FULL PROPOSAL FOR THE CLINICAL STREAM (2009- 2010 ROUND)

This proposal once completed should be a maximum of 10 pages not including appendices, references, tables, charts, figures, and photographs. Please refer to the guidance document for how to complete this application.

Review the guidelines for completing a full proposal. The full proposal should be a maximum of 10 pages.

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Application Information

Title of Project

The economic burden of asthma in Canada

Area of Research Interest ☒ Asthma ☐ COPD

Technical Abstract *(Section can be a maximum of 250 words)*

Background: Asthma is one of the commonest chronic diseases in Canada. There have been no comprehensive assessments of the economic burden of asthma in the country in over ten years. This study will provide population based data on the burden of asthma. Its results will have a major impact on policy decisions relating to the management of asthma at a clinical level but will also impact regulatory agencies as it relates to formulary access. Robust cost effectiveness models need comprehensive population based data to accurately assess the impact of new medications. Policy makers need to know the impact of a common chronic disease such as asthma on the health care system. Employers need to know the impact of lost productivity, especially among workers, who although continuing to attend work, are not working to their full capacity. The proposed assessment tools will allow for such unique assessments which have not previously been evaluated in asthma. **Objectives**: To develop a population-based model of health care utilization and economic costs of asthma in a random sample of patients in selected target areas in BC, and using this data to develop a province-wide and Canada-wide burden of asthma model. In addition an administrative database cohort of all asthma patients in BC will augment our patient level cohort, which will allow for more robust modeling of the burden of asthma in Canada. **Hypothesis**: Asthma results in significant burden on patients and the public healthcare system, and that uncontrolled asthma is a major contributor to the burden of the disease.
***Keywords**: asthma, burden of disease, cohort studies, quality of life, costs*

Detailed Research Plan (Sections A-D)

Section A: Research Question

Background/Rationale *(should be a maximum of 250 words)*

Asthma is one of the most common chronic diseases in the world(1). The economic cost of asthma is high. Globally, the number of disability-adjusted life years (DALYs) lost due to asthma has been estimated to be about

15 million per annum(1). The total direct medical and indirect economic cost of asthma has been estimated to be between $504 million and $648 million dollars in Canada for the year 1990(2). In the same year in the United States it has been estimated that the total cost of asthma was around US $6.2 billion(3).

Four studies have estimated the cost of asthma in Canada(2)(4)(5)(6). None of the studies measured the burden of asthma in a prospective cohort of patients, nor were they based on an objective definition of asthma. Such important shortcomings can only be addressed through a cost-of-illness study with the prospective recruitment of patients who are appropriately diagnosed and are followed over time.

In order to determine whether asthma treatments are an appropriate use of scarce healthcare resources, it is necessary to evaluate the benefits of competing treatments in the light of their associated costs by undertaking economic evaluations such as cost-effectiveness analyses. Despite popularity of such techniques, decision-analytic modelling has not been widely used in asthma.

The proposed study, based on objective evaluation of costs of asthma combined with decision-analytic techniques will significantly contribute to our understanding of the burden of asthma in the country and will provide a framework for estimation of the future burden of asthma and the merit of emerging health technologies.

Objective(s)	**Primary objectives:** 1) To estimate the direct and indirect costs of asthma in British Columbia (BC), and the impact of asthma on quality of life. 2) To estimate the burden of asthma by levels of severity and control. 3) To extrapolate the data and develop a province-wide and Canada-wide burden of asthma estimate. **Secondary objectives:** 1) To examine the determinants of healthcare resource utilization and quality of life in patients with asthma. 2) To examine the impact of asthma on work productivity (absenteeism and presenteeism). 3) Comparing the retrospective versus prospective calculation of direct asthma costs. 4) Developing an algorithm for assigning levels of severity and control based on administrative data. 5) To predict the direct and indirect cost of asthma for the next 10 years.
Hypothesis(es)	- Asthma is associated with a significant burden, in terms of direct and indirect costs, and quality-of-life in Canadians - The burden of asthma is adversely correlated with level of control - Without significant changes in the management of asthma, the burden of asthma in future will increase.
Primary Endpoint(s)	1) Direct and indirect medical costs of asthma in BC and Canada. 2) Quality of life of asthmatics at different levels of severity and control.
Secondary and Other Endpoint(s)	1) Projected direct and indirect costs of asthma for the next 10 years in BC and Canada. 2) Work productivity lost due to asthma (presenteeism and absenteeism)

Section B: Study Design

Study Design and Interventions

The study will consist of three phases: **Phase A**: General population survey for estimation of the prevalence of asthma, and prospective collection of resource utilization and quality-of-life data for 12 months, **Phase B:** comparison of healthcare resource usage collected prospectively to the data collected using administrative data in the population recruited in Phase A, and **Phase C**: Economic modeling of asthma to extrapolate the findings across Canada and into the future years.

Phase A: This phase will be a prospective cohort study of randomly chosen residents of two census subdivisions of BC with a self-reported physician diagnosis of asthma. Patients will be followed for one year and at the end of follow-up will have confirmation of the diagnosis of asthma using an objective diagnostic algorithm based on pulmonary function testing. *Patient selection and sampling:* The study patients will be recruited via landline and cell phone-based random digit dialling (RDD) across two regions in BC: the Census Sub-Division (CSD) of the city of Vancouver (referred to as 'Vancouver') and the Census Division of Central Okanagan (referred to as 'Okanagan'). The target area was chosen based on CSDs as it provides a clear definition of the target population for whom demographic and socioeconomic data is available through national and provincial census and surveys(7). The Okanagan CSD was particularly chosen as it provides data on both urban and rural populations (18.6% rural population in 2006). According to 2006 census profile, the population of these two CSDs is, respectively, 578,041 and 162,276. Accordingly, about 78% of volunteers would be recruited from Vancouver, and 22% from Okanagan. The study will randomly sample subjects from the all area codes in these three regions. The target population will include household residents residing in telephone exchanges within the target CSDs. RDD will be geographically stratified with an associated sample weight that will approximate a probability sample of the individuals in the population. Previous studies have shown that acceptably high response rates can be achieved among Canadian subjects with asthma(8).

RDD samples have been shown to be more representative than population samples drawn using alternative methods such as telephone directories or electronic white pages(9). However, RDD is not free of bias. Non-random non-response is an issue, and it has been shown that reducing the non-response rate may directly reduce non-response bias(9). Non-responders in RDD may not have been contacted because they work multiple minimum-wage jobs. We will place multiple calls and leave messages on answering machines. RDD is also subject to no-telephone bias(10) - households without telephones are out of reach by RDD, and these households probably differ in socioeconomic status than the overall population. However, for the urban, suburban, and semi-rural subpopulations within BC, telephone coverage is almost universal.

Inclusion of cell phones in RDD is an attempt to mitigate such biases and increase the fraction of population covered by sampling. More importantly, the inclusion of cell phones is likely to result in inclusion of participants that might be absent from landline RDD (younger and more educated groups) thus mitigating the sampling bias of RDD(11). Cell phone RDD is an active area of research and it is too soon to know with confidence what should and should not be regarded as a “Best Practice”. For inclusion of cell phones in RDD, we will use the “Screening Approach”(11). In this approach the interview is only conducted with people sampled via the cell phone frame who do not have a landline, thus excluding numbers from the cell phone sample in the overlap (i.e., screening out those persons with both a cell phone and a landline). In this alternative sampling design, persons who have at least one household landline telephone and use at least one cell phone would be eligible for inclusion only from the landline frame. This decreases the bias due to higher probability of sampling from households who have both a landline and cell phone.

The study will employ the Waksberg method of random digit sampling(12). In this method, all telephone numbers are initially split into blocks of equal size, called "primary sampling units". The primary sampling unit will be a mixture of landlines and cell phones. One randomly selected telephone number is called from each selected primary sampling unit. When a residential connection is reached in the first stage, the primary sampling unit qualifies for inclusion in the second stage.

Respondents will be asked the following question: “Is there a member of your household between ages of 1 to 85 who has had asthma ever diagnosed by a physician”. If the response is affirmative the study assistant will ask if the subject in question can continue the conversation directly (parents in case of children). Eligible subjects (or in the case of children their parents or guardians) will be informed of the objectives of the study, verbally consented, and then screened for eligibility based on age and history of asthma. Patients who meet eligibility

criteria and who verbally consent over the phone will be asked to come to the study laboratory (one at Vancouver and one at Kelowna, corresponding to the two CSDs) and they will receive a detailed explanation of the study and the study consent form at that time. All patients who provide signed consent will then proceed to spirometry (simple spirometry without bronchodilator response) and study data collection.

Participants who do not consent to participate in the prospective phase will be asked, pending their consent, to provide baseline data (age, gender, severity of asthma based on self report) and household income. Such data will be recorded and compared to those who enter the prospective phase in order to assess the representativeness of the final sample.

After the baseline visit, participants enter a 12-months period of follow-up with visits at months 3, 6, 9, and 12. Participants will be asked to attend one of the study centres and data on the quality of life and asthma-related resource utilization will be gathered (see Section C for details). On the final visit, participants will undergo spirometry for objective diagnosis of asthma with possible metacholine challenge test for those in who masthma cannot reliability be included or excluded (Figure 1).

Inclusion criteria:

1) Patient must state that they have had a diagnosis of asthma by a physician. In addition, the patient must have had a self-reported health care interaction related to asthma (physician visit, ED visit, hospitalization) in the past 5 years.
2) Patient must be 1 to 85 years old.

Exclusion Criteria:

1) Patients unable to provide informed consent due to language difficulties or cognitive impairment.
2) Patients who have a greater than 10 pack-year smoking history (this will exclude patients with possible COPD).
3) Patients who know that they will be moving out of the province within 12 months of study entry.
4) Patients in whom metacholine challenge test is contraindicated due to non-asthma-related reasons: patients with recent history of stroke or heart attack, or cerebral aneurysm, and pregnant and breastfeeding participants.

Note that we will not exclude participants for whom metacholine-challenge test is contraindicated or non-informative due to asthma-related reasons (e.g. patients on oral corticosteroids) as these patients are likely to have high resource utilization. The diagnosis of asthma in such cases will be based on physician diagnosis

Phase B: In this phase of the study, health records of individuals who have participated in the phase A of the study for their entire follow-up period and the 12 months period prior to their enrolment will be retrieved from the BC Linked Health Database (BCLHD). In addition, we will indentify cases of asthma in the entire BC population based on the administrative data for the same period of time. The BCLHD is a longitudinal administrative health care database containing person-specific, anonymized health data from 1985 onwards on BC's 4 million residents with health insurance(13). Records will be matched based on individuals' unique Personal Health number (PHN) and hence the matching will be almost completely accurate. Data extracted from the BCLHD will include Medical Services Plan (MSP) data, which encompass fee-for-service physicians, the Discharge Abstracts Database (DAD) of hospital inpatient separation records, as well as records of death certificates. Prescription drug use will be determined from the BC Pharmanet database. This is a population-based prescription drug database that captures essentially all dispensing episodes by outpatients residing in the province on a prescription-by-prescription basis (regardless of funding source)..

One request thought the BC ministry of health (personal communication with Data Stewardship Secretariat) is required to retrieve data on the study participants as well as cases of asthma across the entire province, without additional cost for the latter group. We will use this opportunity to retrieve data on cases of asthma in the entire province (using the same case definition algorithm described in our earlier work(6)) and compare different aspects of resource utilization between objectively verified cases of asthma and those retrieved using a case definition algorithm on an administrative database. Such data will be used to retrospectively estimate the direct costs of asthma during the follow-up and in the 12 months prior to the enrolment in the study (See section D for details of data analysis). The direct medical costs calculated in this way will be compared with the direct costs calculated in the prospective phase of the study. In addition, we will examine the representativeness of our sample population by comparing their health records with those of case of asthma in BC identified through the BCLHD. Given the objective validation of the diagnosis of asthma at the end of the follow-up period in Phase A, we will also be able to explore the sensitivity of existing case ascertainment algorithms based on administrative data at levels of severity and control.

Phase C: Economic model of asthma: The data collected from patients during this study will be extrapolated to the population of BC and Canada by appropriate adjustment for demographic and socioeconomic differences and

reported prevalence of asthma in the country. The data will also be used to populate a Markov model of asthma to project the burden of asthma for the next 10 years. The Markov model of asthma will extend the model previously developed by Price et al(14). However, we will model all 4 states of severity as defined by the Global Initiative in Asthma (GINA) and whether at each year the patient's symptoms are controlled or uncontrolled. The Markov model will hence consist of 8 states (plus state of death) for all permutations of levels of severity and control (Figure 2-A). The model will also incorporate both the steady-state of chronic asthma and the acute state associated with an asthma exacerbation (Figure 2-B). Whenever possible, we will estimate the parameters of the model from the cohort of patients in the Phase A and B of the study. This will include the initial distribution of individuals according to levels of severity and control, and the quality of life weights and annual direct and indirect costs estimated from the statistical analysis of the cohort data. The long term transition probabilities among levels of severity and control cannot reliably be estimated given the short follow-up of the patients in this study. We will use values estimated from the literature for these and other components of the model.

Study Population	**Phase A** of the study will be based on the survey of the general population (1-85 y/o) of two well-defined target areas and recruitment of those with a self-reported physician diagnosis of asthma. **Phase B** of the study is the retrospective elicitation of the health record of participants. In **Phase C** of the study builds upon the data of Phase A and B and other published studies to extrapolate the results to the Canadian population for the next 10 years, as such it does not involve direct population sampling.

Section C: Study Assessments and Procedures

Baseline visit: On entry to the study, the research staff at each site will record the patient's age, gender, ethnicity (including country of origin, if born in Canada parents country of origin as well as primary language spoken at home) asthma medication use (type of medication used and duration of use), height, weight, body-mass index, date of onset of respiratory symptoms, date of asthma diagnosis, name of the physician who diagnosed asthma and his/her specialty, and co-morbid disease history. Exposures to cigarette smoke, occupational exposures, and exposures to allergens (such as pets, molds, etc) will be documented. History of any emergency visits, or hospitalizations for exacerbations of asthma within the previous 12 months will also be recorded. Adults will complete the Asthma Quality of Life Questionnaire (AQLQ), the EuroQol's EQ-5D, Asthma Control Test (ACT) (see the Questionnaires section) and will undergo screening for depression and anxiety using the Beck Depression Inventory II and the Beck Anxiety Inventory. For children 7-17 years old, AQLQ and ACT will be replaced by the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Children Asthma Control Test (C-ACT), respectively. Quality of life and asthma control status will not be measured in younger children. Alternative diagnoses that could be mistaken for asthma will be recorded including: symptoms of gastro-esophageal reflux (assessed using the validated 'Reflux Symptom Questionnaire'), history of confirmed gastro-esophageal reflux, and history of anemia, vocal cord dysfunction, congestive heart failure, bronchiectasis, COPD, or lung cancer. Baseline spirometry will be performed on all subjects in order to detect participants with severe uncontrolled asthma, whom will be referred to their primary physicians for review of their asthma management .We will use a cut off of 60% predicted FEV1 as an arbitrary cut off to ensure patient safety. These patients will continue to be followed in the study.

Follow-up visits: Each participant will undergo four follow-up visits at month 3, 6, 9, and 12. Visits will take place at study sites. We will contact participants two weeks and one week in advance and will provide them with a range of dates they can attend the clinic. During the follow-up visits participants will be asked to report exposure to cigarette smoke, occupational exposures, and exposures to allergens during the time since their last visit. The follow-up questionnaire will consist of the AQLQ (PAQLQ in children), EQ-5D (only in adults), Valuation of Lost Productivity Questionnaire (VOLP, only in adults), Work Productivity and Activity Impairment Questionnaire: General Health (WAPI-GH, only in adults), and ACT (C-ACT in children). All questionnaires will be administered at the same visit and will be delivered in a single binder, except ACT and C-ACT that will be administered using a handheld device.

Patients will also fill a form describing their use of healthcare resources during the previous three months. If a patient has visited a physician, for scheduled or unscheduled reasons or ED or had been hospitalized, we will contact the patient's treating physician to assess if the medical encounter had been asthma-related and a full report, including physician, emergency department, and hospital records that described the circumstances of each encounter will be reviewed. An adjudication committee will confirm whether the encounter has been asthma-related. We will also correlate patient reported data by linking to their MSP health care utilization profile which will

overcome the problem of recall bias in reporting health care resource utilization (see Phase B).

Pulmonary function: Objective evaluation of asthma at the end of follow-up period using objective assessments for the presence of asthma will be used. By objective verification of the diagnosis of asthma using spirometry, we will be able to use the established criteria (15)(16) for the diagnosis of asthma; this will enable us to separate the burden of true asthma from misdiagnosed asthma and provides answer to the critical question that what the burden of misdiagnosed asthma is in the target population (and by extrapolation in BC). This will differentiate our study from previous burden-of-disease projects, none of which have been based on a standardized and objective definition of asthma, and will also allow us to include children <5 y/o and elderly >65 y/o who are often excluded due to difficulty of establishing the diagnosis of asthma without spirometry. We will use a modified protocol as employed by Aaron et al (17) for the objective definition of asthma in adults. We recognize the challenge of diagnosing asthma in children (symptom overlap with other conditions and lack of reliability of spirometry) but will use the framework suggested by GINA(18). Spirometry will not be performed on participants younger than 5 years of age.

On the final visit at month 12, all participants will undergo spirometry according to the American Thoracic Society standards(16). Following spirometry, subjects will receive 200 µg of salbutamol by pressurized metered-dose inhaler with a spacer device and spirometry will be repeated 15 minutes later. Patients whose forced expiratory volume in 1 second (FEV_1) improves by at least 12% and at least 200 mls after inhalation of the bronchodilator will be considered to have reversible airflow obstruction consistent with the diagnosis of asthma(19).

Participants who do not exhibit reversible airflow obstruction will return to the pulmonary function laboratory within a week for a methacholine challenge test. Patients who have no evidence of airway hyper responsiveness will have the result forwarded to their family physician for re-evaluation of asthma diagnosis.

Questionnaires

The following questionnaires will be filled for each participant:

1. Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)*:* The Work Productivity and Activity Impairment (WPAI) questionnaire measures work time missed and work and activity impairment because of a general health problem during the past 7 days(20) (http://www.reillyassociates.net/WPAI_GH.html). The validity of the WPAI has been established for asthma(21), and also for a number of other diseases, e.g. allergies(22), dermatitis(23), GERD(24), nocturia (25). Data from this questionnaire and the Valuation of Lost Productivity Questionnaire will help us calculate the loss of productivity and resulting indirect costs attributable to asthma.

2. Valuation of Lost Productivity Questionnaire (VOLP)*:* VOLP is a new questionnaire that values productivity loss (monetary estimates of output loss) among the general population or a population with specific disease (http://www.thevolp.com/). It tries to address the limitation of the previous questionnaires; especially, it has established the components of “presenteeism” related to economic output (secondary objective) and incorporated questions on team production to enable a comprehensive economic outcome of productivity to be evaluated using patient questionnaire. It has recently been validated in a group of patients with rheumatoid arthritis(26). We will apply this questionnaire to the situation in asthma to fully determine the economic aspects of productivity loss associated specifically with this condition.

3. EQ-5D*:* EQ-5D is a standardised instrument for use as a measure of health outcome(27). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be incorporated into the calculation of quality adjusted life years (QALYs). EQ-5D was originally designed to complement other instruments but is now increasingly used as a 'stand alone' measure. EQ-5D is relatively brief compared with other generic instruments measuring quality of life, which has resulted in better completion rates (28). EQ-5D will be administered at baseline and all follow-up visits.

4. AQLQ*:* The asthma quality-of-life questionnaire (AQLQ) is a 32-item disease-specific self-administered questionnaire that has been designed to measure the functional-specific impairments that are most troublesome to adults with asthma(29). Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale, with higher scores representing a better health status. The overall AQLQ score is the mean response to all 32 questions. Four independent studies have established that the AQLQ has strong measurement properties and validity(30). AQLQ, as a disease specific questionnaire, has been found to be better responsive to changes in levels of severity and better correlates with the objective outcomes associates with asthma severity than the generic multi-attribute instruments(31). AQLQ will be administered at baseline and all follow-up visits.

5. Standardized Paediatric Asthma Quality of Life Questionnaire (PAQLQs): is a 23-item (plus five patient-specific activities) developed to measure the functional problems (physical, emotional and social) that are most troublesome to children with asthma(32). The validity and reliability of PAQLQ has been established in several independent studies (33)(34)(35). This questionnaire will be interviewer-administered for those <11 y/o, and self- or interviewer- administered for older children.

6. Asthma Control Test (ACT): ACT is a patient-completed questionnaire with 5 items assessing asthma symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning (36). Each item corresponding to a 5-point Likert-type response scale to yield a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma). It has shown high levels of reliability and correlation with specialist assessments of asthma control, as well as correlating with pulmonary function measurements and treatment decisions that are based on specialist-assessed asthma control(37)(38)(39).

7. Childhood Asthma Control Test (C-ATC): Similar to ACT, C-ACT is validated, simple and quick tool that is completed by the patient and parents/caregivers for assessing the level of asthma control for children 4-11 y/o(40). It consists of 7 questions with 4 to 6 levels of response; 4 questions are filled out by the child and 3 by the caregiver. A score below 18-22 indicates lack of proper control. C-ACT has shown good clinical and construct validity(40).

***8. Measurement of resource utilization*:** Information on the utilization of medical care will be based on a combination of patient recall and information retrieved from the provincial health authorities for the study participants. The provincial administrative data will help us verify the hospitalizations and physician encounter, and asthma-related procedures (e.g. outpatient spirometry) and medications. Patients' self report will reveal ambulatory laboratory, diagnostic, and radiology services, home health services, supplementary oxygen for home use, over-the-counter medications, usage of nursing facilities, and hospice care.

Section D: Data Analysis

Sample Size Calculation / Justification	Several layers of statistical analysis are needed to calculate provincial and national burden of asthma based on the data of Phase A of the study. We consider the estimated prevalence of asthma in the target population to be an important factor affecting downstream calculations and associated uncertainty (e.g. confidence interval) in the results. As such, the sample size calculation is based on the estimation of the prevalence of asthma in the target population. The sample size is determined such that the Coefficient of Variation (CV, defined as the ratio of standard error to point estimate) is less than or equal to 0.15. Given the estimated prevalence of 8% of asthma in BC, 511 subjects must be recruited in order to have a CV=0.15. This corresponds to a 95% confidence interval of 5.6% - 10.4% for an observed prevalence of 8%. We will assume 20% loss-to-follow-up at the end of the study period (based on our experience with similar studies on asthmatics in BC). This will increase the sample size required at the baseline visit to 613.The study will randomly sample subjects from the all area codes in the two target CSDs, with regional sample size proportional to the target areas' population estimated from the 2006 census data. Table 1 in appendix shows different required sample size as a function of the prevalence of asthma using the aforementioned criteria.

Data Collection and Statistical Analysis Plan for all endpoints

The analysis of the data will be based on the following steps in accordance with the specified objectives of the study.

Statistical weighting of the study sample to generalize the estimates to BC and Canadian population: For practical reasons, the sample of the study is limited to two census subdivisions in BC. This, combined with potential biases inherent in RDD sampling, requires that statistical analyses be adjusted to generalize the results across the province and country. We will use proper statistical methods to assign 1) a weight to each individual representing the relative proportion of persons with such characteristics in the province; 2) a weight to each individual representing the relative proportion of persons with such characteristics across Canada. Factors that will be considered for weighting include demographic factors such as age, gender, socioeconomic status, as well as factors elicited during the follow-up, and geographical and demographic data obtained from the census data (e.g. urban/rural status based on postal code and Health Services Delivery Area). All relevant statistical analyses will employ these weights to generalize the results across BC and Canada and for brevity are not mentioned in the subsequent sections.

Part A

1. Estimating the direct and indirect costs of asthma, and the impact of asthma on quality of life (primary objective 1):

1.1 Calculating quality of life of patients with asthma*:* We will report mean AQLQ (pAQLQ in children) score for each patient. The mean AQLQ score for baseline and each follow-up visit among all patients will also be calculated. We will use a linear mixed model (with a random effect parameter for each patient) to calculate the rate of change in AQLQ over the study period.

Likewise, similar analysis will be performed on the EQ-5D data. Based on the available EQ-5D responses for each patient we will calculate Quality Adjusted Life Years (QALY) for each participant, assuming linear change in EQ-5D scores between successive measurements. QALY will also be calculated indirectly by transforming AAQLQ to AQ-5D scores(41), and derived QALYs will be statistically compared for equivalence.

1.2 Calculating direct and indirect costs per patient: Costs per patients will be calculated by multiplying the amount of healthcare resources used by the corresponding unit costs. We will adjust all unit costs to 2010 CAN$ according to the medical care component of the Consumer Price Index(42). The lowest price for available (generic drugs if exists) versions of medications will be used based on province-specific data. The value of time spent by family and friends in caring for patients will be calculated on the basis of the average wage for workers 20 to 64 years of age reported by Statistics Canada(43). Likewise, the value of the time patients spend receiving treatment will be calculated on the basis of the average wage for workers with the same age. Costs for transportation to and from health care facilities will be determined by multiplying the travel distances by the federal average reimbursement rate per kilometre.

Several methods will be used to estimate asthma-related utilization of nonmedical goods and services. For example, travel distances to care facilities will be estimated based on the distances travelled from patient's residence to the facilities. Participants will give estimates of the weekly average number of hours of care provided to them by unpaid caregivers (family and friends). For the purpose of this study, we will exclude cost of research and development on asthma and related health technologies.

1.3: Estimating the average and total costs and QALYs: Based on the results of the previous two steps, we will calculate the average direct costs, average indirect costs, and average QALYs for an adult resident of BC or and an adult Canadian with asthma. We will use the statistical weighting approach described earlier for such extrapolation.

2. **Burden of disease by level of severity and level of asthma control (primary objective 2):** All the analyses described above will also be performed within the groups of patients classified as having mild, moderate, or severe asthma, and in addition using the now more conventional criteria of controlled, partly controlled and uncontrolled asthma. Appropriate statistical methods will be used to compare the costs and quality of life of patients across levels of severity. We will use the classification of asthma severity developed by the National Asthma Education Program (44). This algorithm classifies patients into four levels of severity: mild intermittent, mild persistent, moderate persistent and severe persistent. The classification is based on symptoms, frequency of asthma exacerbations, physical activity, and peek expiratory flow rate (PEFR) measured on spirometry. In addition we will estimate the costs of asthma using the levels of control. We will use both the level of control defined by GINA and the mean ACT (and C-ACT) scores for assigning patients to different levels of control.

3. Determining factors affecting burden of disease (secondary objective 1): We will investigate if individual-level covariates are predictive of quality of life and pattern of healthcare utilization in patients with asthma. We will determine if, and to what extent, an increase in the level of asthma severity is associated with higher costs and/or lower levels of quality of life. Similarly, we will investigate if parameters of the lung function test are associated with

the cost and quality of life associated with asthma in the following year. Specifically, we will regress the costs (log-transformed) and QALYs (logit-transformed) on 1) lung function parameters (FEV1, FVC, FEV1/FVC, and PEFR) measured at the baseline visit, 2) on the level of severity/control, and 3) on age, baseline weight and height, and socio-economic factors.

4. To evaluate the impact of "absenteeism" and "presenteeism" (secondary objective 2): The WPAI and VOLP questionnaires both allow for quantifying the economic impact of absenteeism and "presenteeism" related to asthma. These figures will be multiplied by the average hourly wages (stratified by age, gender, and type of job) in order to estimate the economic value of productivity loss.

Part B:

1. Comparing the retrospective versus prospective calculation of direct asthma costs (secondary objective 3): The detailed methodology for calculating asthma-related direct costs is explained in our related publication(6). In brief, a unit cost will be assigned for each item of resource utilization. This will be similar to our previous analysis of BCLHD data (for the period of 1996 to 2000), with detailed methodology previously been reported(6). Using such analysis, we will be able to calculate the person-specific costs for the follow-up period as well as 12 month period before enrolment of each subject in the study. Results from Phase A and B of the analysis will be used to compare the annual direct medical costs estimated using a retrospective, administrative-data base and a prospective follow-up survey of patients. We will statistically test the mean direct costs measured in these two methods, and will regress the different in costs over the baseline variables of participants.

2. Comparison of resource utilization between an objectively verified cohort of asthmatics vs. cases defined based on administrative database.

We will compare the pattern of resource utilization among cohort of patients recruited in the Phase A of the study versus the cases of asthma in the entire BC population. We will particularly focus on the data for the year prior to recruitment (to exclude possible interference of the study protocol). Such comparison will be made between the study population and cases found in the province, and also between the study population and cases found in the administrative data in the same geographical location (target CSDs). We will try to find factors that might explain possible discrepancy in direct medical costs between the two methods of cost calculation.

3. Estimating the sensitivity of case definition of asthma based on administrative data: Knowing the true asthma status in all individuals from the prospective phase of the study, we will be able to estimate the specificity of case definition of asthma based on administrative data. We will apply the case definition of asthma to each individual using the resource utilization data, and will classify them as asthmatics and non-asthmatics. Within the group of individuals who have been diagnosed of having asthma from phase A of the study, the proportion of those who have been diagnosed of having asthma based on resource utilization data is an estimate of the sensitivity of the asthma diagnosis algorithm. We will also examine the accuracy of algorithms used to assign patients to levels of severity and control based on administrative data(45).

4. Developing an algorithm for assigning levels of severity and control based on administrative data (secondary objective 4): Individuals from phase A of the study will eventually be classified as those who truly have asthma or not; and also their level of severity and control. This objective classification will act as a gold standard for the discriminatory ability of any case definition of asthma based on resource utilization data. We will use several different algorithms, developed through consulting with clinicians, and find the one that has the highest accuracy (defined as sum of the sensitivity and specificity of the algorithm) in classifying patients into levels of severity and control.

Part C: **Statistical/Economic analysis**

1. Calibration of the economic model of asthma: the transition probabilities and other parameters will be calibrated such that the distribution of patients across levels of severity and asthma control will remain stationary over time and similar to the observed pattern in the prospectively collected data.

2. Predicting the future burden of asthma (secondary objective 5): once developed and calibrated, the model will be used to predict the societal burden of asthma separately for up to 10 years into the future. The model will be run taking into account the projected changes in the prevalence of asthma, population growth, and future changes in the demographic characteristics of the Canadian population over time. Costs per patient, per capita, per province, and national costs for asthma and separately for categories of asthma severity will be determined. Model simulations and calculations will be conducted on a standard spreadsheet platform with an interface that allows for changes in input parameters to conduct sensitivity analyses.

Anticipated Results and their	Scientific evidence is key to improving public health, because health policies should be based on accurate and meaningful health data. Poorly informed policy-making can be one

Interpretation	of the reasons why attempts to improve public health fail(46). Burden of disease studies provide information that is otherwise difficult to gather from fragmented epidemiological studies. Unfortunately, studies investigating the burden of asthma in Canada are few and mostly outdated. The incidence and prevalence of asthma in North America has increased at an alarming rate, and asthma is a major public health problem affecting more than 8% of the Canadian population. In this dynamic setting, the current estimates of the burden of asthma are outdated and the only recent study suffers from problems inherent to administrative data(6). Estimation of the societal cost of asthma and future burden of this disease, validating existing algorithms for finding asthma cases in administrative datasets, and providing a valid framework for conducting economic evaluation of health technologies in asthma are thus very important from a policy as well as a patient perspective. This study is a cost-effective way of spending research dollars; its budget equals the lifetime cost of disease for a handful of asthmatics whose disease, due to caveats in our healthcare system, is not properly controlled. The wealth of data generated through this project can be used to answer several important research questions, many of which omitted in this protocol due to space limitations.

Projected Timelines and Potential Risks to Research Plan *(based on a May 2010 funding decision). In Appendix III, please include a Gantt chart to outline the timelines associated with the project plan.*

Study Start Date	06/2010	First Subject First Visit Date	09/2010
Study End Date	06/2012	Last Subject First Visit Date	05/2011
Anticipated Publication Date	12/2012		
Potential Risk to Research Plan & Contingency Planning	Due to budget limitations and logistical reasons, we limited the study to only two census subdivision areas in BC. This will limit our ability to generalize the results across provincial and national levels. However, we will use appropriate statistical methods to adjust for possible demographic differences between the target sample and populations. This will not only include data elicited through the phase A of study, but also pattern of healthcare utilization derived from the administrative data. We already have access to the population based BC cohort of patients and this provides a rich data source. In a previous analysis of 185,000 patients drawn from a previous dataset for the period 1996-2000 we have been able to estimate preliminary costs. Another risk to this project relates to a potential lack of interest in subjects participating in the random digit dialing portion of the study but our previous extensive experience in participating in the COLD study as well as the recruitment of subjects into the obesity and asthma study in Canada make us confident that we will be able to recruit a valid sample.		

Presentation / Publication Plan

Abstract	Targeted Conferences for Presentation: American Thoracic Society annual conferences	Estimated Submission Date: 01/2012
Manuscript	Target Journal for Primary Publication: American Journal of Respiratory and Critical Care Medicine. We anticipate multiple secondary publications which will be submitted to CMAJ, CDRJ as well as health economics journals	Estimated Submission Date: 12/2012

Description of Facility/Resources for Conducting Research

Subjects recruited into this study will be evaluated at The Lung Centre at VGH. JMF's research staff have completed multiple asthma related studies and there is the necessary space to interview subjects, as well as perform spirometry and if needed Methacholine inhalation challenge tests. WTH has experience in the completion of BOLD and more recently COLD. CM and LL have the appropriate expertise in economic evaluations as well as

working with administrative databases. D.R is a community respirologist in Kelowna who has experience in completing asthma studies and has the appropriate space and personnel to complete the Kelowna sub study.

THIS COMPLETES THE 10 PAGE LIMIT, PLEASE ATTACH OTHER APPENDICES AS NECESSARY.

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APPENDIX II - Estimated Study Budget / Requested Support (*include Institutional overhead percentage*)

The study budget is divided into the fixed costs (initial set up and final analysis) and per-participant costs. Details of the budget calculations are presented in the supplementary tables below. In brief, subtotal costs are as follows:

Fixed startup and final costs	**$40,173**
RDD	**$70,805**
Phase A	**$197,430**
Phase B	**$38,750**
Phase C	**$37,500**
Unexpectd administrative costs	**$5,000**
Total	**$389,658**

Supplementary tables

APPENDIX II - Estimated Study Budget / Requested Support (*include Institutional overhead percentage*)

LAND LINE	Value	Comment
Sample size	588	514 Vancouver / 74 Central Okanagan CD
Participation rate	0.7	The proportion of households who participate in the phone interview
Prevalence of asthma	0.1	Assumed to be for household
Volunteer to be contacted	0.4	Proportion who agree to be contacted by the study operating center for recruitment
Proportion of households elgible	**0.028**	
Number of interview atttemps	**21000**	
Number of full interviews with asthmatics	**1470**	
Recruitment per hour of interview	0.77	
Expected number of CATI hours	**1909.091**	
Cost of interviewing/hour	28	
Total field cost	**53454.55**	
CELL PHONE	**Value**	**Comment**
Sample size	25	25 Vancouver & Okanagan
Participation rate	0.7	The proportion of households who participate in the phone interview
Prevalence of asthma	0.1	Assumed to be for household
Volunteer to be contacted	0.4	Proportion who agree to be contacted by the study operating center for recruitment
Proportion of households elgible	**0.028**	
Number of interview atttemps	**892.8571**	
Number of full interviews with asthmatics	**62.5**	
Recruitment per hour of interview	0.77	
Recruitment per hour adjusted for CELL PHONE sample	0.35	This adjustment includes the negative effect of cell phone calling on sample goodness and on the cooperation rate
Expected number of CATI hours	**178.5714**	
Cost of interviewing/hour	28	
Total field cost	**5000**	
Number of list deliveries	**31**	
Data processing hour per list	1	to extract the data from the CATI system and create the appropriate data files. It also requires the project manager to manage the project operations, format the volunteer lists as they are sent to you, verify the integrity and quality of the data, and prepare disposition and progress reports
Data processing cost/hour	80	
Data pprocessing cost	**2480**	
Project management hours per list	0.6	
Project managment cost/hour	100	
Project management costs	**1860**	
survey programming, procurement, cleaning,loading hours	7	
Cost of survey programming, procurement, cleaning,loading /hour	80	
Cost of survey programming, procurement, cleaning,loading	**560**	
Additional cost for CELL PHONE sample purchase	**5000**	
Profession consultation hours	14	
Cost of professional consultation/hour	175	
Cost of professional consultation	**2450**	
TOTAL COST OF Volunteer recruitment	70804.55	

Table B1: Breakdown of RDD costs

APPENDIX II - Estimated Study Budget / Requested Support (*include Institutional overhead percentage*)

Start up fees			
	Pre-screening activities	$2,000	
	Computing costs (Source document preparation)	$5,000	
	Study Administration (REB submission, protocol amendments, safety reporting)	$5,000	
	Long Term Record Storage	$1,000	
	Ethics (IRB) fees	$3,000	
	Secretarial Costs	$3,000	
	Travel costs of personnel between cordinating and satellite centers	$20,000	
	Office supplies	$1,173	Computer software licenses ($213), photocopying ($500), local and long distance telephone ($210), office supplies ($250)
Phase A (minus RDD)			
	Data analysis	$13,750	Estimated as 3 months of full time by a master-level statistician
	Handhelp device (palm) for part of the questionnaire	$400	
	RDD		See RDD secion (presented separately)
Phase B			
	Access to data from MSP, hospital separations, vital statistics, Pharmanet	$25,000	Communication with data Stewadship secretariat: $10,000 for coordination and data preparation, $15,000 for the use of Population Data BC's Secure Research Environment (based on a 3 year project, $5,000/year)
	Data analysis	$13,750	Estimated as 3 months of full time by a master-level statistician
Phase C			
	Developing the economic model	$27,500	Estimated six month of full time work by a master-level Health eEconomist
	Research asstitant	$10,000	Estimated as half-time work of a resaerch assistant, for a period of 6 months

Table B2: fixed costs

Per recruitment costs

	Baseline visit	Visit 1	Visit 2	Visit 3	Visit 4	Comments
Contacting particpants	2	2	2	2	2	Up to 3 times calling the participants. Assumed to take 3 minutes per call of a research assistant (20$/hour) plus telephone bills
Questionnaires	15	15	15	15	15	
Physcial exam	0	0	0	0	0	No costs assignes as it will be performed by inhouse staff
Spirometry	25	0	0	0	25	
Meta-coline chalenge test +	0	0	0	0	100	It was assumed 40% of participants will need meta-coline challenge test and repeat spitrometry
Incentive	20	20	20	20	20	
Data entry	5	5	5	5	5	Assumed to take 15 minutes for data entrist for 20$/hour
Number of participants	613	588	564	539	511	Asusming constant attrition rate reaching 20% at the last visit
Subtotal costs	**$41,071**	**$24,696**	**$23,688**	**$22,638**	**$85,337**	

Table B3: per-patient costs (Phase A)

Funding requested from any other source?

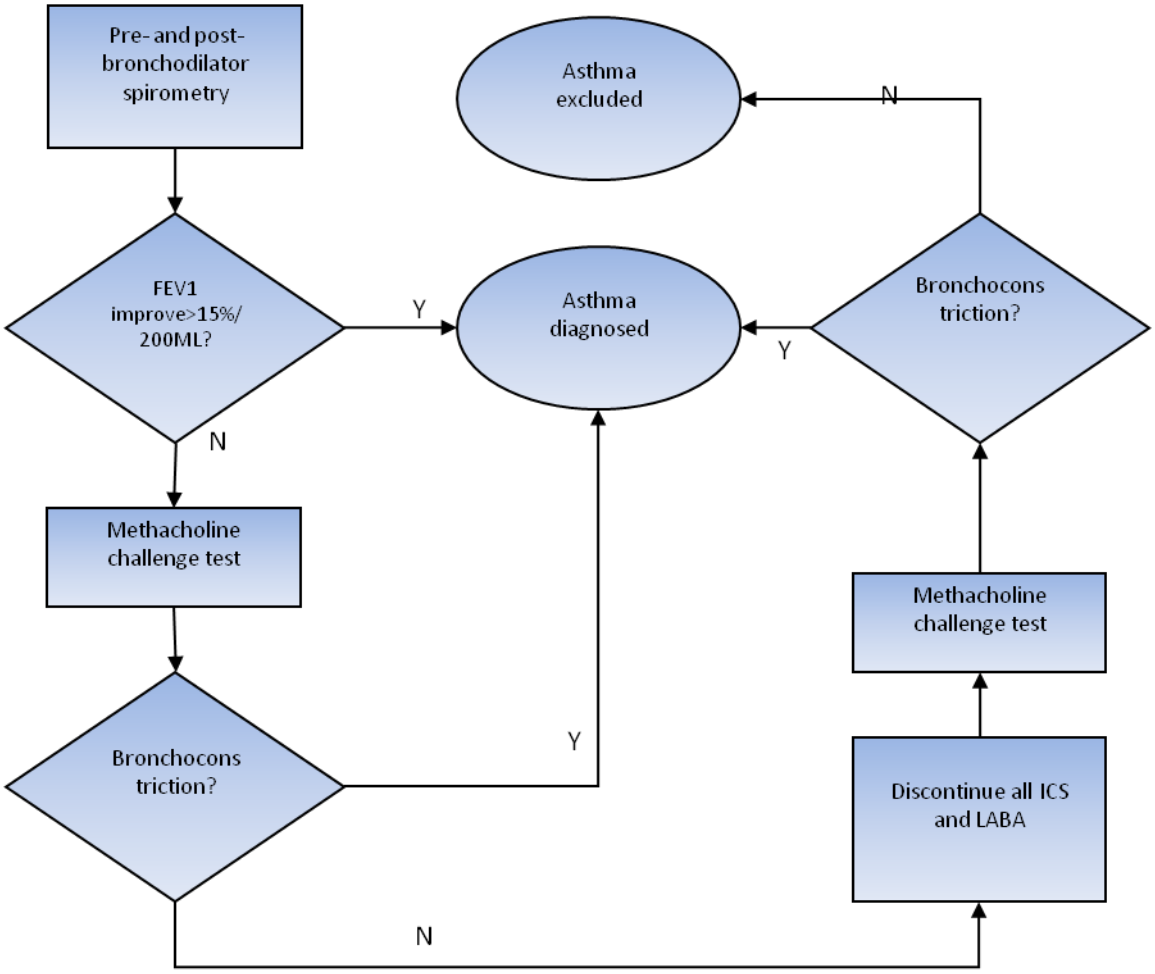
No ☒ (double-click on box to check)

Yes ☐ – If yes, please provide details:

APPENDIX III – Time and Events and/or Project Schematic Diagram(s) and Gantt chart to outline timelines for completion of studies that are part of the project plan.

Diagram(s) (e.g. figures, flow charts) can be submitted as a separate file(s) along with the completed full proposal.

Figure 1: The flowchart of objective evaluation of asthma at the final visit



APPENDIX III – Time and Events and/or Project Schematic Diagram(s) and Gantt chart to outline timelines for completion of studies that are part of the project plan.

Figure 2A: the Markov model of asthma with associated levels of severity and control.

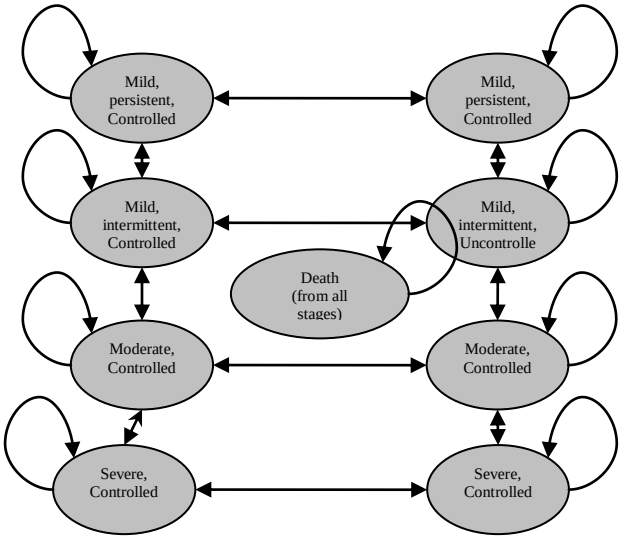


Figure 2B: Possible outcomes after an asthma exacerbation episode (bottom).

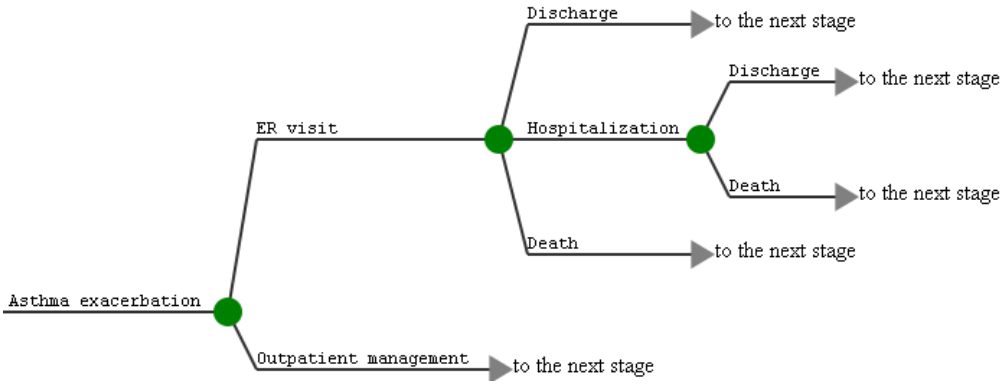


Table 1: Estimated sample size (not considering attrition) required as a function of the prevalence of asthma

Prevalence	Sample size required	Lower bound of 95% CI	Upper bound of 95% CI
1%	4400	0.7%	1.3%
2%	2178	1.4%	2.6%
3%	1437	2.1%	3.9%
4%	1067	2.8%	5.2%
5%	844	3.5%	6.5%
6%	696	4.2%	7.8%
7%	590	4.9%	9.1%
8%	**511**	**5.6%**	**10.4%**
9%	449	6.4%	11.6%
10%	400	7.1%	12.9%
11%	360	7.8%	14.2%
12%	326	8.5%	15.5%
13%	297	9.2%	16.8%
14%	273	9.9%	18.1%
15%	252	10.6%	19.4%

Note: Please include abbreviated versions of the Principal Investigator and Co-Investigator(s) current curriculum vitae with your full proposal, if any have changed since the submission of the Letter of Intent.

THANK YOU FOR COMPLETING THIS PROPOSAL FORM AND FOR YOUR INTEREST IN COLLABORATING WITH US.