ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Allergen Immunotherapy Products

FINAL CONSOLIDATED COMPREHENSIVE RESEARCH PLAN

June 2015

A. Introduction

The objective of the drug class review on allergen immunotherapy is to provide evidence-informed recommendations for the use of allergen immunotherapy through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- reimbursement-based analyses,
- drug utilization studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of patients and prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models.

B. Research Questions

Patient population and inclusion criteria

- All patients with a diagnosis of allergic rhinitis and/or asthma
- Subgroup analysis: where possible, the review may consider age, gender, socioeconomic status and geographic location (e.g. urban/rural), co-morbid conditions, different formulations

Drugs of interest

- Allergen immunotherapy therapies
    - Sublingual (SLIT):
        - Oralair
        - Grastek
        - Ragwitek
    - Subcutaneous (SCIT):
        - Pollinex-R
        - Allergen extracts and serums (patient-specific)

Comparator(s)

- Placebo-controlled trials
- All drugs of interest (as listed above)
- Standard pharmacotherapy for allergic rhinitis (e.g., intranasal steroids, antihistamines)
- Multiallergen vs. single allergen SCIT

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	What is the perceived effectiveness of allergen immunotherapies? What is the impact of allergen immunotherapies on perceived quality of life? What is the experience of patients using allergen immunotherapies regarding access of these drugs? What is the experience of prescribing these therapies? To what extent are the policy recommendations feasible and acceptable?
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	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? 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? Is the efficacy and safety of allergen immunotherapy different in adult or pediatric subpopulations with allergic rhinitis and/or asthma?
Environmental Scan and Barriers to Implementation Local and Historical Context	Formulary Modernization Unit	How is allergen immunotherapy currently being accessed in publicly funded programs across Canada as well as internationally? What is the impact of different reimbursement schemes for allergen immunotherapy on patient access, quality of life and/or utilization and costs? Does sex, gender or socioeconomic status play an important role in any of the analyses described?
Costs and Utilization Trends	Pharmacoepidemiology Unit	To examine national and provincial trends in use of allergen immunotherapy across Canada To perform cross provincial comparisons of the trends in allergen immunotherapy utilization in public drug programs To describe characteristics of individuals prescribed publically-funded allergen immunotherapy in Ontario To describe the details of submissions for public drug funding for allergen immunotherapy serums in Ontario
Health Equity	All units	Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?
Reimbursement-based Economics	Pharmacoeconomics Program	What is the current evidence for the comparative cost-effectiveness of allergen immunotherapy for the treatment of allergic rhinitis and/or asthma? What is the budget impact of alternative policies for reimbursing allergen immunotherapy options for the treatment of allergic rhinitis and/or asthma?

C. Specific Proposals

The Drug Class Review is comprised of five different reviews, namely the Qualitative Research Unit, Systematic Review Unit, Pharmacoepidemiology Unit, Environment Scan/local and historical context and Pharmacoeconomics Unit. Further information on each of the proposals is can be found on our website: www.odprn.ca

1. Qualitative Review Unit

Objectives:

- To explore factors related to the experience of prescription and use of allergen immunotherapies.
- To determine the social acceptability of reimbursement policy recommendations for allergen immunotherapies.

Study Questions:

- What is the perceived effectiveness of allergen immunotherapies?
- What is the impact of allergen immunotherapies on perceived quality of life?
- What is the experience of patients using allergen immunotherapies regarding access of these drugs?
- What is the experience of prescribing these therapies?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of allergen immunotherapy

Study Design – This phase will use a qualitative framework approach to guide the data collection and analysis processes. One-on-one interviews and accompanying field notes will be the primary and secondary data sources, respectively.

Study Population – Identified stakeholders for the allergen immunotherapy review include 1) allergists; 2) primary care physicians (PCPs); 3) adult patients who have used allergen immunotherapies

Methods – A purposive sampling approach using a convenience sample will be used in order to elicit the specific perceptions and opinions of those who will be involved in or affected by drug policy decisions. Clinicians will be recruited through circles of contact, professional networks and snowball recruitment. Publicly available contact information will also be searched to develop contact lists. An ODPRN member or study coordinator will make contact with clinicians by phone, e-mail or fax. Patients will be recruited through circles of contact. A patient recruitment flyer will also be sent to participating clinicians who agree to distribute the flyer to patients. Patient networks will be used to send recruitment notices by e-mail. General calls for recruitment of all eligible groups will be placed in professional newsletters, e-blasts and social media (Twitter, Facebook).

We will aim to recruit 6 to 8 allergists, 2-3 PCPs, and 6-8 adult patients, which may be sufficient to reach saturation amongst homogenous groups of participants.

Outcomes:

- Experiences of living with allergies and of taking allergen immunotherapies
- Experiences accessing allergen immunotherapies
- Experiences treating patients with allergen immunotherapies
- Perceived safety and effectiveness of allergen immunotherapies
- Perceived barriers to access and health equity issues

- Any unanticipated issues related to allergen immunotherapies

Phase 2: Assessment of the social acceptability of recommended policy actions related to allergen immunotherapies

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public; stakeholder groups (i.e. among the groups described in Phase 1 above); patient advocacy groups; topic-specific interest groups; and industry

Methods – Members of the general public will be recruited to participate in a meeting/webinar to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. An online survey will also be distributed to assess aspects of social acceptability, including affordability, accessibility, and appropriateness. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.

Outcomes -The primary outcome of interest is the feasibility and acceptability of draft recommendations

2. Systematic Review Unit

Study Questions:

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

PICO (Population, interventions, comparator, outcomes)

Note: Efficacy and safety outcome lists may be truncated if we identify many studies for inclusion, as this is a rapid review. We will work with all stakeholders to select the most important efficacy and safety outcomes with sufficient data to conduct network meta-analysis.

PICO Element	Details
Population	Adult or pediatric patients with seasonal or perennial allergic rhinitis (also known as hayfever or rhinoconjunctivitis)or allergic asthma.
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,

PICO Element	Details
	swelling, pruritus, induration • Local (SLIT) oral cavity irritation, itching, swelling, irritation, pain) • Systematic: respiratory, cardiovascular, gastrointestinal • Severe: life-threatening • Death
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.

Methods

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). No language restrictions will be used. Validated study type filters may be employed to maximize the specificity of the search.

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.

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in allergen immunotherapy

Study question: Cross-sectional analysis with quarterly time intervals
Short description of analysis: We will examine trends in use of allergen immunotherapy between October 2009 and March 2015.

Analysis 2 – Cross-provincial comparisons of the trends in allergen immunotherapy utilization in public drug programs

Study question: Cross-sectional analysis with quarterly time intervals
Short description of analysis: We will examine changes in allergen immunotherapy prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and British Columbia between January 2000 and December 2014.

Analysis 3 – Characteristics of individuals prescribed publically-funded allergen immunotherapy in Ontario

Study question: To characterize patients prescribed allergen immunotherapy in Ontario
Short description of analysis: We will look at descriptive characteristics (April 2012-March 2014), including age, gender, socioeconomic status, prescriber of initial prescription (specialist or general practitioner), number of physician office visits within the last 1 year, comorbidities, asthma, past medication use (including intranasal cortiocsteroids, leukotriene

receptor antagonists, inhaled corticosteroids, inhaled corticosteroids + long-acting beta agonist combination products, omalizumab)

Analysis 4 – Details of submissions for public drug funding for allergen immunotherapy serums in Ontario

Study questions: To describe the details of submissions for public drug funding for allergen immunotherapy serums in Ontario
Short description of analysis: We will summarize a sample of Allergen Program application forms including age of patient, number of allergens in serums, type of allergens and cost

4. Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the comparative cost-effectiveness of allergen immunotherapy for the treatment of allergic rhinitis and/or asthma?
- What is the budget impact of alternative policies for reimbursing allergen immunotherapy options for the treatment of allergic rhinitis and/or asthma?

Methods

RQ1 Systematic Review of Published Economic Evaluations
We will conduct a review of the available literature on the cost-effectiveness of allergen immunotherapies for the treatment of allergic disorders. Selected comparators will include subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), multiallergen versus single allergen SCIT, as compared with each other, placebo and/or standard pharmacotherapy (e.g., intranasal steroids, antihistamines).

RQ2 Reimbursement Based Budget Impact Analysis
We will develop a model which will identify the budget impact analysis that will facilitate the reimbursement decision-making process. Emphasis will be placed on identifying the budget impact of alternative approaches to the current reimbursement status of pharmacologic treatments for patients with allergic rhinitis and/or asthma.

5. Environmental Scan

Research Questions

1. ***To summarize the pharmacy benefit programs for allergen immunotherapy in Ontario, across Canada and in select international jurisdictions***

Method: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan
Interventions:
- venom subcutaneous immunotherapy (SCIT)
- environmental (pollen and non-pollen) subcutaneous immunotherapy (SCIT)
- sublingual immunotherapy (SLIT)

2. ***To determine the impact of different reimbursement schemes for allergen immunotherapy on patient access, quality of life and/or utilization and costs***

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization
Outcome(s) of interest: Indirect/direct measurements of clinical outcomes, patient satisfaction, quality of life, utilization and/or costs, functionality at work, days of productivity at work

3. To summarize the guidelines for allergen immunotherapy, as well as guidelines for management of patients with allergic rhinitis

Method: Literature review
Intervention: Guidelines/recommendations for the use of allergen immunotherapy