Allergen immunotherapy for the treatment of allergic rhinitis and/or asthma

FINAL COMPREHENSIVE RESEARCH PLAN

June 2015

Study Team: Systematic Review Unit
Objective
This systemic review of reviews aims to rapidly summarize clinical and safety evidence from multiple systematic reviews of allergen immunotherapy for the treatment of allergic rhinitis and/or asthma, including subcutaneous (SCIT) and sublingual immunotherapy (SLIT).

Research Questions
RQ1. What is the current evidence for the efficacy or effectiveness of allergen immunotherapy interventions for the treatment of allergic rhinitis and/or asthma compared to placebo, standard care or each other?

RQ2. What is the current evidence for the safety of allergen immunotherapy interventions for the treatment of allergic rhinitis and/or asthma compared to placebo, standard care or each other?

RQ3. Is the efficacy and safety of allergen immunotherapy different in adult or pediatric subpopulations with allergic rhinitis and/or asthma?

Methods
This is a focused rapid systematic review of existing systematic reviews with a limited search. In order to adequately assess a large body of research literature within a limited time frame, the scope of the review will be limited in the following ways:

1. Only secondary evidence assessments will be eligible for inclusion, including health technology assessments, indirect treatment comparisons, network meta-analyses, systematic reviews and/or meta-analyses. Primary studies published after the date of the latest included systematic review literature search may be summarized narratively to ensure currency.

2. A date-limited (5 years) search strategy will be developed, and a limited grey literature search will be conducted.

3. Although we aim to capture all relevant evidence syntheses regardless of language or publication status, it may not be possible to retrieve all located articles and/or translate them within the timelines of this review. Irretrievable and foreign language articles will be listed in the final report for transparency.

Although this is a rapid assessment of existing evidence syntheses, systematic and structured methods will be used throughout to limit bias and ensure a transparent, comprehensive review of the current literature.

Identifying relevant secondary studies
To be considered for inclusion in this study, reviews must:

• Describe a search strategy and a criteria for including and excluding studies;

• Be published in English (or a language that can be translated within the time frame of this review) and be retrievable within the condensed time frame for this review;

• Meet the requirements of the Population, Intervention, Comparator and Outcome (PICO) framework and eligibility requirements outlined below.

PICO Framework
A PICO framework will be used to evaluate the relevance of eligible evidence syntheses:
<table>
<thead>
<tr>
<th>PICO Element</th>
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<tr>
<td>Population</td>
<td>Adult or pediatric patients with seasonal or perennial allergic rhinitis (also known as hayfever or rhinoconjunctivitis) or allergic asthma.</td>
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| Interventions             | • Sublingual immunotherapy (SLIT)  
  o Oralair  
  o Grastek  
  o Ragwitek  
  • Subcutaneous immunotherapy (SCIT)  
  o Pollinex-R  
  o Allergen extracts and serums  
  • Venom immunotherapy (VIT)                                                                                                                  |
| Comparators               | • Placebo  
  • Usual care  
  • Active control (SCIT or SLIT to each other, environmental control, medications such as topical nasal corticosteroid or cromolyn preparations, oral antihistamines, decongestants, beta-agonists, oral steroids, bronchodilators, ocular corticosteroids, and montelukast.)  
  • Single or multi-allergen SLIT                                                                                                               |
| Outcomes: Efficacy/Effectiveness | All outcomes will be considered, although certain clinical outcomes may be prioritized for reporting. Outcomes will not be used to assess eligibility of relevant reviews; however, the study must report on the efficacy or effectiveness of allergen immunotherapy(ies). We will not include reviews focused on pharmacokinetic outcomes (considered out of scope) or those solely focused on economic or cost outcomes (as those will be covered by the pharmacoeconomics team in their review). Key outcomes may include:  
  • Total Combined Symptom plus Medication Score (TCS)  
  • Symptom improvement (asthma or rhinitis)  
  • Decrease in medication use (asthma or rhinitis)  
  • Disease-specific quality of life  
  • Adherence/Discontinuation                                                                                                                      |
| Outcomes: Safety          | All outcomes will be considered, and the study must report on the safety of allergen immunotherapies; however, we do not aim to summarize all adverse effects in depth individually. We will aim to provide a summary of local, systemic or gastrointestinal reactions, withdrawals or discontinuations due to adverse effects, and serious adverse events or death. Certain outcomes may be categorized for summary of findings if possible. Key outcomes may include:  
  • Local (SCIT) injection site reactions including redness,  
  • Systemic reactions including anaphylaxis  
  • Gastrointestinal reactions including diarrhea, nausea, vomiting, abdominal pain  
  • Allergic reactions including urticaria, angioedema, anaphylaxis  
  • Adverse effects specific to medications used in combination with immunotherapy (e.g., oral steroids, beta-agonists)  
  • Other adverse effects such as injection site reactions (SCIT)  
  • Allergic reactions specific to venom immunotherapy  
  • Adverse effects specific to medications used in combination with venom immunotherapy (e.g., oral steroids, beta-agonists)  
  • Other adverse effects specific to venom immunotherapy  
  • Deaths due to adverse effects  
  • Other deaths not related to adverse effects  
  • Serious adverse events not related to adverse effects  |

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<table>
<thead>
<tr>
<th>PICO Element</th>
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<tbody>
<tr>
<td></td>
<td>swelling, pruritus, induration</td>
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<tr>
<td></td>
<td>• Local (SLIT) oral cavity irritation, itching, swelling, irritation, pain</td>
</tr>
<tr>
<td></td>
<td>• Systematic: respiratory, cardiovascular, gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>• Severe: life-threatening</td>
</tr>
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<td></td>
<td>• Death</td>
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**Study Types**

- Health technology assessments, indirect treatment comparisons/network meta-analyses, systematic reviews and/or meta-analyses assessing and including primary studies.
- A study will be considered if it presents a defined search strategy, searched two or more databases and presents explicit eligibility criteria.
- For efficacy, reviews must include randomized controlled trials, however, for safety, reviews may summarize any prospective controlled primary study design (randomized, quasi- or non-randomized).
- Primary studies will only be included if they were published after the search date of the latest included study literature search. In this case we will narratively summarize RCTs for efficacy and effectiveness and any prospective controlled studies we locate for safety.

**Excluded**

- Non-allergic or occupational rhinitis, or rhinitis caused by hormones/hypothyroidism, medication, atrophic mucosa, or other inflammatory or immunologic disorders.
- Non-allergic asthma.
- Non-systematic or simple literature or topic reviews.
- If they have a broader approach than this current review and do not provide a specific systematic sub-analysis relevant to this review.
- Where a relevant systematic review is ongoing at the time searches are undertaken and/or published after the searches, it will be noted in the final manuscript but not included in the summary of findings.
- Reviews of reviews.

**Search Strategy**

A literature search will be conducted by a professional Information Scientist (IS). Literature search strategies will be developed using medical subject headings (MeSH) and text words related to the population, interventions and comparators specified in the PICO statement. Databases [at minimum MEDLINE (OVID interface, indexed, in-process and other non-indexed citations, 1946 onwards), EMBASE (OVID interface, 1947 onwards) and Cochrane Central] will be searched back 5 years in order to capture all recent relevant literature. A limited grey-literature search will be carried out by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases (following CADTH “Grey Matters Light”)(available at: [http://www.cadth.ca/media/is/cadth_Handout_greymatters_light_e.pdf](http://www.cadth.ca/media/is/cadth_Handout_greymatters_light_e.pdf)). No language
restrictions will be used. Validated study type filters may be employed to maximize the specificity of the search.

All citations will be imported into an electronic reference management database (EndNote©, Thomson Reuters).

**Article Selection**
Studies will be selected according to a criteria established a priori using a multi-step vetting process. Where possible, portions of foreign language reviews will be translated to assist with selection decisions.

Selection eligibility criteria will be applied to each title and abstract by two independent review authors in a standardized manner using electronic tools customized for the project in DistillerSR, an online systematic review management and screening tool. Any uncertainties will be resolved by discussion and consensus with a third review author. All studies that meet the selection criteria will be obtained in full-text format. Two independent review authors will apply the eligibility criteria and a final decision will be made for inclusion. The reviewers will not be blinded as to the study authors or centre of publication prior to study selection because this can complicate the review process and only weak evidence suggests that this would improve the results. The screening process will be piloted on a sample returned by the literature search and revised if necessary.

**Quality Assessment**
Only reviews meeting a minimum quality threshold will be considered for the summary of findings. We will apply the AMSTAR checklist to each included study to ensure that the following requirements have been met:

- A comprehensive search strategy involving two or more electronic databases;
- An explicit statement describing the inclusion (and ideally exclusion) criteria applied to candidate studies. Ideally the review mentions a priori development of this criteria and/or use of a protocol;
- Illustrate use of a formal critical appraisal or quality assessment process for all included studies and report the outcome of that process.
- Report findings on efficacy or safety outcomes of interest using details on the study and patient characteristics of two or more studies, and provide the direction of the findings from any pooled analyses (narrative or meta-analysis) carried out.
- Direction of effect and any statistical significance, if meta-analyses were conducted.

Any reviews not meeting these minimum requirements will remain included, however, no data will be extracted. In the event that included reviews report significantly overlapping lists of included studies reporting the same outcome(s), we will report findings from the higher quality, more recent review with the largest number of studies.

If primary studies are included, a modified assessment of risk of bias will be performed using the SIGN-50 checklist.

**Summary of findings**
A framework will be developed specifically for this review to extract results from each included review and produce summaries of findings based on the outcomes of interest. Included reviews will be summarized by:
• Review characteristics (First author, year of publication, county of origin).
• Study design, length of study (primary studies only).
• Patient characteristics, sample size.
• Interventions, comparators, main outcomes assessed. If a review reports results by the number of ingredients in a serum, we will capture.

Data will be extracted by a single review author and checked for accuracy and completeness by a second review author. Any disagreements will be resolved through discussion and consensus with a third review author.

The findings from reviews with similar topics will be grouped and synthesized using a narrative approach. Where possible, review findings will be summarized and presented by clinical or safety outcome with further detail by comparison, e.g., for patient-reported symptom scores:
• SLIT versus placebo
• SCIT versus placebo
• SLIT versus SCIT
• SLIT or SCIT versus active control

Data for children and adults will be presented separately. The main results will be summarized along with the authors main conclusions. Data will also be described for single or multi-allergen SLIT comparisons, and long term sustained effects, if available.

Strengths and limitations of the included studies, as assessed by AMSTAR, will also be presented.

**Deliverables**

We will provide a written report detailing methods adopted, results, discussion and key findings. The report will summarize findings with a brief executive summary followed by a detailed technical report. The review of clinical and safety evidence will be completed within 7 weeks of project inception.