Comprehensive Research Plan: Inhaled long-acting muscarinic antagonists (LAMAs; long-acting anticholinergics) for the treatment of chronic obstructive pulmonary disease (COPD)

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A. Introduction

Inhaled long-acting muscarinic antagonists (LAMAs; also known as long-acting anticholinergics) are available in Canada for the management of chronic obstructive pulmonary disease. There are currently three products marketed in Canada:
- Tiotropium (Spiriva)
- Glycopyrronium (Seebri Breezhaler)
- Aclidinium (Tudorza)

In addition, two combination products (LAMAs + long-acting beta2-agonists) have recently received their notice of compliance (NOC) from Health Canada.
- Indacaterol + glycopyrronium (Ultibro)
- Vilanterol + umeclidinium (Anora Ellipta)

The objective of the LAMA for COPD review is to provide evidence-informed recommendations for the use of LAMA for COPD 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

Patient population and inclusion criteria
- Adult patients with COPD, 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
- Tiotropium (Spiriva)
- Glycopyrronium (Seebri Breezhaler)
- Aclidinium (Tudorza)

NOTE: LABA+LAMA combination products will not be looked at specifically in most analyses as they are not available in Canada. However, recommendations will be contextualized with the impending availability of the combination products.

Comparator(s)
ICS, inhaled LABA, inhaled long-acting anticholinergic agents (LAMAs), placebo (alone or *in any*

combination)
Note: For the purposes of LABA+LAMA combination products, this will include dual therapy with LAMA and LABA single entity products

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	What is the impact of COPD on a patient's quality of life? What is the perceived effectiveness of LAMAs for the treatment of COPD? What is the perceived impact of LAMAs on a patient's quality of life? What is the patient experience of accessing LAMAs for the treatment of COPD? What is the clinician experience of prescribing or dispensing LAMAs for the treatment of COPD? 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 inhaled LAMAs (alone or in combination) versus ICS, inhaled LABA, inhaled LAMA, and placebo [in any combination] for adults with COPD? Which intervention (or combination) is the most effective and safe for adults with COPD?
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	How are LAMA 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	To examine national and provincial trends in use of COPD drug therapies over the past 4 years To describe the characteristics of COPD patients treated with LAMA products among public drug plan beneficiaries in Ontario To determine the prevalence and adherence of single, dual and triple therapy with LAMA 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	What is the current evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS? Based on the economic model developed for the LABA/ICS review, what is the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS? What is the economic impact of alternatives policies for reimbursing LAMA?

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.

1. Qualitative Review Unit

Objectives:
- To explore factors related to the experience of LAMA prescription, dispensing and use for COPD.
- To determine the social acceptability of policy recommendations for LAMA use

Study Questions:
- What is the perceived effectiveness of LAMAs?
- What is the impact of LAMAs on quality of life?
- What is the experience of patients using LAMAs 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, pharmacists, and patients (patient caregivers may be considered). Inclusion criteria are: clinicians (PCPs, respirologists, pharmacists) who have prescribed or dispensed LAMAs; and patients with COPD who have current or prior experience using LAMAs. The same individuals who participated in the ICS/LABA drug class review will be asked to participate in the current review on LAMAs.

Methods – Individuals who participated in the ICS/LABA qualitative study and who agreed to be contacted for follow up will be approached to complete a follow-up survey regarding LAMAs. Given that many of the issues regarding COPD management from stakeholder perspectives were already captured in the ICS/LABA interviews, as well as information on LAMAs themselves as part of an overall approach to COPD management, the survey will be distributed to probe additional details on the use, prescription and dispensing of LAMAs and associated factors such as effectives, patient adherence and access. If all individuals do not agree to participate in a follow up survey, additional individuals (i.e. those not part of the original ICS/LABA study) will be recruited to participate in full-length one-on-one telephone interviews. Additionally, a sample of patients who are using LAMAs but not ICS/LABA will be invited to participate in interviews.

We will aim to include 6 to 8 participants from each identified clinician (i.e. physicians and pharmacists) group and 20-25 patients, which may be sufficient to reach saturation amongst homogenous groups of participants.

Outcomes – The primary outcomes of interest include experiences with: COPD and COPD therapy; accessing LAMAs through Ontario Drug Benefit; accessing LAMAs through other means; treating and dispensing medication to patients with LAMAs. Other outcomes of interest will include perceived safety

and effectiveness of LAMAs, 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, pharmacists, patients), 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

Objective:
To examine the comparative safety and efficacy of long-acting inhaled agents (inhaled corticosteroids [ICS], inhaled long-acting beta$_2$-agonists [LABA], inhaled long-acting muscarinic antagonists [LAMA]) for patients with COPD.

Study Questions
- What is the comparative safety and efficacy of LAMAs (alone or in combination) versus ICS, inhaled LABA, inhaled LAMA, and placebo [in any combination] for adults with COPD?
- Which intervention (or combination) is the most effective and safe for adults with COPD?

PICOS (Population, Intervention, Comparator, Outcome, Study designs) Criteria
Study Population:
- Adults with COPD. We will report the way that COPD was diagnosed across the included RCTs and conduct a sub-group analysis on this (please see the synthesis section below for further details). We will also consider sub-group analysis by severity of COPD, gender, and age (e.g., ≥65 years of age). Since the GOLD criteria have changed over time, a clinician (SES) will review all of the included studies to establish the COPD severity using the most recent GOLD guidelines.

Interventions:
- Inclusion: inhaled LABA (formoterol, indacaterol, salmeterol), ICS (beclomethasone, budesonide, fluticasone, mometasone), LAMA (aclidinium bromide, glycopyrronium bromide, tiotropium), and their combinations in one inhaler (e.g., LABA and ICS: formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, vilanterol/fluticasone). We will focus on dosages/devices approved for use in Canada. For example, we will not include Spiriva Respimat (5 mcg tiotropium) because it is not approved in Canada.

Comparators:
- Eligible comparators are all inhaled long-acting agents (LABA, ICS, inhaled LAMA) in any combination and placebo. Concomitant COPD medications will be included if both groups receive the same interventions

Outcomes of Interest:
- Efficacy outcomes:
    - Proportion of patients with exacerbations (primary outcome of interest)
    - Number of hospitalizations (overall and due to exacerbations)
    - Number of emergency room visits (overall and due to exacerbations)
    - Function (e.g., 6 minute walk test, paced shuttle walk test)
    - Forced expiratory volume (FEV)
    - Quality of life
    - Number of patients with ischemic heart disease
    - Dyspnea
    - Mortality
- Safety outcomes:
    - Harms (including all harms, serious harms, withdrawals due to lack of efficacy, treatment-related withdrawals, and the following specific harms: pneumonia, fractures, bone mineral density, heart failure, arrhythmia, oral thrush, palpitations)

Notes: this list may be truncated if we identify many studies for inclusion, as this is a rapid review. We will not perform a meta-analysis (or network meta-analysis) on all of these outcomes and will work with all stakeholders to select the two most important efficacy outcomes and safety outcomes with sufficient data to conduct network meta-analysis. Prior to conducting network meta-analysis, we will ensure that all factors are considered (definition of outcomes, use of rescue medication, patient population, disease severity) because this analysis only is valid when homogenous studies and patient populations are included.

Study Designs:
- Randomized controlled trials

Methods

Information sources and literature search:
We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to January 2014. This will be supplemented by searching conference abstracts, trial protocols, trial registries, and websites of manufacturers of the inhaled long-acting agents. We will also search the reference lists of included studies and reference lists of relevant reviews.

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. These include the diagnosis of COPD (e.g., according to the GOLD criteria versus all others), severity of COPD (e.g., moderate-severe versus all others), gender, and definitions of outcomes (exacerbations in particular).

3. Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in COPD therapies

Study questions: How are COPD medications being used across Canada?
Short description of analysis: We will examine trends in the use of LAMAs and other COPD therapies (for example, inhaled corticosteroid single agents, LABA single agents, inhaled corticosteroid+LABAs) between 2009 and 2013. In Ontario, the analysis will be done from October 2009 to March 2014. Note: Aclidinium (Tudorza Genuair) is not listed on the Ontario public drug formulary; we are therefore unable to obtain utilization information on this drug.

Analysis 2 – Trends in indication of use of LAMAs

Study question: What conditions are LAMAs used to treat?
Short description of analysis: We will look at Ontario residents prescribed LAMA products between 2000 and 2013 and identify the indication for treatment (COPD and/or asthma).

Analysis 3 – Characteristics of COPD patients treated with LAMA products in Ontario

Study question: What are the characteristics of Ontario patients with COPD who use LAMA products today?
Short description of analysis: We will look at descriptive characteristics, including age, gender, socioeconomic status, disease severity, past medication use dispensed among Ontario public drug plan beneficiaries with COPD, stratified by LAMA product.

Analysis 4 – Prevalence and adherence of single, dual and triple LAMA therapy

Study questions: What is the prevalence and adherence of single, dual and triple therapy with LAMAs in Ontario?
Short description of analysis: We will look at COPD patients aged 35 and older who are prescribed a LAMA product either alone or in combination with other medications for COPD (e.g., LABA, ICS, ICS+LABA products). We will describe the prevalence of use by type of therapy. The information will be stratified by age (<65 and 65+) and COPD severity. We will also look at duration of LAMA therapy among patients aged 66 and older. This information will be stratified by type of therapy (LAMA alone or in combination with other COPD medications) and COPD severity.

Analysis 5 – Summary of observational studies evaluating the comparative effectiveness of LAMA products among patients with COPD

Study question: Are there any population-based studies conducted in Canadian patients investigating the comparative effectiveness and safety of LAMA products among patients with COPD?
Short description of analysis: We will perform a literature search to examine the body of evidence on comparative effectiveness and/or safety LAMA products among Canadian patients with COPD.

4. Pharmacoeconomic Unit

Research Questions
- What is the current evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS?

- Based on the economic model developed for the LABA/ICS review, what is the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABAand ICS?
- What is the economic impact of alternatives policies for reimbursing LAMA?

Methods

RQ1   Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

RQ2   De Novo Economic Model

We will use the economic model developed for assessing the cost effectiveness of ICS combined with LABA to assess the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

RQ3   Reimbursement Based Economic Assessment

We will develop a model which will identify the optimal policy relating to reimbursing LAMA. Analysis will identify the change in the forecasted drug budget associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical and cost effectiveness.

5. Environmental Scan

Research Questions

To summarize the pharmacy benefit programs LAMAs 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: LAMAs and LABA+LAMA combination products (where available) for treatment of COPD:
- LAMAs: Tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler), aclidinium (Tudorza)
- LAMA+LABA (combination products): Indacaterol + glycopyrronium (Ultibro*), vilanterol + umeclidinium (Anora Ellipta*)

To determine the impact of different drug reimbursement schemes for LAMAs and LABA+LAMA combination products (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 COPD, in particular the role of LAMAs and LAMA+LABA combination products

Method: Literature review
Intervention: Guidelines/recommendations for the management of adult patients with COPD