1 SUMMARY AND OBJECTIVES

Chronic obstructive pulmonary disease (COPD) affects the lives of 2.6 million Canadians. Acute exacerbations of COPD, periods of intensified disease activity, are currently the most common cause for medical hospital admissions in Canada[1]. The burden of inpatient care due to COPD exacerbations is projected to increase substantially during the next 20 years[2]. This is mainly due to population growth and aging, despite declines in smoking rates in the past decades.

The current standards of COPD care largely fail to consider individual patient characteristics in formulating disease management strategies. This is mainly because unlike many other diseases, between-individual variability (heterogeneity) in the disease course and outcomes has not been rigorously quantified; consequently, there is a dearth of widely adopted clinical prediction tools that use detailed patient characteristics to enable individualized decision making. Without such evidence and tools, existing and emerging therapies cannot efficiently be translated into better clinical practice and we risk missing opportunities to improve patient and population outcomes and reduce costs. Recognizing this gap, our group recently took a major initiative to develop a first-of-a-kind framework for individualized prediction of lung function decline in COPD[3] and implemented it in a Web App as a tool for shared decision making for patients and care providers[4]. In the current application, we propose to continue this rewarding line of work to **1) develop and validate individualized prediction equations for acute exacerbations of COPD; 2) implement the equations into a user-friendly interactive Web App; and 3) demonstrate the applicability of the tool for informing decisions on preventive exacerbation therapy with azithromycin.**

To achieve these, we will merge data from three landmark clinical trials of COPD in which exacerbations were the primary endpoint and a rich set of patient- and disease-related variables were collected. We will use previously developed mixed-effect regression models that jointly parameterize exacerbation rate and severity to quantify heterogeneity[5]. We will externally validate the resulting prediction equations in an independent COPD cohort. In collaboration with an innovative and growing eHealth vendor, an interactive Web App will be developed and will be combined with our previously developed Web App for lung function decline to create a suite of eHealth tools for personalized COPD management. An advisory committee consisting of patients and care providers will oversee the process to ensure the development and implementation of the tool is in a patient- and provider-friendly manner.

Feasibility and Value-added: All the data for the proposed research are already obtained. Our team has proven expertise in all relevant aspects to carry out this research. We have laid significant groundwork in terms of development of the analytical framework and Web implementation. We have engaged clinical guideline developers, patient advocacy groups, and the research community to ensure uptake and promote the use of the tool. The proposed research is directly aligned with the competition's emphasis on "*the creation of both predictive analytic models that can stratify patients by expected outcome and risk, and the eHealth delivery platforms required*".

2 METHODS

Our approach is a four-stage process consisting of **1)** development of prediction equations for COPD exacerbations, **2)** internal and external validation of the equations, **3)** eHealth implementation through an interactive Web App, and **4)** demonstration of applicability in informing preventive exacerbation therapy with azithromycin. The tool will be applicable at point of care for COPD patients with at least one previous exacerbation who are currently outside of an episode of exacerbation or its post-acute phase (30 days). The emphasis is on generating metrics that communicate individualized risk (e.g., prediction intervals around individualized rate) which is distinct from measures of sampling variability (e.g., confidence intervals around the mean), enabling full communication of individualized risk and uncertainty, facilitating shared decision making between patients and their care provider. The process will be informed by active participation of a Patient and Care Provider Advisory Committee (PCAC, comprised of patients and COPD clinicians) which will engage in two planned focus groups as well as *ad hoc* meetings, conference calls, and email exchanges.

Data sources: All the data for this project are at hand through our related research activities (attached letters #1 & #2). We will use data from three randomized clinical trials (RCTs) as the derivation set for the development of the prediction equations, and a prospective international cohort study for external validation (Table). All data sources used a consistent definition of COPD (based on cut-off point on FEV_1 to its predicted value of 0.7). In all studies, exacerbations have been defined based on health care utilization (visit to physician for antibiotic or systemic corticosteroid prescriptions for COPD, or referral to emergency department or hospital). The three RCTs have similar inclusion criteria namely enrolling spirometrically-confirmed COPD patients with a positive smoking history and with a history of past exacerbations (similar to the intended use of the prediction tool). All studies have measured a rich set of socio-demographic, clinical, anthropometric, and biological measures.

Data source	N (total follow-up in years)	# of exacerbations (severe exacerbations)
MACRO	1,142 (1,051*)	1,641 (356)
STATCOPE	885 (1,537†)	1982 (445)
OPTIMAL	449 (404*)	636 (116)
ECLIPSE	2,138 (~6,000‡)	7,760 (1,411)
*1y follow-up	†2y follow-up	‡3y follow-up

MACRO (2010-2013)[6] was an RCT of azithromycin (250mg orally once a day) versus placebo across 17 sites in the US. Spirometrically-confirmed COPD patients 40 years or older who were either using oxygen or had received systemic corticosteroids or had gone to an inpatient care facility for exacerbation were included and were followed for one year. ***STATCOPE (2010-2013)***[7] was a two-year RCT of statins versus placebo in the US and Canada. The inclusion criteria were similar to MACRO with the addition of the exclusion of patients who were already using statins or should have received statins. The trial was prematurely stopped due to futility (lack of effect on reducing exacerbations). The average follow-up was 641 days. ***OPTIMAL (2003 – 2006)***[8] was a three-arm RCT of monotherapy with inhaled anticholinergics, double therapy (with addition of inhaled long-acting beta-agonists), and triple therapy (with addition of inhaled corticosteroids) as maintenance therapies in 27 centres in Canada. Spirometrically-confirmed COPD patients 35 years of age or older with at least one moderate/severe exacerbation in the past 12 months were included and were followed for a year. Finally, ***ECLIPSE (2005 – 2010)***[9] was a prospective longitudinal cohort (non-interventional) study of 2,138 patients 40 to 75 years of age with spirometrically diagnosed COPD who were followed for three years. While ECLIPSE did not apply the same inclusion criteria (especially previous history of exacerbations) as the RCTs, its three-year follow-up time enables us to apply the inclusion criteria in the first year and use the subsequent two years for the analysis.

2.1 Stage I: Development of prediction equations

MACRO, STATCOPE, and OPTIMAL will be used for derivation; together, they provide data on 2,476 patients, 2,992 follow-up years, and 4,259 exacerbations, with 917 exacerbations being severe.

*** Statistical methodology:** The burden of exacerbations is a function of both their frequency (rate) and severity. The backbone of the equations will be our novel joint frailty-ordinal model[5]. This is a combination of a frailty model for exacerbation rate with a random-effects logistic model for exacerbation severity. An attractive feature of this framework (compared with alternatives such as competing risk models that treat exacerbations of different severity as independent event types) is that while enabling us to model exacerbation severity, it retains the ability to make inference on the occurrence of any exacerbations.

The rate component: The basis of the model is a parametric random-effects (frailty) accelerated failure time (AFT) model. For the i^{th} individual, the instantaneous exacerbation rate at time t (hazard) is

$$\lambda_i(t) = \theta_i.\lambda_0(t.\theta_i), \text{ with } \theta_i = e^{\boldsymbol{\beta}.\mathbf{X_i}+z_i},$$

with $\mathbf{X}_i$ being the vector of observed, time-fixed characteristics (covariates), $\boldsymbol{\beta}$ the vector of regression coefficients, and z_i an unobserved normally distributed random-effect term that is specific to each person and captures between-individual variability in exacerbation rate over and beyond the variability due to observed characteristics. λ_0 is the baseline hazard function. AFT models are popular for modeling time to event and event rates as they provide all the quantities that are needed for prediction. For example, they have been the basis of the original Framingham risk prediction equations for cardiovascular disease[10]. For a parametric survival model, a baseline hazard function needs to be specified[11]. The Weibull model was shown to provide excellent fit in MACRO[5] but this might not hold in the expanded dataset. We will

evaluate different hazard functions (Weibull, log-normal, log-logistic, generalized gamma) and will use the Akaike Information Criterion as an objective measure to find the best fitting function[12]. Due to the small number of deaths (<5%), and in line with the primary analysis of the original studies[6,7,13], we will not adjust for the competing risk of death in the main analysis but will investigate its effect in alternative analyses that will consider death as an event.

The severity component: this will be a random-effects logistic model for the severity of exacerbations. In line with our analysis of MACRO[5], we will primarily focus on distinguishing severe from mild/moderate exacerbations (given the significant difference in the burden of severe versus mild/moderate exacerbations). This model predicts the probability that the j^{th} exacerbation of the i^{th} individual (denoted by $Y_{i,j}$) is severe (coded as 1 compared with 0 for mild/moderate exacerbations):

$$P(Y_{i,j}=1)=\frac{\theta_i'}{1+\theta_i'},\ \theta_i'=e^{\boldsymbol{\beta}'.\mathbf{X}_i+z_i'}$$

, with $\boldsymbol{\beta}'$ the regression coefficients, and z_i' a normally distributed random-effect term (with potential correlation with random-effect term for rate) that captures between-individual variability in the proportion of severe to total exacerbations. Regression coefficients from this component can be expressed in terms of odds ratio associating the covariate to the probability of an exacerbation being severe. Individuals with at least one exacerbation during follow-up contribute to the severity component. All analyses will be performed in SAS® (SAS Institute, Carey, NC, USA), with the joint model already implemented in the NLMIXED procedure[5]. Modification of this model (e.g., a proportional odds ordinal model) to capture all three levels of exacerbation severity will be considered in alternative analyses.

Variable selection: A focus group at the design stage will involve PCAC to identify all relevant features of the disease (starting from a comprehensive literature search and expert opinion). From the identified list, we will use objective variable selection techniques using machine learning algorithms[14] to generate a final 'reference' model. Predictors can be divided into variables describing socio-demographic (e.g., gender, age, education and income), smoking status, COPD status (lung function metrics, disease duration, previous history of exacerbation), health status and functional capacity (St. George's Respiratory Questionnaire[15], Medical Research Council's functional capacity score), serum markers (e.g., C-reactive protein), current COPD maintenance therapies, meteorological season, and burden of comorbidities. For the most part these variables have been consistently recorded for patients across all four studies. If a variable is recorded in at least two of the three RCTs it will be included in the main model and its values will be imputed for the third dataset.

In addition to the main model, to ensure maximum applicability, we will fit alternative models with reduced set of predictors to enable predictions based on available clinical characteristics. Models can range from simple ones (e.g., including seasonality and previous history of exacerbations) to models with multiple predictors including lung function metrics and serum markers.

Sex and gender effects: In our previous analyses[5], we found differences in the burden of exacerbation such that women showed more frequent exacerbations whereas men appeared to have greater severity in their exacerbations. Hence, we will explore multiple ways to accurately obtain separate prediction models. At minimum, we will include an interaction term between key predictors and the sex variable; we will also test fitting of gender-specific prediction models to more flexibly account for non-linear effects or other differences in the joint distribution of severity and rate. The increase in the predictive power of separate models will be gauged against the loss of precision due to smaller sample size. Our power calculations are favourable for obtaining models specific to women and men.

Power calculation: The amount of uncertainty in predictions can be decomposed into uncertainty due to patient heterogeneity and uncertainty in regression coefficients due to the finite sample size (sampling variability). A robust individualized prediction framework is the one that minimizes the relative contribution of the sampling variability to the overall uncertainty in predictions. As such, a relevant figure of merit for the adequacy of statistical power is the ratio of the variance of the mean rate of exacerbation to the variance of individualized exacerbation rates (Appendix 2). Based on the estimates of the variance components from our previous work[5] and the number of exacerbations in the derivation sample, we have

estimated this quantity to be less than 2% (Appendix 2), demonstrating minimal perturbation in predictions due to sampling variability; within sexes, the ratio will be less than 5%, supporting the feasibility of gender-specific prediction if required.

2.1.1 Stage II: Internal/external validation

Internal validation involves testing the prediction against the data that were used to fit the model. First, observed and predicted cumulative incidence of exacerbations will be compared, as a whole and across identifiable subgroups (e.g., sex, age groups, within each of RCTs). Second, we will calculate the Mean Squared Error based on the expected versus observed exacerbation rate for each patient in the sample. Third, we will calculate the actual coverage probability of 95% prediction intervals (the closer the coverage probability to 95%, the more accurate the modeling of uncertainty) around the predicted rate of exacerbations. All these steps will be repeated for overall as well as for severe exacerbations. We have applied such methods extensively in our previous work[3]. External validation will involve testing the robustness of predictions in an independent dataset (the ECLIPSE cohort) that had not been used to fit the model. Similar metrics as described above will be used for external validation. If required, we will calibrate the intercept parameters (the background rate of exacerbation and the proportion of severe to total exacerbations) for any discrepancy between the cohort and RCT data and will repeat the validation exercises to achieve balance between internal and external validity.

2.1.2 Stage III: eHealth Implementation

Once developed and internally/externally validated, and in partnership with an eHealth vendor (TechSamurais), we will implement the prediction equations into a freely-accessible Web App. Our eHealth vendor is particularly chosen for the quality of the Web design and expertise in implementation, its experience in health-related projects (the company's Million Dollar Meds was a finalist in the Vancouver User Experience Award in 2016), its capacity in developing Web Apps with interactive graphics (e.g., TELUS e-commerce project), and our previously successful collaboration (letter of confirmation #3 outlining these is attached).

We will use this project as a catalyst to incorporate the exacerbation prediction and the previously developed lung function prediction Web Apps into a single, patient- and care-provider-friendly website which will be properly rendered on PCs, tablets, and mobile phones. We will provide detailed documentation and animated videos demonstrating the use of the tool.

The output of the prediction equations can be presented in a variety of ways (Appendix 3 provides illustrations of exemplary outputs). These include **1)** predicted annual rate of exacerbations (with 95% prediction interval), **2)** probability of remaining exacerbation-free during a given time window, **3)** time to the next exacerbation (with 95% prediction interval), and **4)** probability of experiencing a given number of exacerbations during a time window. Of note, output 4, and 95% prediction intervals around outputs 1 and 3 can only be generated using an individualized prediction model (and not marginal models for the mean). All these metrics can be produced for all exacerbations combined, as well as for severe exacerbations alone. A second focus group (year 2) will involve PCAC to decide on the overall layout of the Web App, the merits of different presentation modalities, proper wording of the text eliciting the value of predictors, and the contents of documents and animated videos.

2.2 Stage IV: Demonstration of applicability: facilitating shared decision making for preventive azithromycin therapy for exacerbations

The MACRO is currently the only major (and the only randomized) source of evidence on the effectiveness of azithromycin for the prevention of exacerbation[6], which showed 27% reduction in exacerbation rate with daily maintenance therapy. However, the benefit of maintenance therapy is in terms of the number of (severe) exacerbations avoided. This quantity in a patient can be a function of both the background exacerbation rate and the interaction effect of patient characteristic with relative treatment effect. Subgroup-specific treatment effect estimates will be derived using interaction effects between treatment and subgroup-defining variables. Through eliciting detailed patient characteristics and previous exacerbation history, the Web App can therefore estimate the individualized estimates of benefit from preventive therapy. Such information can be a basis for shared decision making between patients and their

care provider considering patient preferences and values regarding the burden of exacerbations versus potential adverse events and costs of therapy.

To implement this, upon user request the Web App will provide results pertaining to the individualized benefit of azithromycin therapy. All the results (described in Section 3.1.2 – implementation) will be generated under two scenarios of receiving or not receiving azithromycin therapy (with animated graphs showing the change from one scenario to the other). In addition, the benefit of therapy will be presented in terms of the number of patient-years needed to treat (NNT) to prevent one exacerbation, absolute reduction in exacerbation risk, and number of exacerbations avoided with a given length of therapy. Finally, the probability of the benefit of azithromycin therapy being above a pre-specified treatment threshold (the maximum acceptable NNT for the patient which will be an input parameter) given the uncertainty in individualized risk will be calculated. All these results will be generated for overall as well as severe exacerbations.

3 POTENTIAL LIMITATIONS AND ALTERNATIVE STRATEGIES

- The three trials might be considered 'efficacy' studies. However, the samples are very similar to the target population of this project (patients with an established COPD diagnosis with a history of exacerbations and currently being in an exacerbation-free state). The rate of exacerbations in these trials closely resembles those in population-based COPD cohorts[16]. In our previous work, prediction equations for FEV_1 developed from a trial (the Lung Health Study[17]) showed excellent external validity in two independent cohorts[3]. If required, we will use statistical calibration techniques to reach balance between internal and external validity.

- STATCOPE has excluded patients who were receiving, or were eligible to receive, statins. This has likely resulted in this sample being different with regard to comorbid cardiovascular diseases than the rest of the sample. We will examine the potential impact of this difference by evaluating the internal validity of models across RCTs and by comparing regression coefficients with and without inclusion of STATCOPE.

- We are not able to capture all relevant determinants of COPD exacerbations. For example, imaging characteristics as predictors of exacerbations are not captured within all the data. As a result, the tool cannot incorporate such variables in the prediction. With the acquisition of more data, we will attempt to gradually expand this framework to capture a more complete picture of heterogeneity in COPD exacerbations.

- The predictions are unlikely to be applicable to certain COPD patients such as those with asthma-COPD overlap (as they were excluded from the RCTs). We will examine this in the validation dataset and will seek further opportunities to include data for such patients to expand the scope of the prediction tool.

4 TIMELINE AND FUTURE DIRECTIONS

To achieve the stated objective and considering the developments we have made thus far, we propose a **24-month timeline** for this study. Details are provided in the Gantt chart in Appendix 5. Our longer-term activities beyond three years will include **1)** integration of other prediction tools under development for lung health in the general population, FEV_1 decline, EPIC, and exacerbation prediction tools into a single suite of eHealth tools, **2)** integration of more sources and data to strengthen the accuracy of predictions, and **3)** implementing additional applications into the Web App such as the benefit of maintenance COPD therapies given individual patient characteristics. Through the Co-I Sin who is a member of the GOLD Scientific Committee, we will reach out to GOLD for potential promotion of the tool beyond Canada.

References

1. The Canadian Thoracic Society. The Human and Economic Burden of COPD - A Leading Cause of Hospital Admission in Canada [Internet]. 2010 Feb [cited 2011 Nov 24]. Available from: http://www.respiratoryguidelines.ca/the-human-and-economic-burden-of-copd-a-leading-cause-of-hospital-admission-in-canada
2. Khakban A, Sin DD, FitzGerald JM, McManus BM, Ng R, Hollander Z, et al. The Projected Epidemic of Chronic Obstructive Pulmonary Disease Hospitalizations over the Next 15 Years. A Population-based Perspective. Am J Respir Crit Care Med. 2017 Feb 1;195(3):287–91.
3. Zafari Z, Sin DD, Postma DS, Löfdahl C-G, Vonk J, Bryan S, et al. Individualized prediction of lung-function decline in chronic obstructive pulmonary disease. CMAJ. 2016 Oct 4;188(14):1004–11.
4. Zafari Z. Individualized Lung Function Predictor [Internet]. [cited 2017 Apr 11]. Available from: http://resp.core.ubc.ca/software/ipress/epic/fev1pred/
5. Sadatsafavi M, Sin DD, Zafari Z, Criner G, Connett JE, Lazarus S, et al. The Association Between Rate and Severity of Exacerbations in Chronic Obstructive Pulmonary Disease: An Application of a Joint Frailty-Logistic Model. Am J Epidemiol. 2016 Nov 1;184(9):681–9.
6. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JAD, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011 Aug 25;365(8):689–98.
7. Criner GJ, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, et al. Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD. N Engl J Med. 2014 Jun 5;370(23):2201–10.
8. Aaron S, Vandemheen K, Fergusson D, FitzGerald M, Maltais F, Bourbeau J, et al. The Canadian Optimal Therapy of COPD Trial: design, organization and patient recruitment. Can Respir J. 2004;11(8):581–5.
9. Bourbeau J, Tan WC, Benedetti A, Aaron SD, Chapman KR, Coxson HO, et al. Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the Need for Longitudinal Observational Studies in COPD. COPD. 2012 Mar 20;
10. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. American heart journal. 1991 Jan;121(1 Pt 2):293–298.
11. Cox C, Chu H, Schneider MF, Muñoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Stat Med. 2007 Oct 15;26(23):4352–74.
12. Akaike H. Information Theory and an Extension of the Maximum Likelihood Principle. In: Parzen E, Tanabe K, Kitagawa G, editors. Selected Papers of Hirotugu Akaike. Springer New York; 1998. p. 199–213. (Springer Series in Statistics).
13. Aaron S, Vandemheen K, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545–55.
14. Guyon I, Elisseeff A. An introduction to variable and feature selection. Journal of machine learning research. 2003 Mar 3;1157–82.
15. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992 Jun;145(6):1321–7.
16. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010 Sep 16;363(12):1128–38.
17. Buist AS. The US Lung Health Study. Respirology. 1997 Dec;2(4):303–7.
18. Council of Canadian Academies. The State of Science and Technology in Canada, 2012 [Internet]. 2012 [cited 2013 Dec 10]. Available from: http://www.scienceadvice.ca/en/assessments/completed/science-tech.aspx