



Comprehensive Research Plan: Inhaled corticosteroids + long-acting beta agonists (ICS+LABA) for the treatment of asthma

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A. Introduction

Inhaled corticosteroids + long acting beta agonists are available in Canada for the management of asthma and/or chronic obstructive pulmonary disease. There are currently four products marketed in Canada:

- Advair: salmeterol+fluticasone; indicated for asthma and COPD
- Symbicort: formoterol+budesonide; indicated for asthma and COPD
- Zenhale: formoterol+mometasone; indicated for asthma only
- BreoEllipta, vilanterol+fluticasone): indicated for the treatment of COPD.

The objective of the ICS+LABA for asthma review is to provide evidence-informed recommendations for the use of ICS+LABA for asthma through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- cost-effectiveness and reimbursement-based analyses, and 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, pharmacists and prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models

B. Research Questions

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	What is the perceived effectiveness of ICS/LABA for the treatment of asthma? What is the perceived impact of ICS/LABA on a patient's quality of life? What is the patient experience of accessing ICS/LABA for the treatment of asthma? What is the clinician experience of prescribing or dispensing ICS/LABA for the treatment of asthma? To what extent are the policy recommendations feasible and acceptable?
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	What is the comparative safety and efficacy of ICS (alone or in combination) versus inhaled LABA and placebo (in any combination) for patients with chronic asthma aged 12 years and greater? Which intervention (or combination) is the most effective and safe for patients with chronic asthma aged 12 years and older?

Proposal	Research unit	Research question(s)
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	How are ICS/LABA combination products currently being funded in public programs in Canada as well as internationally? What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?
Costs and Utilization Trends	Pharmacoepidemiology Unit	<ul style="list-style-type: none"> • To examine national and provincial trends in use of asthma drug therapies across Canada • To examine trends in use of ICS/LABA combination products for asthma in Ontario • To describe characteristics of asthma patients prescribed ICS/LABA combination products • To investigate course of therapy and adherence with asthma drugs in Ontario • To summarize any observational studies evaluating the comparative effectiveness of ICS/LABA combination products
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	<p>What is the current evidence for the cost-effectiveness of ICS plus LABA compared to ICS alone in the chronic management of asthma?</p> <p>Based on a de novo economic model, what is the cost-effectiveness of ICS plus LABA compared to ICS alone in the chronic management of asthma?</p> <p>What is the economic impact of alternatives policies for reimbursing ICS plus LABA combination products in the chronic management of asthma?</p>

Patient population and inclusion criteria

- Children 12 years of age and older AND adults with asthma
- Inclusion Criteria:
 - Children aged 12 years and older
 - Adults
 - Diagnosis of asthma, regardless of severity of disease
- Subgroup analysis: where possible, the review will consider age, gender, socioeconomic status and geographic location (e.g. urban/rural)

Drugs of interest

- ICS + LABA (single inhaler or as 2 separate inhalers):
 - Advair (salmeterol/fluticasone)
 - Symbicort (formoterol/budesonide)

- BreoEllipta (vilanterol/fluticasone)
- Zenhale (formoterol/mometasone)

Comparator(s)

ICS, short-acting beta-agonists, long-acting beta-agonists, leukotriene receptor antagonists (alone or *in any combination*)

Note: This will include dual therapy with ICS and LABA single entity products

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 provided below.

Qualitative Review Unit

Objectives:

- To explore factors related to the experience of ICS/LABA prescription, dispensing and use for asthma.
- To determine the social acceptability of reimbursement policy recommendations for ICS/LABA use (asthma indication).

Study Questions:

- What is the perceived effectiveness of ICS/LABA?
- What is the impact of ICS/LABA on quality of life?
- What is the experience of patients using ICS/LABA regarding the access of these drugs?
- What is the experience of clinicians/pharmacists in prescribing/dispensing these drugs?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs within the drug class of interest

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 include primary care physicians (PCPs), respirologists, allergists, respiratory therapists/patient educators, pharmacists, and patients (patient caregivers may be considered). Inclusion criteria are: clinicians (PCPs, respirologists, pharmacists) who have prescribed or dispensed ICS/LABA, or educated patients on the use of the products; and adult asthma patients, as well as parents of children 12 years of age or older with asthma who have current or prior experience using ICS/LABA.

Methods – A purposive sampling approach will be used to elicit specific perceptions and opinions for those who will be involved or affected by drug policy decisions. Clinicians and patients will be recruited through various recruitment strategies, including professional associations, faxing/e-mailing and circles of contact. This phase will aim to recruit 6-8 participants from each identified stakeholder group and 20-25 patients. Qualitative data will be collected through interviews and accompanying field notes. A framework analysis will be applied to the data to derive key policy-relevant concepts.

Outcomes – The primary outcomes of interest include experiences with: asthma and asthma therapy; accessing ICS/LABA through Ontario Drug Benefit; accessing ICS/LABA through other means; treating and dispensing medication to patients with ICS/LABA. Other outcomes of interest will include perceived safety and effectiveness of ICS/LABA, and perceived barriers to access and health equity issues.

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drug class of interest

Study Design – RAND Appropriateness Method and Survey

Study Population – Representatives of the general public, stakeholder groups (PCPs, respirologists, allergists, respiratory therapists/patient educators, pharmacists, patients/parents), 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

Systematic Review Unit

Objective:

To examine the comparative safety and efficacy of long-acting inhaled agents (ICS and LABA) for patients with chronic asthma aged 12 years and greater.

Study Questions

- 1) What is the comparative safety and efficacy of inhaled ICSs (alone or in combination) versus inhaled LABA and placebo [in any combination] for patients with chronic asthma aged 12 years and greater?
- 2) Which intervention (or combination) is the most effective and safe for patients with chronic asthma aged 12 years and greater?

PICOS (Population, Intervention, Comparator, Outcome, Study designs) Criteria

Study Population:

- Children (≥ 12 years of age) and adults with asthma

Interventions:

- Inhaled ICS and LABA (e.g., fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol, and fluticasone and vilanterol)

Comparators:

- ICS, ICS+SABA, ICS+LABA, ICS+LTRA, LTRA, SABA in any combination and placebo. Concomitant asthma medications will be included if both groups receive the same interventions.

Outcomes of Interest:

Potential efficacy outcomes:

- Symptoms – daytime symptoms (frequency per week, and number of days per week), nighttime symptoms, rescue bronchodilator use, work or school absenteeism, limitation in physical activity
- Symptom scores - 30 second asthma control test, Juniper's Asthma Control Questionnaire,

Asthma Control Test, Asthma Control Scoring System, Pediatric/Adolescent Asthma Therapy Assessment Questionnaire

- Forced expiratory volume (FEV), peak expiratory flow
- Exacerbation – overall, resulting in ED visits/hospitalization/unscheduled doctor visit, requiring the use of steroids,
- Growth (children only)
- Measures of inflammation – eosinophilia, serum eosinophil cationic protein and sputum eosinophils
- Quality of life - Asthma Quality of Life Questionnaire, mini- Quality of Life Questionnaire
- Mortality – overall, asthma-related, respiratory-related, cardiovascular-related
- Severity – Methacholine challenge test

Potential safety outcomes:

- Adverse events
- Serious adverse events
- Withdrawals – overall, treatment-related

Study Designs:

- Randomized (parallel) controlled trials

Methods

Information sources and literature search:

To identify RCTs, we will assess all included and excluded studies identified in the 8 Cochrane reviews mentioned above. We will further scan the reference list of the reviews carried out by Loymans and van der Mark, as well as collaborate with the authors (Loymans and van der Mark) in conducting this review. In order to identify unpublished and difficult to locate material (also called grey literature), we will search conference abstracts, trial registries (e.g., www.clinicaltrials.gov), and websites of manufacturers of the inhaled long-acting agents. We will contact authors of conference abstracts, trial protocols, and trial registries to determine whether the RCT has been published in full.

Study selection, data abstraction, and risk of bias appraisal:

Two reviewers will independently screen titles and abstracts for inclusion (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

We will abstract data on study characteristics (e.g., year of conduct, sample size, setting), participant characteristics (e.g., number of patients, age mean and standard deviation), definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation]), and outcome results (e.g. number of patients with exacerbations, number of patients hospitalized) for the longest duration of follow-up. We will appraise the included studies using the Cochrane Risk of Bias Tool.

Synthesis of included studies:

We will first describe our systematic review results, reporting study and patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Subsequently, we will conduct meta-analysis, meta-regression, and Bayesian network meta-analysis, if deemed appropriate. We will explore the effects of subgroups on outcomes to establish the robustness of findings. Subgroups that we will explore include the diagnosis of asthma, severity of asthma, age, and definitions of outcomes (exacerbations in particular).

Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in asthma therapies

Study questions: How are asthma medications being used across Canada?

Short description of analysis: We will examine trends in the use of combination inhaled corticosteroids / long-acting beta agonist (ICS/LABA) products and other asthma therapies (for example, inhaled corticosteroids, long-acting beta-agonists, long-acting anticholinergics, short-acting beta agonists, short-acting muscarinic antagonist, leukotriene receptor antagonists) between 2009 and 2013.

Analysis 2 – Trends in use of ICS+LABA combination products for asthma in Ontario

Study question: What are the trends in use of ICS+LABA combination products for asthma in Ontario?

Short description of analysis: We will look at Ontario residents prescribed ICS+LABA products between 2000 and 2013 and identify the rate of use of ICS+LABA products among asthma patients, and number of ICS+LABA prescriptions dispensed to asthma patients?

Analysis 3 – Characteristics of asthma patients treated with ICS+LABA combination products in Ontario

Study question: What are the characteristics of Ontario patients with asthma who use ICS+LABA combination products today?

Short description of analysis: We will look at descriptive characteristics, including age, gender, socioeconomic status, disease severity, past medication use, past hospitalization or ED visit for asthma exacerbations, among Ontario public drug plan beneficiaries with asthma

Analysis 4a –Adherence to ICS+LABA combination therapy for asthma in Ontario

Study questions: How long do patients with asthma usually stay on combination therapy in Ontario?

Short description of analysis: We will look at patients with asthma aged 12-17, 18-65 and 66 and older who newly start ICS/LABA combination therapy or dual therapy with individual ICS and LABA components, and assess the type of treatment initiated, duration of therapy, and whether they switched between multiple therapies during their course of treatment.

Analysis 4b – Typical course of therapy through asthma drugs in Ontario

Study questions: Do patients usually take other asthma medications prior to starting therapy with ICS/LABA combination products? What other medications are usually prescribed?

Short description of analysis: We will look at patients with asthma aged 12-17, 18-65 and 66 and older who newly start ICS/LABA combination therapy, and assess whether they were prescribed any previous asthma medications. We will describe any prior therapy, and will also examine whether they used other asthma medications during their period of combination therapy.

Analysis 5 – Summary of observational studies evaluating the comparative effectiveness of ICS+LABA combination products

Study question: Are there any population-based studies on comparative effectiveness and safety of ICS/LABA combination products among patients with asthma?

Short description of analysis: We will perform a literature search to examine the body of evidence on

comparative effectiveness and/or safety ICS/LABA combination products among patients with asthma.

Pharmacoconomic Unit

Research Questions

What is the current evidence for the cost-effectiveness of ICS plus LABA compared to ICS alone in the chronic management of asthma?

Based on a de novo economic model, what is the cost-effectiveness of ICS plus LABA compared to ICS alone in the chronic management of asthma?

What is the economic impact of alternatives policies for reimbursing ICS plus LABA in the chronic management of asthma?

Methods

RQ1 Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of ICS combined with LABA for chronic management of asthma compared to ICS alone.

RQ2 De Novo Economic Model

We will develop a new economic model assessing the cost effectiveness of ICS combined with LABA for chronic treatment of asthma compared to ICS alone.

RQ3 Reimbursement Based Economic Assessment

We will develop a model which will identify the optimal policy relating to reimbursing ICS combined with LABA. Analysis will identify the change in the forecasted drug budget for the next three years associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical effectiveness.

Environmental Scan

To summarize the pharmacy benefit programs for ICS/LABA for asthma 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: ICS/LABA [Advair (fluticasone/salmeterol), Symbicort (formoterol/budesonide), Zenhale (formoterol/mometasone), BreoEllipta (vilanterol/fluticasone)]

To determine the impact of different drug reimbursement schemes for ICS/LABA, in particular for patients with asthma (e.g., restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization

To summarize the guidelines for management of asthma, in particular the role of ICS/LABA

Method: Literature review

Intervention: Guidelines/recommendations for the management of patients (12 years and older) with asthma