Validating the Use of Frailty Measurements to Predict Care Expectations and Deteriorations in Quality of Life Among People with COPD: A Prospective Cohort Study

Study Protocol, version 3

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1.0 PROJECT SUMMARY

Frailty is a comprehensive measure of health status that describes the vulnerability of a person to health stressors (1–4). Frailty is measured along a continuum from '*managing well*' to '*severely frail*', and is characterized by progressive impairment in activities of daily living (4). More than one out of every four patients with Chronic Obstructive Pulmonary Disease (COPD) are frail, and frailty is associated with frequent exacerbations, hospital readmission, mortality, and poor quality of life (3,5–10). Further, intervening with specialized exercise, nutritional, and personal supportive care programs has the potential to reverse, or stabilize frailty when identified at the earlier stages (2,3,7).

However, little is known about whether frailty measurements can be used to predict the risk of deteriorations in validated patient-reported outcomes, if frailty measurements are reproducible among patients with COPD, and if patient care preferences differ between degrees of frailty. Further, it is unknown whether frailty categories could be used to guide tailored interventions to address and manage frailty, and whether frailty-focused interventions could improve long term outcomes in addition to conventional treatments (6,10).

We hypothesize that progressive degrees of frailty will reliably predict important deteriorations in patient-centered outcomes over time, including health-related quality of life, symptom burden, psychosocial wellbeing, and measures of survival and health service use.

If this association between frailty and health is confirmed, then it follows that frailty could be used as a risk stratification tool to guide tailored interventions for population subgroups with varying degrees of frailty.

To inform the development and testing of effective care interventions within categories of frailty, the following questions must first be addressed:(1) What is the predictive value of progressive degrees of frailty on deterioration in patient-centered outcomes and increased health care utilization among people with COPD? (2) What are the differences in expectations of clinical care between patients and physicians within different degrees of frailty? (3) What is the inter-rater agreement between patients and physicians who use the Clinical Frailty Scale (CFS) to measure frailty? (4) What is the test-retest reliability of the CFS when used by the same patient at 2 different time-points, 6 months apart?

2.0 BACKGROUND

What is the Problem to be Addressed? Patients with Chronic Obstructive Pulmonary Disease (COPD) feel that their needs are not met within the current healthcare system (11). In a scoping review of a decade's worth of qualitative evidence, patients with COPD reported feeling poorly informed about their condition, vulnerable when hospitalized, unconfident in community based services, and lacked an understanding of their disease

trajectory and significance of their exacerbations (11). Most importantly, patients reported that their subjective distress seemed *invisible* to clinicians who tended to focus on objective health indicators, and that clinicians infrequently addressed or referred patients for assistance with their substantial non-medical needs (7).

From a health system perspective, COPD exacerbations are a leading cause of hospitalizations and re-admissions in Canada, and cost our health system over 700 million dollars annually (12,13). In a closer review of hospital-related costs for COPD care, the highest costs were incurred by patients with acute illness, but also by *frail* patients who developed significant functional limitations and could not return home (14).

Both the patient and health system perspectives suggest that our current paradigm for COPD care in Canada is not optimal. While health providers focus on COPD-specific metrics, which have been correlated with future risk of mortality and hospitalization (15–17), clinicians lack appropriate evidence based tools to evaluate the non-pulmonary complications of COPD and overall wellbeing of these patients (18).

In this setting, there is a need for innovative care approaches which (1) reliably predict the outcomes that are important to patients living with COPD, (2) are easily implemented in the health system, and (3) have a direct impact on front line COPD management across health care settings. Care models which incorporate assessments of '*Frailty*' may provide this desired innovative approach to enhance patient-centered COPD care. There are currently no studies to determine whether health providers could use measurements of frailty to accurately predict current and future decline in patient-centered outcomes, and whether patients' expectations of healthcare change between different degrees of frailty.

The aim of this research program is to validate *frailty* measurements as a risk stratification tool to predict deteriorations in patient-reported outcomes, to gain a better understanding of patient preferences for care within varying degrees of frailty, and to assess differences in frailty measurement between patients and their care team.

This work will provide a foundation in the development of customized interventions for people with COPD and varying degrees of frailty, with the goal of improving quality of life and optimizing health system service delivery for patients and their care givers.

What is Frailty and Why is it a Relevant Health Measure? Frailty is a common and important multi-dimensional syndrome characterized by a loss of reserve in multiple domains including physical ability, energy, cognition, and health (4). Loss of reserve in the frail patient leads to an increased vulnerability to adverse health outcomes such as hospitalization and death (1,4,19). As frailty progresses, the ability to recover from

both chronic and acute health stressors becomes more difficult, and leads to progressive functional disability (19).

More than half of patients over 85 years of age are identified as frail (1). However, age alone does not account for functional decline (20). The frailty construct offers a comprehensive approach to identify patients at risk of decline who would benefit from additional resources in order to address their needs. For example, frail people have been found to benefit from exercise programs to reduce falls, nutritional interventions, cognitive assessment and support, and mobility and balance training (21).

Frailty has also been identified as an important prognostic tool in patients with other chronic diseases such as heart and kidney disease (22,23). Experts hypothesize that using frailty assessments may help clarify which interventions and treatments can benefit or harm patients, help to refine clinical decisions, improve prognostication, and enhance informed decision making (24–26).

For healthcare providers, recognition of frailty in patients is crucial to facilitate identification of patients at high risk of poor health outcomes such as progressive disability, hospitalization and death (2).

Why is Frailty Relevant to COPD Care, and Why is it not Currently Used in Patient Evaluation? The prevalence of frailty among people with COPD ranges widely from 16-75%, depending on the population studied, and the frailty measurement tool used (3). In our own prospective assessment of 50 hospitalized patients with COPD exacerbation, 54% were found to be at least mildly frail at their baseline, two weeks prior to their hospitalization (27).

Studies demonstrate that people with COPD have a two-fold increase in the prevalence of frailty compared to patients without COPD, after adjustment for confounding factors including age, smoking, steroid use, and comorbidities (6). Presence of frailty is also correlated with COPD-specific markers, including severe airflow obstruction, shortness of breath, and frequent exacerbations (6). Among people with COPD, frailty is associated with increased risk of death, poor recovery after hospitalization, and re-admission to hospital (5,6,8). Emerging evidence suggests that higher degrees of frailty are also associated with poorer acceptance of illness, which may have significant implications for adherence to treatment and self-management (28).

Traditional care discussions of treatment and prognosis between patients and physicians often center around the current COPD guidelines, which focus on disease-specific metrics (i.e. lung function and exacerbation history) (16,29). While these metrics are important, one of the limitations of this approach is that it overlooks clinically relevant complications of COPD, such as co-morbidities, reduced functional capacity, and psychological well-being. These factors contribute to poor quality of life and clinical outcomes and are equally important to address (30). Frailty measurements could complement disease specific metrics when evaluating

patients and could influence care in a way that FEV1 measurements do not; however, we lack the research studies to support this hypothesis.

Given the association between frailty and poor outcomes among patients with COPD, an understanding and early recognition of frailty by health providers *and* patients could determine the choice and timing of interventions, and improve the long term clinical response (3,7).

How is Frailty Measured? There are multiple validated tools that can assess and quantify the degree of frailty in a patient (31). The Clinical Frailty Scale (CFS) is a bedside clinical tool that is easy to use, freely available, validated in the Canadian population, and correlates with objective clinical outcomes of death and need for long term care (***Figure 1***) (4). The CFS is also validated for use by patients to self-report frailty (32). Although there are no direct comparisons between frailty tools in the COPD population, among patients with cirrhosis, the CFS had greater discriminatory power for outcomes in comparison with the Fried Criteria, and Short Physical Performance Battery Scale (33).

The CFS uses an ordinal scale from '1' to '9' to characterizes degrees of frailty from 'managing well' to 'terminally ill'. Each degree of frailty is accompanied by a description of physical symptoms and functional ability to perform instrumental activities of daily living (IADL's) and activities of daily living (ADL's). Although there is a degree of subjectivity in assigning a score, increasing degrees of frailty are objectively associated with increased risk of death and need for long term care in adult patients over 65 years of age (4).

Why is it Important for Patients and their Providers to have a Mutual Understanding of Frailty? There is rightfully a heightened focus on patient-centered care in our health system (34). Patient-centered care refers to the active collaboration and shared decision-making between patients, families and health providers to create and implement a personal comprehensive care plan (34). To operationalize this, patients must also have a sound understanding of their disease, prognosis and care needs.

Poor recognition of frailty or discordance between patient and healthcare providers' frailty assessments, may impact patient-centered care.

If a patient under-perceives their degree of frailty, they may not agree with or adhere to the prescribed treatment plans; for example, recognizing the need for pulmonary rehabilitation, home care services, or dialogue regarding symptom management and end of life care. If the healthcare team underperceives a patient's frailty, this can lead to delays in requesting additional resources, and possible over treatment with more invasive therapies that may not benefit a very frail patient. A discordance between patients and their healthcare providers may be a factor which contributes to the increased dissatisfaction and fragmentation of care, that is voiced by patients with COPD (11).

3.0 OBJECTIVES

The aim of this research program is to evaluate *frailty* measurements as a risk stratification tool to predict deteriorations in patient-reported outcomes, to gain a better understanding of patient and physician preferences for care within varying degrees of frailty, and to assess the change of frailty measurements over time. More specifically, our study objectives are:

1. To determine the predictive value of progressive degrees of frailty on deterioration in patient-centered outcomes and increased health care utilization among people with COPD, after adjustment for important clinical factors including age, sex, comorbidity, home support, number of medications, pulmonary rehabilitation, lung function, dyspnea, and exacerbation history.
2. To describe the differences in expectations of clinical care between physicians and patients within different degrees of frailty.
3. Determine the inter-rater agreement between patients and physicians who use the Clinical Frailty Scale (CFS) to measure frailty.

4.0 Investigate the change in frailty scores over 12 months**HYPOTHESIS**

We hypothesize that progressive degrees of frailty will reliably predict important deteriorations in patient-centered outcomes over time, including health-related quality of life, symptom burden, and psychosocial well being, and measures of survival and health service use. If this association between frailty and health is confirmed, then it follows that frailty could be used as a risk stratification tool to guide tailored interventions for population subgroups with varying degrees of frailty.

5.0 METHODS

5.1 **Design & Setting:** A prospective cohort study at The Ottawa Hospital (TOH) over two years. TOH is a quaternary care academic hospital with an ambulatory care respiratory clinic, staffed by seven respirologists. It is a regional referral center with a catchment area of approximately 1 million individuals.

5.2 **Study population and Inclusion Criteria:** We will include literate English or French-speaking outpatients with COPD, objectively confirmed by lung function testing[1]. In patients with multiple respiratory conditions and comorbidities, COPD will be the primary diagnosis, as confirmed by the treating respirologist. Participants will be recruited from the respirology ambulatory care clinics at TOH. We will exclude patients with a known diagnosis of severe cognitive impairment[2], if the

[1] post-bronchodilator Forced Expiratory Volume in 1 second / Forced Vital Capacity ratio below the lower limit of normal, and >10pack years history of tobacco smoking
[2] as per the medical record

recruiting physician feels the impairment would preclude participation in the study.

5.3 Study flow: Prior to the clinic, members of the study team (PI and coordinator) will review the list of patients scheduled for a routine visit in the Respirology clinic of TOH during the study period. Patients who have a diagnosis of COPD will be flagged as "identified" in EPIC for the study. The name (first and last) and MRN will be included in a Master List. This list will link patients' identifiable information (MRN and name) with a screen ID. The screen ID will be included in an "*appointment note*" within the physician's schedule in EPIC, flagging the care team that the patient is possibly eligible for the study.

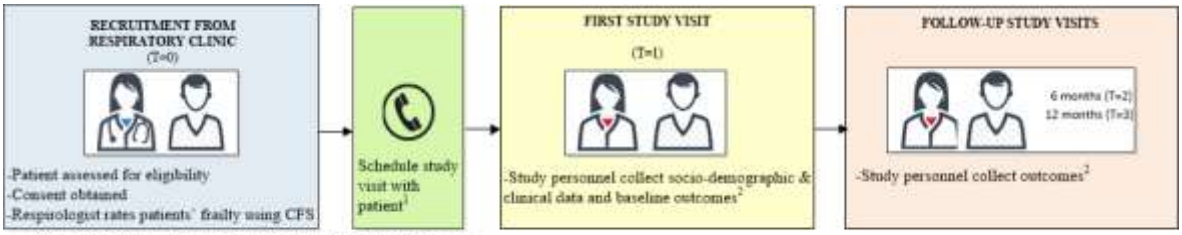
During their routine visit with respirologist in the Respirology outpatient clinic of TOH, patients will be assessed for eligibility. Prior to meeting with the respirologist, the nurse will complete their standard patient assessment. They will review the posted note left by the research team for that specific patient and assess the patient for eligibility. If eligible, the nurse will ask the patient if they agree to have a member of the study team approach them about the study. If the patient agrees to be contacted, the physician would assess patients' frailty using the CFS, include the frailty rating and their care expectations for the patient in a form (see **Recruitment Survey**), with the screen ID, provided in the ***appointment note***. This form would be automatically available to the research team, which would allow them to contact the patient to obtain verbal consent (**see Verbal Consent**) and schedule a baseline study visit. Please note, once the patient has been assessed for eligibility, the screen ID becomes the study ID for that patient.

Consent: The study team will call the patient to obtain verbal consent. If the patient agrees, the study team will schedule a baseline visit by phone with a member of the study team. Once consented, the study team will request an e-mail address to send the baseline electronic survey (see Patient Baseline Survey) and the informed consent document for additional information on the study.

Baseline visit: Prior to each scheduled visit, the baseline survey will be e-mailed to the patient with a reminder of their upcoming appointment with a member of the study team. For those who do not have or have not provided an e-mail address, a member of the team will call the patient to remind them of their upcoming appointment. During the telephone baseline visit, patients will be asked questions on their lung health (see **Data Collection Sheet – Baseline Visit**). If the electronic

Baseline Survey was not completed, the study team will go through the questions with the patient. At the end of the visit, the study team will schedule the 6-month telephone visits and ask the patient to confirm their mailing address to send the first of three gift coffee cards (of 20$), as a token of appreciation.

6-month and 12-month follow-up visits: Prior to the scheduled 6-month or 12-month follow-up visit, the study team will send an e-mail to patient with a link to the *COPD & Frailty – 6-month follow-up survey* or *COPD & Frailty – 12-month follow-up survey*. Patients who did not provide an e-mail address will receive an appointment reminder call from a member of the study team and complete the survey with the study team during their 6 and 12-months telephone follow-up visits. At the end of each telephone visit, patients will be asked to confirm their mailing address to send the second and third gift cards (of 20$).



[1] Study coordinator will call patient within 1 week to schedule study visit.
[2] Outcomes: SGRQ-C, CAT, mMRC scale, anxiety and depression questionnaires (GAD-7, PHQ-9), health service utilization (Emergency room visits, hospitalization, changes in dwelling, exacerbations).

***5.4* Sample Size:** Sample size calculations were performed based on the primary analysis strategy, which uses multiple variable linear regression with a fixed model. We will determine the adjusted association between frailty (categorized in 4 groups using the CFS: 'vulnerable', 'mildly frail', 'moderately frail' and 'severely/very severely frail') and respiratory health-related quality of life as measured by the validated SGRQ-C, scored from 1-100. The minimally important clinical difference (MCID) for the SGRQ-C is 4 (41). We will adjust the model for confounding variables including age, sex, dyspnea severity (mMRC), hospitalization, lung function, home support services, and comorbidity scores.

In a previous sample of patients with COPD, the standard deviation of SGRQ scores ranged from 13 to 18 (9,42–44). To detect an effect size of 0.2 to 0.3, with 10 predictors and α error 0.05 and power 0.80 (1-β error), we require a range between 64 to 84 individuals (G*Power 3.1.9.2. Copyright (C) 1992-2014, see **Appendix 1**).

Further, Harrell suggested that **10 subjects per variable** is the minimum required sample size for linear regression models. To ensure accurate prediction in subsequent study participants, we will need 100 individuals to include 10 predictors in our statistical model (50).

Based on the above calculations, we aim to recruit a minimum of **120** patients into this study over 6 months with a minimum of 30 patients in each of the four frailty categories vulnerable, mild, moderate, and severe/very severe. We will continue to recruit patients from the ambulatory clinic until the minimum targets are met.

5.5 Data collection methods

5.5.1 ***Patient Self-Assessed Frailty****:* Patients will use the CFS to self-assess frailty at their clinical baseline, which measures nine distinct degrees of frailty from 'managing well' to 'terminally ill' **(Figure 1).** The wording in the CFS has been adapted and validated for patient-use (32).

5.5.2 ***Patient Expectations of Health Care***: Patients will review and rank items on a standardized list of care interventions (i.e. pulmonary exercise programs, homecare, self-management education). The study team developed the list based on services recommended in Health Quality Ontario's updated 'Quality Standards for COPD' document (38), and currently available community-based programs to help individuals with their functional, social, and lung health needs. The document will be written in lay language and a member of the research team will ensure items on the list are well understood by patient participants. Patient participants will rank each item on a likert scale from 1 (least important), to 5 (most important), to indicate their care preferences. (**COPD & Frailty - Baseline survey**)

5.5.3 ***Patient Baseline Health Data*** (see **Data Collection Sheet – Baseline visit**): We will collect variables from direct patient assessment and review of the electronic medical record at the time of recruitment:

- Socio-Demographic Data (age, sex, body mass index, physician-assessed clinical frailty scale score, current dwelling, caregiver support, marital status, education level, type of home assistance services, and duration of time since initial diagnosis).

- COPD-Specific Factors (Spirometry values (FEV1, FVC, FEV1/FVC), smoking history in pack-years, home-oxygen use, 6-minute walk test distance (if available), influenza and pneumococcal vaccination status, use of pulmonary rehabilitation, and number of flare-ups in the last year.
- General Health Data (co-morbidities, presence of family physician).
- Previous Health Service Utilization (hospitalizations, intensive care unit admissions, emergency room visits in last 1-year).

5.5.4 ***Physician Data Collection****:* We will ask the referring respirologist (in the patient's circle of care) to provide a frailty measurement at the time of study enrolment, using the CFS (Figure 1). This physician will also rank their desired care interventions for the patient using the same standardized list given to study participants (**see Recruitment Survey**).

5.5.5 ***Frailty assessment by research team***: Frailty will be assessed during the 6-month and 12-month follow-up telephone visits, using the standardized CFS classification tree. (**Appendix 2**)

5.6 Outcomes

5.6.1 **Primary:** The primary outcome is respiratory Health Related Quality of Life (HRQOL), as measured by the validated short version of St. Georges Respiratory Questionnaire (SGRQ-C) (39). The SGRQ-C is a 40-item questionnaire which generates an overall score between 1 and 100, with lower scores indicating better quality of life (39,40). The minimally important clinical difference in SGRQ-C scores is well established at 4 (41). The SGRQ is a widely used outcome in respiratory research, and there are established standard deviation measurements in the COPD patient population (42–44). These will be collected with the COPD & Frailty – baseline, 6-month, and 12-month surveys.

5.6.2 **Secondary:** We will measure burden of symptoms with the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) scales (45,46). Both scales are validated and widely used in respiratory research. These will be collected with the COPD & Frailty – baseline, 6-month, and 12-month online surveys.

Psycho-social well being will be measured with the validated Generalized Anxiety Disorder (GAD)-7 and Patient Health Questionnaire (PHQ)-9 scales (47,48). The GAD-7 is a screen for generalized anxiety disorder, while the PHQ-9 scale measures the

presence of depressive symptoms in the prior two weeks (47–49) . Both scales are composed of seven items, based on the DSM-IV criteria, and a score above 7 on each scale will indicate the presence of anxiety or depression for this study (48,49). We will also collect outcomes of mortality, and health service utilization including hospitalizations (during study period), emergency room visits, and changes of dwelling to an assisted living environment. These will be collected with the COPD & Frailty – baseline, 6-month, and 12-month online surveys.

5.7 **Statistical Methods:**

5.7.1 ***Quantitative Analysis (Objective 1)***: The primary outcome (HRQOL using SGRQ-C scores) will be analyzed using multiple variable linear regression, with degree of frailty as the main predictor ('vulnerable', 'mildly frail', 'moderately frail', and 'severely/very severely frail'). Secondary outcomes for symptom burden (CAT and mMRC scales) and psycho-social wellbeing (GAD-7 and PHQ-9) will be described with median (IQR) statistics within each degree of frailty and analyzed with multiple variable linear regression to determine their associations with progressive degrees of frailty. Finally, the association between frailty and health service utilization (hospitalization, emergency room visit) and mortality will be analyzed with multivariable logistic regression. Potential confounding variables will be selected a-priori and forced into the model, regardless of statistical significance. Backwards selection will be used to obtain the most parsimonious model.

5.7.2 ***Quantitative Analysis (Objective 2):*** We will use descriptive statistics (proportions, means ± SD, medians (IQR)) to characterize the ranked care expectations, socio-demographic, and disease-specific, variables. Variables will be stratified by physician-assessed degrees of frailty, and chi-square and ANOVA testing will be used to analyze differences in variables across degrees of frailty, for categorical and continuous variables, respectively.

5.7.3 ***Quantitative Analysis (Objective 3 & 4):*** We will calculate the percentage of agreement to assess inter-rater agreement between patients' self-assessed and physician-assessed frailty ratings at the baseline visit. This will be presented as a

cross-tabulation table. We will graph the trajectory of frailty rating between baseline, 6-month, and 12-month visits for the study cohort.

5.8 Data sources

- **Patient surveys**: For each study visit, patients will be asked to complete surveys relating to: CFS, SGRQ-C, mMRC Dyspnea Scale, CAT, GAD-7 and PHQ-9 .
- **Physician surveys:** CFS and care expectations for patient at time of enrolment
- **Electronic Medical Record:** Baseline health data, socio-demographic data, COPD-specific data, previous health care service utilization (1 year prior to study enrolment)
- **Baseline telephone visit with research team:** baseline health data, COPD specific data, previous health care service utilization.
- **6 & 12 month telephone visits with research team:** CFS, change in health status (stress event or falls) since last visit.

6.0 STUDY TIMELINE

- **Pre-implementation & Education of study staff and co-investigators** (December 2019 – February 2020):
    - Research Ethics Board application and study set-up
    - Prepare study documents (patient information sheets, physician reminders, poster of CFS) to increase awareness and reminder to enroll patients
    - Host session with respirologists from TOH General Campus to review how to use the CFS, review study process, and research plan
- **Hire** (February-April 2020):
    - Hire research assistant to assist with the collection of data.
    - Acquire equipment necessary for the study conduct (iPad, study laptop).
- **Implementation & Data Collection** (November 2022- March 2024):
    - Recruit patients from the Respirology outpatient clinic of TOH, General campus, obtain consent (Novemberl 2022 to March 2024)
    - Collect patient data (at baseline, 6 months, and 12-month follow-ups) with study staff.
- **Data Analysis** (March 2024):

- Quantitative data analysis performed by an OHRI methodologist from the Ottawa Hospital Performance Measurement team.

- **Knowledge Translation & Next Steps** (April 2024 and beyond):
  - Manuscript submissions and plan for next steps

7.0 DATA MANAGEMENT

The data collected will be password protected and will not leave TOH. Only study personnel will have access to the study data. A study master list (containing MRN and patient name) will be linked to a study ID. This master linking file will be kept separate from the main study dataset in a protected folder on a secure TOH sever. Only the unique study ID will be used on the patient surveys and study case report forms. The study files will not be stored on the hard drives of portable devices or on USB keys.

8.0 CHALLENGES AND MITIGATION STRATEGIES

8.1 **Patient Recruitment & Transportation**: We may experience difficulty recruiting patients who are severely frail. However, we have chosen The Ottawa Hospital ambulatory care clinic as a referral base, where the level of staff engagement for research is high, and patient volume is adequate. To ensure adequate recruitment in the higher degrees of frailty, we have grouped the 'severe' and 'very severe' categories together. Since patients will not require to be on site for study visits, we believe that this will help with participation.

8.2 **Study Adherence:** We will provide a $20 coffee gift card incentive for patients to attend the initial study visit, 6 month visit, 12-month visit. This is intended to improve adherence to the study protocol and mitigate losses to follow up. Enrolled patient participants will receive personalized communication from the study coordinator to increase their engagement and participation in the study.

8.3 **Patient Participation:** While frailty is a widely accepted medical construct that is frequently used by health professionals to describe health status, the term 'frailty' may be associated with negative perceptions from the patient perspective (37,55). We anticipate that patients may feel stigma attached to using the frailty construct to describe their health and may decline to participate as a result. To mitigate this potential challenge, the initial introduction and consent for the study will be done by the patient's respirology circle of care (respirologist or nurse), with whom they have a therapeutic alliance. We will also ensure the use of impartial language during the study visits to enhance patient comfort-level.

9.0 EXPECTED IMPACT OF THIS WORK

Our study will inform several aspects of care for patients with COPD: a) the validity of frailty assessments as a long-term predictor of patient-centered outcomes; b) the reliability and accuracy of the assessments of frailty, c) the patient's preferences of care according to the different levels of frailty; and d) any potential differences in the perception of frailty between patients and physicians and whether this may have a potential impact on clinical outcomes. We believe that these results will facilitate a practice change to introduce frailty measurements as a risk stratification tool for health providers (and patients), and to enhance personalized care according to patient preferences. This study will provide important context for our next steps to design and test the impact of personalized, patient-centered care interventions in subgroups of frail patients with chronic lung disease.

10.0 FUNDING & COLLABORATION

10.1 **Funding:** This study is funded by a research grant: CIHR-ICRH/AZ Canada/CLA Emerging Clinician Scientist Award (2019). We were awarded $174,480.75 for a duration of two years with one-year extension due to COVID-19 (April 1, 2020 to March 31, 2024).

10.2 **Multidisciplinary team**: We have assembled a multidisciplinary team of pulmonary physicians: **S. Mulpuru** (early career investigator, OHRI), **M. Chin (**early career investigator, OHRI), **Dr G. Alvarez** (mid-career investigator, OHRI), **S. Pakhale** (mid-career investigator, OHRI); Dr. S. Aaron (senior investigators, OHRI), Dr. N Voduc Clinical frailty experts: **Dr M. Andrew** (mid-career investigator, Dalhousie University), **S.Huang** (early career investigator, OHRI); Health Service Researchers: **A. Forster** (senior investigator, OHRI), **S. Mulpuru, T. Kendzerska** (early career investigator), and highly accomplished senior biostatisticians and measurement experts**: T. Ramsay** (senior investigator, OHRI), **J. Brehaut** (senior investigator, OHRI) to complete this project. Our research team has completed and published preliminary work to support this research proposal (13) (26), and currently conducting ongoing work to study the use of frailty measurements in clinical care re-design (56).

Dr Sunita Mulpuru, the nominated principal applicant, is an early career researcher. She's a respirologist at the Ottawa Hospital, Assistant Professor at the University of Ottawa, and Associate Scientist at the Ottawa Hospital Research Institute. She will receive mentorship from highly accomplished senior scientists who are Co-PI's and CO-I's on this proposal; Dr's Melissa Andrew, Alan Forster, Shawn Aaron, Jamie Brehaut, and Tim Ramsay. All of the listed mentors have provided significant input into developing this research proposal and will assist in its' execution.

10.3 **Research Environment:** The Ottawa Hospital's division of Respirology will provide the home-base for patient recruitment. This respiratory clinic is staffed by seven academic respirologists, and receives 6000 patient visits per year (53). Our group estimates seeing 50 patients with COPD per month (54). This will serve our recruitment target of >=10 patients per month, over 12 months, to ensure a final sample size of 120 patients. Our team has access to methodological, statistical, scientific support, and knowledge translation experts from the Ottawa Hospital Research Institute Methods Center (with whom we are affiliated).

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Figure 1 – Clinical Frailty Scale (CFS)

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Appendix 1 – Sample Size Calculations based on Primary Analysis using Linear Regression, with Standard Deviation Values from the Literature

F tests - Linear multiple regression: Fixed model, R^2 deviation from zero

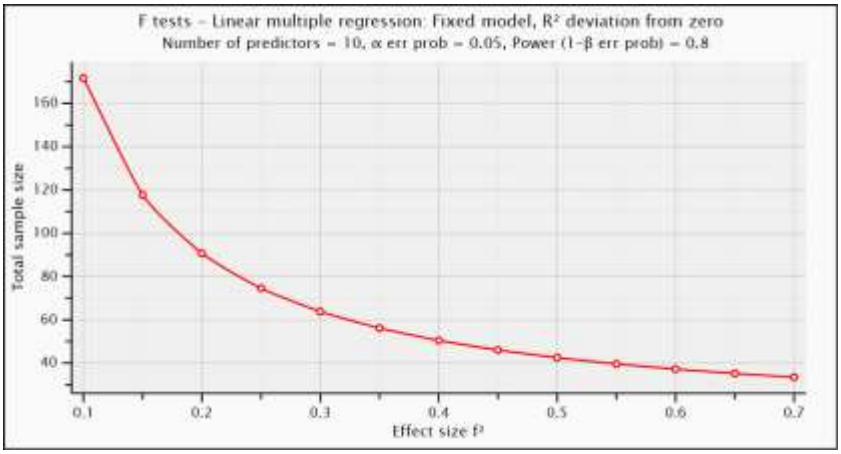
Analysis: A priori: Compute required sample size

Input:	**Effect size f^2**	=	**0.22 (MCID = 4 / SD = 18)**
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Number of predictors	=	10
Output:	Noncentrality parameter λ	=	18.4800000
	Critical F	=	1.9630582
	Numerator df	=	10
	Denominator df	=	73
	Total sample size	=	**84**
	Actual power	=	0.8039786

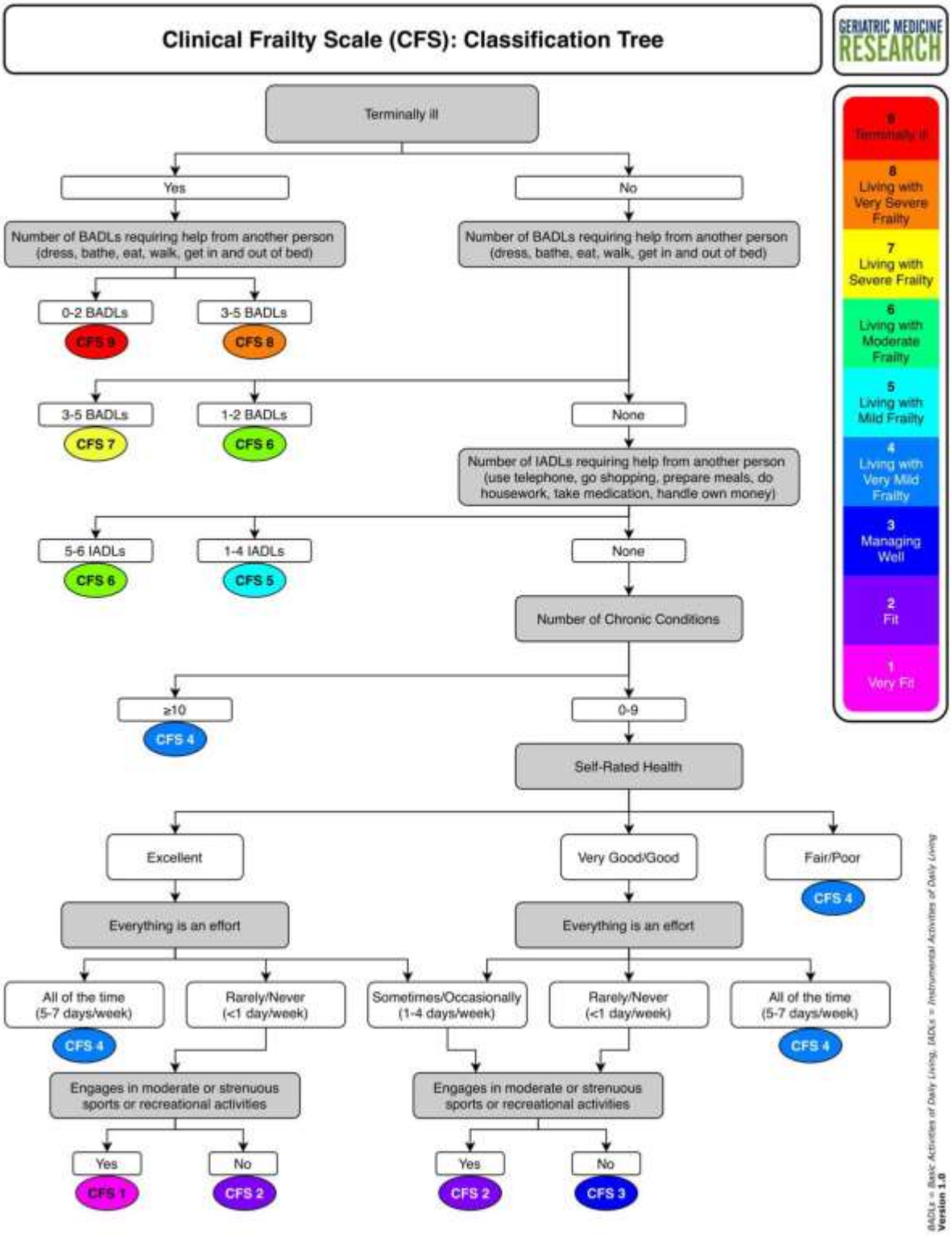
F tests - Linear multiple regression: Fixed model, R^2 deviation from zero

Analysis:	A priori: Compute required sample size		
Input:	**Effect size f^2**	=	**0.30 (MCID = 4 / SD = 12.8)**
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
	Number of predictors	=	10
Output:	Noncentrality parameter λ	=	19.2000000
	Critical F	=	2.0147024
	Numerator df	=	10
	Denominator df	=	53
	Total sample size	=	**64**
	Actual power	=	0.8013694

Reference: Faul F, Erdfelder E, Buchner A, & Lang A.G (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41, 1149-1160.



Appendix 2 – CFS Classification Tree



Theou, O; Perez-Zepeda, M; Van der Valk, A; et al. A classification tree to assist with routine scoring of the Clinical Frailty Scale. *Age and Ageing.* 2021; 50:1406-1411