2. Sublingual immunotherapy	Nasal immunotherapy, oral immunotherapy, placebo
Outcomes	• Frequency of dosing • Duration of therapy • Start of therapy • Onset of improvement of symptoms • Contraindications • Improvement of symptoms, e.g. pain • Medication use • Combined symptom and medication scores • Remission time • Number of symptom-free-days • HRQoL • Local swelling, redness and itching at the injection site/mouth mucosa • Allergic reactions like sneezing, rhinitis, eczema, tearing eyes or mild asthmatic symptoms • Anaphylaxis (difficulty breathing, circulatory problems, gastrointestinal problems) • Risk factors for systemic reactions (e.g. taking beta-blockers) • Long-term negative effects	Nil

	Included	Excluded
	• Asthma + lung damage • Food allergy (prevention) • Epitope spreading	
Study design	Systematic reviews, health technology assessments and clinical practice guidelines	Narrative reviews; expert opinions; primary research; letters' overviews of reviews
* main focus of decision aid is on adults but KSR will check whether or not age is effect modifier. HRQoL = health-related quality of life; KSR = Kleijnen Systematic Reviews		

2.2 FREQUENTLY ASKED QUESTIONS

The following frequently asked questions (FAQs) were identified:

1. What does the treatment involve?
2. Will it help my symptoms?
3. How long will treatment effect last? Will it help maintain remission of my disease?
4. How will treatment impact my quality of life?
5. What are the risks or side effects?
6. Are there long-term negative effects of treatment to be expected?
7. Are there long-term negative effects of no treatment to be expected? What are the long-term benefits of treatment?

2.3 LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and guidelines on allergen immunotherapy for patients with allergic conditions. The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were not limited by language, publication date, or publication status. Also, the team at UKSH/Campus Kiel provided one additional reference.[1]

2.4 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review/health technology assessment (HTA) specific databases were searched on 2-3 November 2020 from date of inception to the most recent date available:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 11 of 12, November 2020
- Database of Abstracts of Reviews of Effects (DARE) (CRD): to 31 Mar 2015
- Health Technology Assessment (HTA) database (CRD): to 31 Mar 2018
- INAHTA International HTA database (https://database.inahta.org/): to 2 November 2020
- KSR Evidence (Internet) (https://ksrevidence.com/): to 2 November 2020
- Epistemonikos (Internet) (https://www.epistemonikos.org/): to 2 November 2020

The following guidelines resources were searched on 2-3 November 2020 from date of inception to the most recent date available:

- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): to 2 November 2020
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): to 2 November 2020
- NICE Evidence (Internet) (www.evidence.nhs.uk/): to 2 November 2020
- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): to 3 November 2020

Full details of all search strategies are presented in Appendix 1.

2.5 HANDLING OF CITATIONS

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.6 STUDY SELECTION AND DATA EXTRACTION

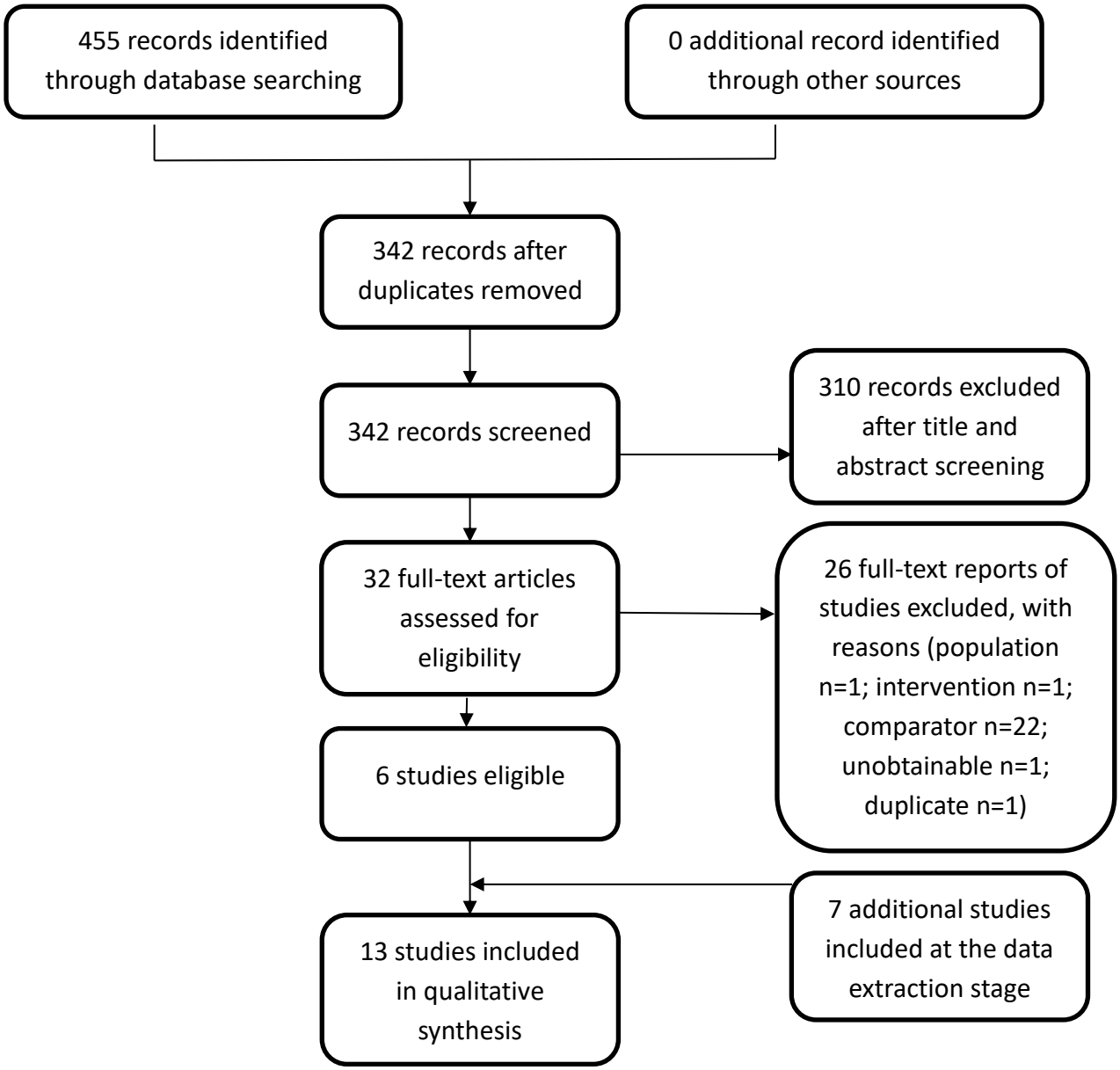
Two reviewers independently screened titles and abstracts of all records identified by the electronic searches. Any disagreements between the reviewers were settled through a consensus. For potentially eligible SRs, HTAs or clinical practice guidelines (CPG), full-text versions were obtained, and screened against inclusion and exclusion criteria by these same two reviewers independently. For each study, data were extracted by one reviewer and another reviewer validated the entries. Any disagreements were resolved through discussion. When evaluating the quality of the evidence, we relied on ratings of the authors of secondary studies if available; if unavailable we rated studies ourselves.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted in November 2020 to identify all relevant SRs, HTAs, or CPGs. A total of 455 records were retrieved from the electronic literature searches. After the removal of duplicate records 342 titles and abstracts were screened by two reviewers. After screening of 32 full-text papers, six met the inclusion criteria. Seven additional publications were provided by the UKSH team at the data extraction stage. A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[2]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Overall, ten systematic reviews (SRs), two clinical practice guidelines (CPG) and one HTA were eligible for inclusion. Table 2 summarises the sources of evidence used to answer the seven FAQs. These SRs, CPGs and HTA included evidence mainly from randomised controlled trials (RCTs). Quantitative evidence from direct comparisons, i.e. subcutaneous immunotherapy (SCIT) versus sublingual immunotherapy (SLIT), was available to answer the respective FAQs. For FAQs 3 and 7, only qualitative evidence was available. FAQs 5 and 6 were conceptually similar and merged together.

Table 2: Evidence sources

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will it help my symptoms?	FAQ3: How long will treatment effect last? Will it help maintain remission of my disease?	FAQ4: How will treatment impact my quality of life?	FAQ5: What are the risks or side effects?	FAQ6: Are there long-term negative effects of treatment to be expected?	FAQ7: Are there long-term negative effects of no-treatment to be expected? What are the long-term benefits of treatment?
Calderon 2011[3]	SR	SLIT	✓						
Di Bona 2012[4]	SR	SLIT	✓						
		SCIT							
Erekosima 2014[5]	SR	SCIT	✓						
Lin 2013[1]	SR	SLIT					✓		
		SCIT							
Kim 2013[6]	SR	SLIT	✓						✓
		SCIT							
Meadows 2013[7]	HTA	SLIT	✓	✓	✓	✓	✓	✓	✓
		SCIT							
Chelladurai 2013[8]	SR	SLIT	✓						
		SCIT							
Dranitsaris 2014[9]	SR	SLIT		✓			✓		
		SCIT							
Radulovic 2010[10]	SR	SLIT	✓						
Dhami 2017[11]	SR	SLIT		✓			✓	✓	
		SCIT							

Roberts 2018[12]	CPG	SLIT SCIT	✓						
Roder 2008[13]	SR	SLIT SCIT	✓						
Pfaar 2014[14]	CPG	SLIT SCIT					✓	✓	

CPG = clinical practice guidelines; HTA = health technology assessment; MA= meta-analysis; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SR = systematic review

3.3 FAQ 1: WHAT DOES THE TREATMENT INVOLVE?

This section covers the two treatment options of allergic rhinoconjuctivitis, i.e. sublingual immunotherapy and subcutaneous immunotherapy. These two options and a description of the condition are given in Table 3. However, no evidence was found for the following outcome:

a. Onset of improvement of symptoms

Table 3: Description of treatments for allergic rhinoconjuctivitis

Allergic rhinoconjuctivitis
Allergic rhinoconjuctivitis (ARC) is an allergen-mediated inflammation of the conjunctiva (also known as allergic conjunctivitis) and the inside of the nose (allergic rhinitis). Allergic rhinitis (AR) typically affects between 10% and 40% of people worldwide, while approximately 90% of patients with AR also experience symptoms of allergic conjunctivitis (AC).[3, 10] Symptoms associated with ARC are typically sneezing, watery rhinorrhoea, nasal blockage, itchy, watery eyes, red, swollen eyes, and itchy throat.[10] The fundamentals of ARC treatment are allergen avoidance (as first-line treatment), followed by pharmacotherapy (to provide symptomatic relief), and specific immunotherapy for patients with more severe disease.[10, 13] Allergen specific immunotherapy (the administration of increasing amounts of a specific or part of an allergen) aims to modify disease by targeting the underlying immunologic mechanisms.[4, 7, 13] This immunotherapy is typically administered through two routes: by injection under the skin (subcutaneous), or under the tongue (sublingual as either drops or tablets) with the aim of reducing the allergic symptoms in medium and long term. Subcutaneous injections and the initial sublingual dose should be given by healthcare personals who are trained in allergen immunotherapy and the management of any adverse events.[12] Several contraindications need to be considered when planning immunotherapy including but not limited to uncontrolled or severe asthma, active, systemic autoimmune disorders, or active malignant neoplasia (cancer). Furthermore, it is not recommended to initiate immunotherapy during pregnancy, but, if already initiated, the therapy may be continued during pregnancy or breastfeeding in agreement with the patient's general practitioner and obstetrician if previously well tolerated.[12] Finally, the Summary of Product Characteristics should also be read for product-specific contraindications which may differ between preparations.[12]
Subcutaneous immunotherapy
Subcutaneous immunotherapy (SCIT; injection under the skin) first introduced by Noon in 1911 is the more traditional means of allergen administration, which has been used for decades.[5, 10] Due to the risk of adverse reactions to allergen injections in sensitised patients, allergen SCIT is a two-phased strategy, consisting of an initial induction phase followed by a maintenance period.[7, 9] SCIT treatment schedules involves a gradual increase in allergen content of injections typically one or two injections weekly, and once

a pre-specified maximum treatment dose has been achieved, or the maximum tolerated dose for any given patient has been attained, treatment continues with this maintenance dose for the duration of therapy, usually monthly for two to three years.[7] Regarding the optimal time to start therapy, pre- and pre-/coseasonal administration of SCIT is recommended for seasonal and perennial ARC for short-term benefit.[12] Local adverse events such as injection site itching or swelling are commonly observed with SCIT administration, and although rare, there is an associated risk of severe systemic reactions.[10] Though proven to be efficacious, as a result of the increased risk of severe allergic reactions, SCIT delivery must be restricted to clinical settings where full resuscitation facilities are available, hence the SCIT treatment schedule will require considerable time commitment from the patient, and intensive resource use.[7, 10]

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) is an alternative means of desensitisation without injections. The allergen is delivered in a dissolvable tablet or aqueous solution formulation and is placed under the tongue, thus SLIT can be self-administered outside of a clinical setting.[7, 8] SLIT is reportedly safer at higher doses than SCIT (up to 500 times SCIT dose can be administered monthly), and as an optimal treatment schedule is yet to be established, up dosing may or may not be necessary to reach a maintenance dosing schedule.[7] A maintenance SLIT dosing schedule can be directly established, with intervals ranging from daily to weekly, while treatment duration usually ranges from six months to three years.[6, 7] Thus SLIT is a good alternative for patients who are not suitable for SCIT i.e. patients with poorly controlled asthma or patients with needle-phobia.[9] Although SLIT has a favourable safety profile, avoids indirect costs due to missed work or school days and intensive clinical resource use as seen in SCIT, maintenance doses for SLIT tend to be up to 200 times the dose used in SCIT, which has implications for treatment cost.[7] Regarding the optimal time to start therapy, pre- and pre-/coseasonal administration (during the pollen season) SCIT is recommended for seasonal ARC for short-term benefit.[12]

3.4 FAQ 2: WILL IT HELP MY SYMPTOMS?

This section explains whether specific types of allergen immunotherapy, i.e. sublingual or subcutaneous will ease such symptoms as sneezing, watery rhinorrhoea, nasal blockage, swollen eyes, and itchy throat. This section also describes which types of allergen immunotherapy are better at reducing anti-allergic medication use or improving composite scores.

Resolution/improvement of symptoms

Two studies reported quantitative data comparing the effectiveness of SCIT and SLIT in the resolution of symptoms pertaining to allergic conditions (see Table 4). Due to the paucity of direct comparative evidence, both studies conducted network meta-analyses (NMA) of these two interventions, on the assumption that there were sufficient similarities between the

placebo-controlled trials, and that the true treatment effect comparing SCIT and SLIT would be similar regardless of whether one or both interventions were included in the trial.[7, 15] Using an unadjusted model from placebo-controlled RCTs, Meadows et al. 2013 pooled data from 17 SCIT RCTs and 42 SLIT RCTs to estimate a relevant difference favouring SCIT over SLIT in improving symptoms of seasonal allergic asthma in treatment-naive adults and children.[7] Similarly Dhami et al. 2017 pooled data separately for SCIT versus placebo (n=16 trials) and SLIT versus placebo (n=41 trials) and suggested that both SCIT and SLIT were more effective in reducing symptom scores (standardised mean difference (SMD) -0.65 (95% CI -0.86 to -0.43)) and SMD -0.48 (95% CI -0.61 to -0.36 respectively.[11] On the other hand, Dranitsaris 2014 compared the sublingual immunotherapy, Oralair™ to SCIT to find a relevant difference in favour of SLIT (mean difference (MD) -0.18; 95% CI −0.31 to −0.047)) with respect to reduction in symptom scores.[9] The certainty of the evidence was predominantly low for this outcome.

Reduced use of medication

Meadows et al. 2013 reported quantitative data from an NMA of SCIT and SLIT on medication scores (see Table 4).[7] They pooled data from 16 SCIT RCTs and 35 SLIT RCTs to estimate a >99% chance of SCIT being the superior intervention in decreasing the use of medications for symptomatic relief.[7] However, Dhami et al. 2017 pooled data separately for SCIT versus placebo (n=16 trials) and SLIT versus placebo (n=29), and suggested that both SCIT and SLIT were more effective in reducing the use of medications SMD -0.52 (95% CI -0.75 to -0.29) and SMD -0.31 (95% CI -0.44 to -0.18) respectively.[11] The certainty of the evidence was low to moderate for this outcome.

Combined symptom and medication scores (CSMS)

Meadows et al. 2013 also reported quantitative data from NMA of SCIT and SLIT on combined symptom-medication scores, although there was some disparity in reporting on the number of included RCTs in the meta-analysis (see Table 4). This study found no relevant difference between SCIT and SLIT concerning the outcome.[7] The certainty of the evidence was low to moderate for this outcome. However, Dhami et al. 2017 pooled data separately for SCIT versus placebo (n=11 trials) and SLIT versus placebo (n=4), and suggested that both SCIT and SLIT were more effective in reducing CSMS (SMD -0.51 (95% CI -0.77 to -0.26) and SMD -0.47 (95% CI -0.81 to -0.12) respectively.[11]

Table 4: FAQ 2 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Resolution of symptoms	Dranitsaris 2014[9]	N = 20 (RCTs)	NR	SCIT	Oralair (SLIT)	MD= -0.18 (95% CI= -0.31 to -0.047)	Low (data of unclear quality and high heterogeneity)	Difference in favour of SLIT but data of low quality ⇗
Resolution of symptoms	Meadows 2013[7]	N= 59 (RCTs)	NR	SCIT (659/1,188)	SLIT (2,440/4,819)	RR = 1.10 (95%CI 1.03 to 1.16)*	Moderate (data of moderate quality and high heterogeneity)	Difference in favour of SCIT but data of moderate quality ⇗
Symptom score	Dhami 2017[11]	N = 16 (RCTs)	NR	SCIT (inestimable)	Placebo	SMD = -0.65 (95% CI -0.86 to -0.43)	Low (unclear risk of bias and high heterogeneity)	
Symptom score	Dhami 2017[11]	N = 41 (RCTs)	NR	SLIT (inestimable)	Placebo	SMD = -0.48 (95% CI -0.61 to -0.36)	Low (unclear risk of bias and high heterogeneity)	
Medication score	Dhami 2017[11]	N = 16 (RCTs)	NR	SCIT (inestimable)	Placebo	SMD = -0.52 (95% CI -0.75 to -0.29)	Low (unclear risk of bias and high heterogeneity)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs , e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Medication score	Dhami 2017[11]	N = 29 (RCTs)	NR	SLIT (inestimable)	Placebo	SMD = -0.31 (95% CI -0.44 to -0.18)	Low (unclear risk of bias and high heterogeneity)	
Medication score	Meadows 2013[7]	N= 51 (RCTs)	NR	SCIT (621/1,104)	SLIT (1,934/3,779)	SSD= 0.273 (95% CrI= 0.027 to 0.529)	Moderate (data of moderate quality and high heterogeneity)	Difference in favour of SCIT but data of moderate quality ⇗
Combined symptom and medication score	Meadows 2013[7]	N= 14 (RCTs)	NR	SCIT	SLIT	SSD= 0.313 (95% CrI= -195.8 to 194.1)	Moderate (data of moderate quality)	No difference shown ⇔
Combined symptom and medication score	Dhami 2017[11]	N = 11 (RCTs)	NR	SCIT (inestimable)	Placebo	SMD -0.51 (95% CI -0.77 to -0.26)	Low (unclear risk of bias and high heterogeneity)	
Combined symptom and medication score	Dhami 2017[11]	N = 4 (RCTs)	NR	SLIT (inestimable)	Placebo	SMD -0.47 (95% CI -0.81 to -0.12)	Low (unclear risk of bias and high heterogeneity)	

CI = confidence interval; CrI = credible interval; MD = Mean Difference; NR = not reported; RCT = randomised controlled trial; SMD = Standardised mean difference; SSD = Standardised score difference; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; *own re-calculation with RevMan 5.4.1 (please refer to the appendix 3).

3.5 FAQ 3: HOW LONG WILL TREATMENT EFFECT LAST? WILL IT HELP MAINTAIN REMISSION OF MY DISEASE?

No quantitative data was found to contribute to evidence on the duration of allergen immunotherapy (AIT) effect and the remission time of the allergic disease. However, the HTA reported conclusions from an RCT of a three-year grass immunotherapy intervention where the effect of the grass AIT persisted for up to three years after terminating use of the intervention.[7, 16] Similarly, for patients with ARC, a minimum of 3 years of either SCIT or SLIT is recommended to achieve long-term efficacy after treatment discontinuation based on high certainty evidence.[12]

3.6 FAQ 4: HOW WILL TREATMENT IMPACT MY QUALITY OF LIFE?

Based on the homogeneity and similarity assumption, Meadows et al. 2013 conducted NMAs on the effect of SCIT and SLIT on quality of life (QoL) – see Table 5 below.[7] Using an unadjusted random effects model, this study found that although there is a high probability of SCIT being the best treatment in terms of improving the patients' QoL, both unadjusted and adjusted standardised score difference (SSDs) were not relevant. However, one might imply that when symptoms decrease, QoL will improve as a result. The certainty of the evidence was low for this outcome.

Table 5: FAQ 4 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Health-related quality of life	Meadows 2013 [7]	N= 15 (RCTs)	NR	SCIT	SLIT	SSD= 0.383 (95% CrI= -0.042 to 0.804)	Low (data of unclear risk of bias and heterogeneity)	No difference shown ⇔

CrI = credible interval; NR = not reported; RCT = randomised controlled trial; SSD = Standardised score difference; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

3.7 FAQ 5 AND 6: WHAT ARE THE RISKS OF SIDE EFFECTS AND ARE THERE LONG-TERM NEGATIVE EFFECTS OF TREATMENT TO BE EXPECTED?

Dranitsaris 2014 conducted an NMA of SCIT and Oralair (SLIT), with respect to discontinuation due to adverse events (AEs), to find that there is no relevant difference in the outcome between the two interventions (relative risk (RR) = 1.55; 95% CI=0.54 to 4.44).[9] The certainty of the evidence was low for this outcome. Roberts 2018[12] described redness, itching, or swelling as the most common local adverse reactions and occurring (at the injection site) in approx. 50% of SCIT patients, whereas temporary local mucosal reactions (oral pruritus or dysesthesia, swelling of the oral mucosa, throat irritation) or abdominal pain has been reported in 40-75% of SLIT patients (depending on the dose administered).

In Meadows 2013, as well as the SCIT group having a higher incidence of AEs when compared to patients on SLIT (79% vs. 65% indirectly compared, respectively), a greater number of mild/ moderate systemic AEs were also experienced (see Table 6 for mild and moderate systemic AEs).[7] Severe systemic AEs defined as being incapacitating or significantly affecting clinical status and requiring intervention in Nelson 2011, also constituted a greater proportion of reported AEs in patients on SCIT when compared to SLIT across six trials (19% versus 3% respectively).[7, 17] Thirteen studies (n= 557) reported on 19 incidents leading to the use of adrenalin following 14,085 SCIT injections (0.13%) whilst two trials (n= 782) reported on two incidents of adrenalin usage following grass SLIT administration; one event was graded as moderate severity (lip angioedema, slight dysphagia, and intermittent cough), and the other as grade 1 systemic reaction (local site reactions, chest discomfort, and rash).[7, 17, 18] No life-threatening events, investigator-diagnosed systemic allergic reactions, anaphylactic shock, or respiratory compromise were reported in the two trials.[17, 18] Post-administration anaphylaxis defined as reactions involving two or more organ systems concurrently and/or severe enough to require epinephrine in Casale 2006 was also reported following both SCIT and SLIT use - 10 patients reported in one trial (n= 159) and 4 patients reported in two trials (n= 427).[7, 19] The certainty of the evidence was low for this outcome.[7]

Based on very low certainty of the evidence, 4% (1/24) of patients have experienced gastrointestinal AEs such as nausea or pain or diarrhoea in SCIT versus 11% (16/149) in SLIT (RR = 0.39; 95% CI 0.05 to 2.79).[1] There are several risk factors for systemic reactions during AIT that need to be mentioned. Those include current allergic symptoms and potential allergen exposure, active infections, mast cell disease, previous systemic reaction to either SCIT or SLIT, uncontrolled or severe asthma, a high degree of sensitisation, excessive dose escalation during initiation phase, the use of beta-blockers, overdose of allergen extract.[12, 14] It is worth noting that the risk and effects of adverse systemic reactions in the setting of AIT can be effectively reduced by training of personnel, adhering to safety standards and prompt use of emergency measures, including early administration of epinephrine.[14] In summary, the safety profile between SCIT and SLIT is comparable.[11]

Table 6: FAQs 5 and 6 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Discontinuation due to side-effects	Dranitsaris 2014[9]	N = 20 (RCTs)	NR	SCIT (15/536) (2.7%)	Oralair (SLIT) (30/879) 3.4%	RR = 1.55 (95% CI=0.54 to 4.44)	Low (data of unclear quality and high heterogeneity)	No difference shown ⇔
Discontinuation due to side-effects	Meadows 2013[7]	N = 5 (RCTs)	NR	SLIT (30/879) (3.4%)	Placebo (14/686) (2%)	NR	Low (data of unclear quality and imprecision)	
Discontinuation due to side-effects	Meadows 2013[7]	N = 2 (RCTs)	NR	SCIT (15/536) (2.7%)	Placebo (4/532) (0.7%)	NR	Low (data of unclear quality and imprecision)	
Local adverse-effects	Dhami 2017[11]	N = 30 (RCTs)	NR	SLIT	Placebo	RR = 1.71 (95% CI= 1.43 to 2.05)	Low (unclear risk of bias and high heterogeneity)	
Local adverse-effects	Dhami 2017[11]	N = 9 (RCTs)	NR	SCIT	Placebo	RR = 2.21 (95% CI= 1.43 to 3.41)	Low (unclear risk of bias and high heterogeneity)	
Mild systemic adverse-events	Meadows 2013[7]	N= 5	NR	SLIT (830/669)[a]	Placebo (314/458)[a]	NR	Low (data of unclear quality and imprecision)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Moderate systemic adverse events	Meadows 2013[7]	N= 5	NR	SLIT (253/669)[a]	Placebo (129/458)[a]	NR	Low (data of unclear quality and imprecision)	
Severe systemic adverse events	Meadows 2013[7]	N= 6	NR	SLIT (30/744)[a]	Placebo (12/498)[a]	NR	Low (data of unclear quality and imprecision)	
Mild systemic adverse events	Meadows 2013[7]	N= 4	NR	SCIT (38/227)[a]	Placebo (8/113)[a]	NR	Low (data of unclear quality and imprecision)	
Moderate systemic adverse events	Meadows 2013[7]	N= 4	NR	SCIT (25/227)[a]	Placebo (25/113)[a]	NR	Low (data of unclear quality and imprecision)	
Severe systemic adverse events	Meadows 2013[7]	N= 6[**]	NR	SCIT (12/302)[a]	Placebo (11/183)[a]	NR	Low (data of unclear quality and imprecision)	
Systemic adverse-effects	Dhami 2017[11]	N= 15	NR	SCIT	Placebo	RR = 1.15 (95% CI= 0.67 to 2.00)	Low (unclear risk of bias and high heterogeneity)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention	Comparator	Effect estimate with 95% CIs, e.g. mean/ median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
				Proportion with event Intervention/control group event rate (n/N)				
Systemic adverse-effects	Dhami 2017[11]	N= 24	NR	SLIT	Placebo	RR = 1.31 (95% CI= 1.05 to 1.63)	Low (unclear risk of bias and high heterogeneity)	
Adverse-effects: gastrointestinal (nausea/pain/diarrhoea)	Lin 2013[1]	N = 4 (RCTs)	NR	SCIT (1/24) (4%)	SLIT (16/149) (11%)	Risk Ratio = 0.39 (95% CI 0.05 to 2.79)*	Very low (high risk of bias and imprecision)	No difference shown ⇔
Total adverse-effects	Dhami 2017[11]	N = 19 (RCTs)	NR	SCIT	Placebo	RR = 1.58 (95% CI= 1.13 to 2.20)	Low (unclear risk of bias and high heterogeneity)	
Total adverse-effects	Dhami 2017[11]	N = 32 (RCTs)	NR	SLIT	Placebo	RR = 1.68 (95% CI= 1.44 to 1.98)	Low (unclear risk of bias and high heterogeneity)	

CI = confidence interval; NR = not reported; RR = relative risk; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; * calculated using RevMan 5.4.1. (fixed-effects model, Mantel-Haenszel; forest plot is available in the Appendix 2); ** Sahin 2011 reported only treatment-related severe AEs[20]; [a] no. of events/no. of participants

3.8 FAQ 7: ARE THERE LONG-TERM NEGATIVE EFFECTS OF NO-TREATMENT TO BE EXPECTED? WHAT ARE THE LONG-TERM BENEFITS OF TREATMENT?

No quantitative evidence was found for the outcome of long term benefits or AEs of AIT.[6, 7] These studies show that there has been a wide variation of conclusions from studies on the long term effects of AIT use. A review reported relevant long term benefits from three studies.[6] Three years post-AIT use, one study showed a 40% decrease in the odds of developing new sensitivities (compared to pharmacotherapy), and three years of SCIT use (compared to placebo) showed 2.5-fold greater odds of preventing new onset of asthma in children with rhinoconjuctivitis, notwithstanding, no difference was found in the development of new sensitivities in mono-sensitised children on SLIT or placebo treatment after eight years follow-up.[6, 21-23] The HTA however reported positive results from a 10-year multi-centre prospective study carried out in children with seasonal allergic rhinitis where AIT was suspected to have prevented the onset of asthma.[7, 24] SR by Bona et al. 2016 evaluated the efficacy of AIT in reducing the likelihood of developing new allergen sensitizations in both adults and children; and reported inconclusive findings based on low quality evidence. [25] In a similar vein, meta-analysis by Kristiansen et al. 2017 found no conclusive evidence that compared with controls, SLIT reduced the risk of developing a first allergic disease over the short term (RR = 0.30; 95% CI: 0.04–2.09; 2 studies).[26]

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

In general terms, although inconsistently, low to moderate certainty evidence suggests that when compared with SLIT, SCIT leads to better resolution of symptoms measured with symptom scores. It is worth mentioning that these symptoms scores are highly heterogeneous as manufacturers use different scoring systems for deriving scores. Thus one study reported favourable results in improving symptoms for SLIT compared with SCIT.[9] Similarly, there were some inconsistencies for medication scores; with one study reporting favourable results and the other one showing no differences.[7, 11] Analogically, for combined symptom and medication score no differences were shown between the two treatments in two studies. [7, 11]

Even though the certainty of the qualitative evidence was inestimable for FAQ 3, some qualitative data suggested that the effect of the grass AIT persisted at three years follow-up.[7, 16]

Low certainty evidence (highly heterogeneous and of unclear risk of bias) shows no difference between SCIT and SLIT for improving QoL of patients with allergic conditions (despite the high probability of SCIT being more effective) in one study.[7]

Findings were rather inconsistent for short and long-term AEs of the interventions. For instance, Dranitsaris 2014 found no relevant difference in discontinuation due to AEs between the two interventions.[9] In contrast 4% of patients have experienced nausea, pain or diarrhoea in SCIT compared with 11% SLIT in another study based on very low certainty evidence.[1] Based on 'indirect' comparisons i.e., SCIT versus placebo and SLIT versus placebo, the safety profile between SCIT and SLIT was comparable.

Even though, the certainty of the qualitative evidence was inestimable for FAQ 7, some qualitative data suggested that AIT modifies and prevents progression of allergies and prevents the development of new sensitisations as well as asthma onset.

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report was developed using evidence from SRs and HTA. The strengths of this report include comprehensive literature searches without date or language restrictions, inclusion of the highest quality evidence as well as coverage of a wide range of FAQs and outcomes of interest.

Nevertheless, some limitations should be taken into account. Firstly, because of an unequal distribution of data under FAQ 5 and 6, we decided to merge those under one umbrella outcome i.e., short and long-term AEs. Secondly, for FAQ 3 and 7, only qualitative data were available. Resolution/improvement of symptoms, medication use and combined symptom and medication scores were the clinical areas where most of the evidence was found. For these outcomes results most consistently favoured SCIT. However, the results were least consistent for short and long-term AEs. Thirdly, there was heterogeneity of populations

studied, diversity of AIT regimens, allergen preparations, potency and dosage, and definitions of outcomes.[27] Also, the number of RCTs ranged from 4 to 59; follow-ups were largely not reported. The majority of outcomes were based on low certainty evidence. The main reasons for downgrading were unclear risk of bias in the primary studies, inconsistency (heterogeneity of the pooled analyses), and imprecision (small sample sizes).

5. REFERENCES

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APPENDIX 1: SEARCH STRATEGIES

Table 7: Systematic reviews and guideline search results

Database	Date searched	Dates	Results
CDSR	02.11.20	Issue 11/12, Nov 2020	72
DARE	02.11.20	inception-31.3.15	48
HTA	02.11.20	inception-31.3.18	17
INAHTA	02.11.20	inception-02.11.20	16
KSR Evidence	02.11.20	inception-02.11.20	99
Epistemonikos	02.11.20	inception-02.11.20	181
NICE Guidance	02.11.20	inception-02.11.20	1
ECRI Guidelines	02.11.20	inception-02.11.20	3
NICE Evidence	02.11.20	inception-02.11.20	8
GIN	03.11.20	inception-03.11.20	10
Total			**455**
Total after de-duplication			**342**

SEARCH STRATEGIES

Cochrane Library (Wiley) - Cochrane Database of Systematic Reviews (CDSR): Issue 11 of 12, August 2020
Date searched: 02.11.20
Records found: 72

#1 MeSH descriptor: [Rhinitis, Allergic] explode all trees 3073
#2 MeSH descriptor: [Conjunctivitis, Allergic] this term only 662
#3 (allergic or allergy or allergies or eosinophil*) and (rhin* or conjunctiv* or keratoconjunctiv*) 11092
#4 (atopic or "giant papillary" or vernal) and (conjunctiv* or keratoconjunctiv*) 388
#5 (perennial or seasonal or nonseasonal or "non-seasonal" or spring* or summer*) and (rhin* or conjunctiv* or keratoconjunctiv*) 5595
#6 "hay fever" or hayfever 782
#7 (allergic or allergy or allergies or rhin* or conjunctiv* or keratoconjuntiv*) and (pollen or birch or betula or hazel or alder or alnus or grass or grasses or poaceae or "phleum pratensae" or rye or secale or dust or dustmite* or housedust or dermatophagoide* or euroglyphus or pyroglyphidae) 5247
#8 pollinos?s or pollenos?s 399
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 13504
#10 MeSH descriptor: [Desensitization, Immunologic] explode all trees 937

#11 immunotherap* or (immun* near/3 therap*) or immunomodulatory or "immuno modulatory" or (immunologic* near/3 response*) 33523
#12 desensiti?ation or desensibili?ation 3093
#13 hyposensibili?ation or "hypo sensibili?ation" or hyposensiti?ation or "hypo sensiti?ation" 213
#14 antianaphylaxis or "anti anaphylaxis"3
#15 MeSH descriptor: [Allergens] explode all trees and with qualifier(s): [administration & dosage - AD] 506
#16 MeSH descriptor: [Allergens] explode all trees and with qualifier(s): [immunology - IM] 816
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16 35931
#18 #9 and #17 in Cochrane Reviews 72

Database of Abstracts of Reviews of Effects (DARE): inception -2015/03/31
https://www.crd.york.ac.uk/CRDWeb/
Date searched: 02.11.20
Records found: 48

Health Technology Assessment (HTA) Database: inception - 2015/03/31
https://www.crd.york.ac.uk/CRDWeb/
Date searched: 02.11.20
Records found: 17
1 MeSH DESCRIPTOR Rhinitis, Allergic EXPLODE ALL TREES 118
2 MeSH DESCRIPTOR Conjunctivitis 1
3 ((allergic or allergy or allergies or eosinophil*) and (rhin* or conjunctiv* or keratoconjunctiv*)) 228
4 ((atopic or giant papillary or vernal) and (conjunctiv* or keratoconjunctiv*)) 5
5 ((perennial or seasonal or nonseasonal or non-seasonal or spring* or summer*) and (rhin* or conjunctiv* or keratoconjunctiv*)) 141
6 (hay fever or hayfever) 13
7 ((allergic or allergy or allergies or rhin* or conjunctiv* or keratoconjuntiv*) and (pollen or birch or betula or hazel or alder or alnus or grass or grasses or poaceae or phleum pratensae or rye or secale or dust or dustmite* or housedust or dermatophagoide* or euroglyphus or pyroglyphidae)) 64
8 (pollinosis or pollenosis or pollinoses or pollenoses) 2
9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 266
10 MeSH DESCRIPTOR Desensitization, Immunologic EXPLODE ALL TREES 64
11 (immunotherap* or (immun* near3 therap*) or immunomodulatory or immuno modulatory or (immunologic* near3 response*)) 1212
12 (desensitisation or desensibilisation or desensitization or desensibilization) 140
13 (hyposensibilisation or hypo sensibilisation or hyposensitisation or hypo sensitisation or hyposensibilization or hypo sensibilization or hyposensitization or hypo sensitization) 3
14 (antianaphylaxis or anti anaphylaxis) 0
15 MeSH DESCRIPTOR Allergens EXPLODE ALL TREES WITH QUALIFIERS AD, IM 29
16 #10 OR #11 OR #12 OR #13 OR #14 OR #15 1300
17 #9 AND #16 86
18 (#17) IN DARE 48

19 (#17) IN HTA 17

INAHTA International HTA database: inception - 02.11.20
https://database.inahta.org/
Date searched: 02.11.20
Records found: 16
1 "Rhinitis, Allergic"[mhe] 14
2 "Conjunctivitis, Allergic"[mh] 4
3 (allergic or allergy or allergies or eosinophil*) and (rhin* or conjunctiv* or keratoconjunctiv*) 28
4 (atopic or "giant papillary" or vernal) and (conjunctiv* or keratoconjunctiv*) 0
5 (perennial or seasonal or nonseasonal or "non-seasonal" or spring* or summer*) and (rhin* or conjunctiv* or keratoconjunctiv*) 9
6 "hay fever" or hayfever 2
7 (allergic or allergy or allergies or rhin* or conjunctiv* or keratoconjuntiv*) and (pollen or birch or betula or hazel or alder or alnus or grass or grasses or poaceae or "phleum pratensae" or rye or secale or dust or dustmite* or housedust or dermatophagoide* or euroglyphus or pyroglyphidae) 9
8 pollinosis or pollenosis or pollinoses or pollenoses 0
9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 31
10 "Desensitization, Immunologic"[mhe] 5
11 immunotherap* or (immun* and therap*) or immunomodulatory or "immuno modulatory" or (immunologic* and response*) 251
12 desensitisation or desensibilisation or desensitization or desensibilization 13
13 hyposensibilisation or "hypo sensibilisation" or hyposensitisation or "hypo sensitisation" or hyposensibilization or "hypo sensibilization" or hyposensitization or "hypo sensitization" 0
14 antianaphylaxis or "anti anaphylaxis"0
15 "Allergens"[mh] 7
16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 267
17 #16 AND #9 16

KSR Evidence: inception - 02.11.20
https://ksrevidence.com/
Date searched: 02.11.20
Records found: 99
1 (allergic or allergy or allergies or eosinophil*) and (rhin* or conjunctiv* or keratoconjunctiv*) in All text 424 results
2 (atopic or "giant papillary" or vernal) and (conjunctiv* or keratoconjunctiv*) in All text 14 results
3 (perennial or seasonal or nonseasonal or "non-seasonal" or spring* or summer*) and (rhin* or conjunctiv* or keratoconjunctiv*) in All text 64 results
4 "hay fever" or hayfever in All text 27 results
5 (allergic or allergy or allergies or rhin* or conjunctiv* or keratoconjuntiv*) and (pollen or birch or betula or hazel or alder or alnus or grass or grasses or poaceae or "phleum pratensae" or rye or secale or dust or dustmite* or housedust or dermatophagoide* or euroglyphus or pyroglyphidae) in All text 70 results

6 pollinosis or pollenosis or pollinoses or pollenoses in All text 1 result
7 #1 or #2 or #3 or #4 or #5 or #6 in All text 479 results
8 immunotherap* or (immun* and therap*) or immunomodulatory or "immuno modulatory" or (immunologic* and response*) in All text 3910 results
9 desensitisation or desensibilisation or desensitization or desensibilization in All text 159 results
10 hyposensibilisation or "hypo sensibilisation" or hyposensitisation or "hypo sensitisation" or hyposensibilization or "hypo sensibilization" or hyposensitization or "hypo sensitization" in All text 0 results
11 antianaphylaxis or "anti anaphylaxis" in All text 0 results
12 #8 or #9 or #10 or #11 in All text 4036 results
13 #7 and #12 in All text 99 results

Epistemonikos: inception - 02.11.20
https://www.epistemonikos.org/
Date searched: 02.11.20
Records found: 181

Publication type: Systematic review

(title:((((allergic OR allergy OR allergies OR eosinophil*) AND (rhin* OR conjunctiv* OR keratoconjunctiv*)) OR ((atopic OR "giant papillary" OR vernal) AND (conjunctiv* OR keratoconjunctiv*)) OR ((perennial OR seasonal OR nonseasonal OR "non-seasonal" OR spring* OR summer*) AND (rhin* OR conjunctiv* OR keratoconjunctiv*)) OR ("hay fever" OR hayfever) OR ((allergic OR allergy OR allergies OR rhin* OR conjunctiv* OR keratoconjuntiv*) AND (pollen OR birch OR betula OR hazel OR alder OR alnus OR grass OR grasses OR poaceae OR "phleum pratensae" OR rye OR secale OR dust OR dustmite* OR housedust OR dermatophagoide* OR euroglyphus OR pyroglyphidae)) OR (pollinosis OR pollenosis OR pollinoses OR pollenoses)) AND ((immunotherap* OR (immun* AND therap*) OR immunomodulatory OR "immuno modulatory" OR (immunologic* AND response*)) OR (desensitisation OR desensibilisation OR desensitization OR desensibilization) OR (hyposensibilisation OR "hypo sensibilisation" OR hyposensitisation OR "hypo sensitisation" OR hyposensibilization OR "hypo sensibilization" OR hyposensitization OR "hypo sensitization") OR (antianaphylaxis OR "anti anaphylaxis"))) OR abstract:((((allergic OR allergy OR allergies OR eosinophil*) AND (rhin* OR conjunctiv* OR keratoconjunctiv*)) OR ((atopic OR "giant papillary" OR vernal) AND (conjunctiv* OR keratoconjunctiv*)) OR ((perennial OR seasonal OR nonseasonal OR "non-seasonal" OR spring* OR summer*) AND (rhin* OR conjunctiv* OR keratoconjunctiv*)) OR ("hay fever" OR hayfever) OR ((allergic OR allergy OR allergies OR rhin* OR conjunctiv* OR keratoconjuntiv*) AND (pollen OR birch OR betula OR hazel OR alder OR alnus OR grass OR grasses OR poaceae OR "phleum pratensae" OR rye OR secale OR dust OR dustmite* OR housedust OR dermatophagoide* OR euroglyphus OR pyroglyphidae)) OR (pollinosis OR pollenosis OR pollinoses OR pollenoses)) AND ((immunotherap* OR (immun* AND therap*) OR immunomodulatory OR "immuno modulatory" OR (immunologic* AND response*)) OR (desensitisation OR desensibilisation OR desensitization OR desensibilization) OR (hyposensibilisation OR "hypo sensibilisation" OR

hyposensitisation OR "hypo sensitisation" OR hyposensibilization OR "hypo sensibilization" OR hyposensitization OR "hypo sensitization") OR (antianaphylaxis OR "anti anaphylaxis"))))

NICE Guidance: inception - 02.11.20
https://www.nice.org.uk/guidance
Date searched: 02.11.20
Records found: 1

Limits -
Document type: Guidance

Search terms	Records (relevant)
Aller*	8 (1)
Rhin*	4 (1)
Conjunctivitis	0
Keratoconjunctiv*	0
Hayfever	0
Hay fever	0
Pollinoses	0
Pollinosis	0
Immunotherap*	0
Desensitisation	0
desensibilisation	0
hyposensibilisation	0
hyposensitisation	0
antianaphylaxis	0
Total before deduplication	**12 (2)**
Total after deduplication	**11 (1)**

ECRI Institute Guidelines Trust (Internet): inception - 02.11.20
https://guidelines.ecri.org/
Date searched: 02.11.20
Records found: 3

Limits -
Document type: Guidance

Search terms	Records (relevant)
Allergic OR allergies OR allergy OR allergen	64 (3)
Rhinitis OR rhinosinusitis OR "rhino sinusitis"	8 (1)
Conjunctivitis	57 (0)
Keratoconjunctivitis	0
Hayfever OR "hay fever"	0
Pollinoses OR pollinosis	1 (1)
Immunotherapy OR "immun* therap*"	17 (2)

Desensitisation OR desensitization	8 (0)
Desensibilisation OR desensibilization	0
Hyposensibilisation OR hyposensibilization	0
Hyposensitisation OR hyposensitization	0
antianaphylaxis	0
Total before deduplication	**155 (7)**
Total after deduplication	**132 (3)**

NICE Evidence: inception - 02.11.20
https://www.evidence.nhs.uk/
Date searched: 02.11.20
Records found: 8

Limits -
Evidence type: Guidance

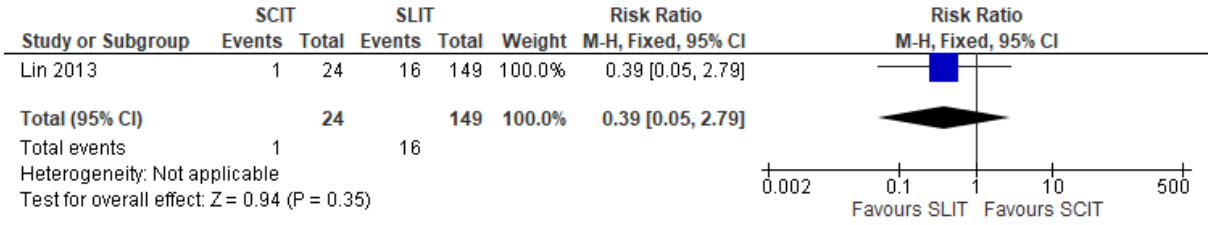
(Allergic OR allergies OR allergy OR allergen OR Rhinitis OR rhinosinusitis OR "rhino sinusitis" OR Conjunctivitis OR Keratoconjunctivitis OR Hayfever OR "hay fever" OR Pollinoses OR pollinosis) AND (Immunotherapy OR "immun* therap*" OR Desensitisation OR desensitization OR Desensibilisation OR desensibilization OR Hyposensibilisation OR hyposensibilization OR Hyposensitisation OR hyposensitization OR antianaphylaxis)

Guidelines International Network (G-I-N): inception - 03.11.20
https://g-i-n.net/home
Date searched: 03.11.20
Records found: 10

Search terms	**Records (relevant)**
Allergic	7 (5)
Allergen	3 (2)
Allergy	16 (1)
Allergies	16 (1)
Rhinitis	5 (5)
Rhinosinusitis	7 (5)
Rhino sinusitis	0
Rhinoconjunctivitis	1 (1)
Conjunctivitis	0
Keratoconjunctivitis	0
Hayfever	0
hay fever	1 (1)
Pollinoses	0
pollinosis	0

Immunotherapy	5 (1)
immuno therapy	0
Desensitisation	0
desensitization	0
Desensibilisation	0
desensibilization	0
Hyposensibilisation	0
hyposensibilization	0
Hyposensitisation	0
hyposensitization	0
antianaphylaxis	0
Total before deduplication	**61 (22)**
Total after deduplication	**27 (10)**

APPENDIX 2: FOREST PLOT OF COMPARISON: SCIT VERSUS SLIT: OUTCOME: GASTROINTESTINAL ADVERSE-EFFECTS



APPENDIX 3: FOREST PLOT OF COMPARISON: SCIT VERSUS SLIT: OUTCOME: RESOLUTION OF SYMPTOMS