Human Subjects Research Protocol

Project Title: Accelerated Pulmonary Rehabilitation in the Preoperative Period (PREHAB)

Protocol Version Date: 4/4/2025

Principal Investigator: Katherine Menson, DO

Check the type of the review:

X	Full convened meeting - The IRBs employ the convened meeting review process for review and approval of studies that are more than minimal risk.
	Expedited review - The IRBs employ the expedited review process for approval of studies that are determined to be minimal risk and only involves activities such as prospective collection of biological specimens for research purposes by noninvasive means (blood collection, salvia, nail clippings), collection of data through noninvasive procedures (ultrasounds, MRI, physical sensors) and research on behavior such as perception, cognition, motivation, identity, language and communication.

Federal regulations mandate that changes cannot occur until after IRB review and approval "except when necessary to eliminate apparent immediate hazards to the subject."

ALL modifications to the approved study materials (including Click forms) must be submitted to the IRB prior to implementation, regardless of the magnitude of change or effect on risk level.

PURPOSE AND OBJECTIVES

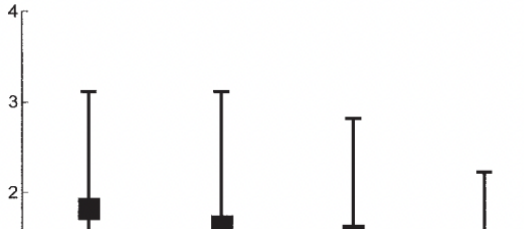
Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

Background

Pulmonary rehabilitation (PR) decreases mortality and hospital readmissions and improves exercise capacity and health-related quality of life in patients with chronic obstructive pulmonary disease (COPD) [1, 2]. PR is defined as a "comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include… exercise training, education, self-management intervention aiming at behavior change, designed to improve the physical and psychological condition…" [20]. The benefits of PR can be extended to the preoperative period ("prehab"), and preliminary evidence suggests that PR conducted prior to lung cancer resection may improve outcomes after surgery [3, 4]. However, the benefits of prehab have not been well-studied in the population that could benefit from them the most, patients with COPD who smoke. Smoking increases the risk of hospital readmissions and post-surgical complications and also contributes to co-morbid conditions (e.g., diabetes, cardiovascular disease) that make those who smoke higher risk for surgery, but also primed to benefit greatly from prehab [5, 6]. Those who smoke and attend PR benefit as much from PR than those who do not [7].

Additionally, lung cancer is the leading cause of cancer death, both in the United States and globally [12]. The National Lung Screening Trial identified a significant mortality reduction for annual low dose CT screening of high-risk patients, primarily through identification of early-stage disease [13, 14]. Early detection allows curative treatment, primarily by surgical resection. However, smoking is a frequent co-morbid condition in those diagnosed with lung cancer and may impact surgical risk due to severity of lung function, poor functional status, and exercise capacity [15]. Optimizing modifiable factors could improve surgical outcomes for those that are already moderate risk.

Smoking Cessation and Pulmonary Rehabilitation Independently Improve Surgical Complications
The impact of smoking cessation on postoperative outcomes has been previously well described. A retrospective analysis of patients undergoing non-cardiac elective surgery was able to demonstrate a 5.5-fold increase in post-operative pulmonary complications in those who smoke compared to non-smokers, and a subsequent metanalysis identified a decrease in the magnitude of post-operative complications by 19% for every week of smoking cessation prior to surgery [16, 17]. Specifically in lung cancer resection, it has been identified that smoking cessation for >1 month had a 30-day mortality benefit and abstaining for >14 days had a reduction in pulmonary complications, similar to those who had abstained from smoking for the prior 12 months [9] [Figure 1]. This population may be highly motivated to quit smoking, as a metanalysis of patients with a



new cancer diagnosis found that the odds ratio of smoking cessation in the perioperative period was 2.31, regardless of the intervention offered [18]. In a survey of patients who smoke with newly diagnosed cancer, >50% intended to quit, but only 37% were able to successfully quit at 6 months [19]. It is therefore possible that capitalizing on this highly motivated window may increase the likelihood of quitting. While smoking cessation for <1 month alone may not improve surgical outcomes, there are no studies to date that identify if other additional interventions may augment this effect.

PR is safe and effective for patients with a multitude of lung diseases, including COPD and lung cancer, and significantly improves mortality, exercise tolerance, quality of life, and decreases healthcare utilization [20]. PR is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as one of the main tenants of therapy in patients with an FEV1 <70% of predicted with stable disease [21]. A retrospective study comparing those who received PR within 90 days of hospitalization for respiratory failure or COPD exacerbation, with those who did not, found a significant mortality benefit (hazard ratio of 0.63) [1]. Hospitalization, length of stay, number of days spent in a nursing home, and number of days spent in the ED are all decreased in participants who received PR within 90 days [2]. PR improves clinically important outcomes in both acute and chronic lung disease.

PR is underutilized due to low referral rates and lack of access [22]. Society guidelines recommend PR regardless of smoking status [20]. Despite this, many programs exclude patients based on smoking status, even though data suggest that people who smoke may have a greater improvement in dyspnea compared to those who do not smoke [7, 23, 24]. Exclusion of those who smoke is likely due to concerns around adherence and misperceptions about insurance coverage [25]. Exploring additive interventions for those who smoke could expand PR coverage to this population.

There are some studies of prehab in lung cancer resection patients. A few studies suggest prehab can reduce the risk of post-operative pulmonary complications by 45-75% [26, 27]. A pilot study enrolled patients with stage I or II lung cancer, COPD, and low exercise capacity (VO2 max ≤15 mL/kg/min) in PR for 4 weeks; they reported significant improvement in exercise capacity, allowing 11 of 12 patients to undergo lobectomy [28]. A small, randomized study attempted to perform a study of a 4-week prehab intervention, but this was not feasible as participants did not want to delay surgical intervention [29]. A shorter, randomized intervention of PR over one week in 19 patients demonstrated fewer days requiring a chest tube, and shorter hospital length of stay (though not significant in this small study) [29]. While these studies support the potential efficacy of prehab, none reported the impact of this intervention on people who smoke.

Leveraging PR and Smoking Cessation Together in the Preoperative Period May Be Safe and Feasible

Exploring the utility of a prehab treatment protocol in this high-risk pre-surgical population is a novel concept. The current delivery of PR typically occurs with two consecutive 1-hour sessions per day, 2-3 days per week, for 6-12 weeks, although longer programs are not necessarily more successful [39]. Most programs utilize 32 sessions (16 total days) and enroll on an intermittent or rolling basis. Prior studies have shown that 20 sessions, or 10 days of PR, provide the clinically maximal benefit, although prior prehab studies have demonstrated benefit in fewer sessions [40]. Due to the traditional structure of PR, patients with lung cancer typically participate in PR after surgery, and do not gain benefits related to potential improvements in operability and surgical outcomes.

There is an opportunity to develop a new prehab model for lung cancer patients to improve outcomes. The median time from radiographic diagnosis to treatment of lung cancer is 36 days, and specialist consultation to treatment is 27 days [41]. An analysis of surgical treatment delayed >12 weeks from radiographic diagnosis was associated with increased risk of disease recurrence and worsened survival in patients with non-small cell lung cancer [42]. Utilizing this time frame to optimize smoking cessation and functional status, but not delay treatment, may improve surgical outcomes. In studies that have evaluated prehab for functional status, a 4-week duration was not feasible due to patient and physician hesitation to prolong surgery [29]. A one-week program operating 5 days per week provided post-operative benefit compared to a control group, however this model does not adapt to how most PR programs are currently provided [29]. Neither of these studies evaluated the impact on outcomes in whose who smoke. There is a significant unmet need, understanding the outcomes of prehab in patients with COPD who smoke.

This study would be innovative in two major ways. First, the impact of prehab in those who smoke could be established. Secondly, the optimal model of prehab, which meets the clinical needs of the patient in the presurgical window, and aligns with the current model of PR, could be determined.

References: Include references to prior human or animal research and references that are relevant to the design and conduct of the study.

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Objectives: Clearly state the primary and secondary objective(s) of the study.

Primary Objective: Measure preliminary acceptability, feasibility, and safety data on prehab for those with newly diagnosed lung cancer who smoke. Acceptability and feasibility will be documented by percent of those eligible

enrolling in the study, attendance (sessions completed), and barriers to completion (patient reported). Safety data will be measured as adverse events occurring during prehab: respiratory exacerbations, infections, cardiac arrhythmias, musculoskeletal injuries, hypertension, and hypoglycemic events. **Hypothesis 1:** This intervention will be acceptable and feasible as demonstrated by successful enrollment and attendance. **Hypothesis 2:** Prehab will have similar rates of adverse events to those reported for PR.

Secondary Objective: Measure initial efficacy data and outcomes of this program. Patients will be assessed prior to and following prehab. Outcomes will include six-minute walk distance (6MWD), respiratory symptoms (St. George Respiratory Questionnaire [SGRQ]), smoking (cigarettes per day [CPD] and carbon monoxide [CO] level), and psychological symptomology (Patient Health Questionnaire-9 [PHQ-9] and General Anxiety Disorder-7 [GAD-7]). A secondary analysis of surgical complications will be measured by post-operative pulmonary complications and hospital length of stay. **Hypothesis 1:** We anticipate an improvement in 6MWD, SGRQ, PHQ-9 and GAD-7 after the intervention. **Hypothesis 2:** We anticipate improved post-surgical outcomes compared to historic controls.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: Provide rationale for subject selection in terms of the scientific objectives and proposed study design.

Pulmonary rehabilitation (PR) decreases mortality and hospital readmissions and improves exercise capacity and health-related quality of life in patients with chronic obstructive pulmonary disease (COPD) [1, 2]. However, the benefits of PR prior to lung resection have not been well-studied in the population that could benefit from it the most, patients who smoke. This study would be innovative in two major ways. First, the impact of prehab in those who smoke could be established. Secondly, the optimal model of prehab, which meets the clinical needs of the patient in the pre-treatment window, and aligns with the current model of PR, could be determined.

We estimate that 20 participants over a two-year period will be sufficient to measure the safety and feasibility of this study. We aim to enroll, on average, 2 participants per month in order to complete this study in a timely fashion. Participants will be enrolled in prehab on a rolling basis, as to not delay treatment timeline.

Patients scheduled for a LMDC, pulmonary or cardiothoracic clinic visit will be pre-screened by the research team. Once a potentially eligible patient is identified, screening and consent will ideally be completed by the study coordinator during the LMDC clinic visit, at which time patients with a lung nodule are first encountering a team of pulmonary, surgical and oncologic specialists. During this initial visit, a patient is evaluated for treatment candidacy and offered participation in any applicable clinical trials. Once treatment candidacy is confirmed and if a patient expresses interest in the study after discussion with a member of the treating team and/or investigator/study physician, the study coordinator and/or investigator/study physician will complete consent and screening.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

X | Not applicable

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined, by whom and how it will be documented in the research record.

Please note: Inclusion and exclusion criteria must be documented for all criteria (e.g., EPIC notes, eligibility checklist with associated source documents, notes to file). Participant reported information must be documented in the research record; a lack of documentation does not prove absence of a criteria.

Inclusion Criteria:

- Age 18 years or older
- Lung nodule that is deemed highly suspicious for lung cancer based on: nodule characteristics, risk factors, CT-PET avidity, previous biopsy results, and assessment by physicians specializing in lung cancers
- Eligible for treatment
- Current cigarette smoking ≥5 cigarettes per day

- Willing to attempt smoking cessation during prehab period
- Willing to take nicotine replacement therapy (NRT) and varenicline
- Able to attend PR at UVMMC for 2, one-hour sequential sessions for a total of 16 sessions over 8 days during treatment
- Willing and able to provide informed consent; ability determined by study physician and/or treatment physicians

Exclusion Criteria:

- Unable to safely participate in PR due to unstable cardiac disease, unstable peripheral vascular disease, musculoskeletal disease that would prevent exercise, significant psychiatric or neurocognitive disease that would limit ability to exercise safely in a group setting as determined by the study physician and/or treatment physicians
- Inability to consistently attend PR during treatment
- Pregnancy, per patient self-report
- Active or recent participation in another clinical trial that, in the opinion of the investigator would impact outcomes measured in this study
- Any other condition in the opinion of the investigator/study physician and or treatment physicians that would jeopardize patient safety or integrity of research results

Inclusion of Minorities and Women: Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.

We plan to recruit both males and females and participants who identify as any racial or ethnic minority group to this study. We anticipate that our study population will be similar to the incidence and prevalence of lung cancer in Vermont and Northern New York. We will exclude women who are pregnant per patient-report.

Inclusion of Children: Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

Children and teenagers younger than 18 years of age will not be recruited based on the limited likelihood of the disease under study.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

N/A

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X | Not applicable

Will the SONA Psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool* Yes [ ] No [X]

METHODS AND PROCEDURES

Study Design: Describe the research design, including a description of any new methodology and its advantage over existing methodologies.

This proposed project will be a single arm, non-masked study. Participants who are actively smoking with a diagnosis of new lung nodule, either confirmed or suspicious for lung cancer, with a plan for lung cancer treatment with or without surgical resection will be recruited from the University of Vermont Medical Center (UVMMC) pulmonary, cardiothoracic surgery, and Lung Multidisciplinary Clinic (LMDC). All patients will be enrolled in prehab and offered smoking cessation

therapy. The acceptability and feasibility of this intervention will be measured by percent enrollment in study, attendance, barriers to completion, and monitoring of adverse events. The effect of prehab will be measured by traditional metrics, including fitness, respiratory symptoms, and depression scale. Research outcomes will be measured by smoking habits, anxiety, and surgical complications.

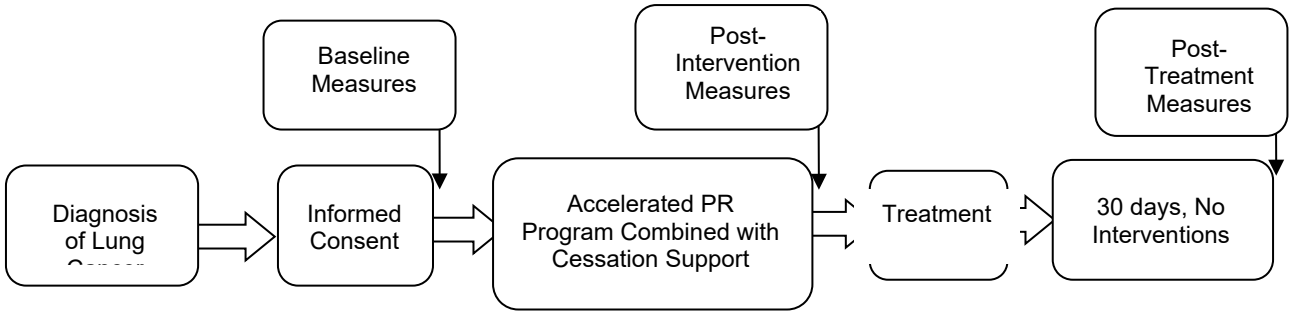

Figure 2. Flow of study from screening to study end.

Procedures and Methods: Describe all procedures (sequentially) to which human participants will be subjected. Describe required screening procedures performed before enrollment and while on study. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc.

Note: A clinical research protocol may involve interventions that are strictly experimental, or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Screening and Recruitment
We estimate that 20 participants over a two-year period will be sufficient to measure the safety and feasibility of this study. We aim to enroll, on average, 2 participants per month in order to complete this study in a timely fashion. Participants will be enrolled in prehab on a rolling basis, as to not delay surgical timeline.

Some procedures will be performed as a component of standard of care and some will be for research purposes only. This distinction is outlined in the sections below.

Intake and Baseline Assessment
After informed consent, participants will complete the initial assessment with study coordinator. This will include anthropometrics, demographics like age, sex, race and ethnicity, and other sociodemographic and economic characteristics such as education, marital status, income, etc. This assessment will also include thorough medical, and surgical history review, healthcare resource utilization, medication usage, substance use and smoking history, specifically recall of average cigarettes per day, carbon monoxide measurements, Fagerström nicotine dependence scale, and readiness to change. We will also administer the General Anxiety Disorder-7 (GAD-7) questionnaire to assess for anxiety. Following intake, participants will be enrolled in the prehab program, which will include standard of care intake measurements including 6-minute walk distance (6MWD), mMRC, SGRQ, short physical performance battery (SPPB), and PHQ-9. For ease of the patient, we will offer that this be performed on the same day, in a private medical setting at our PR facility. If the patient chooses, we can offer intake at the Vermont Lung Center on a separate day.

Prehab
Prehab will include 2, one-hour sequential sessions of PR per day as is standard, however this intervention will increase the frequency from standard 2 days per week up to 4 days per week, while initiating treatment or awaiting surgery but not to exceed 4 weeks, thus completing 16 sessions of PR prior to or in the early stages of treatment. An exercise prescription will be written by the medical director based on initial 6MWD, age, height, weight, and co-morbidities, as

is standard of care. Prior to each session, patients are evaluated for symptoms and vital signs are measured. Exercise will include 30 minutes of warm-up and upper and lower extremity resistance training, either against gravity or with resistance bands as appropriate. Exercise will then move to the open gym, where patients utilize endurance equipment of their choosing, such as a treadmill or recumbent bicycle. As with traditional PR, participants will be given online education videos regarding lung health to complete at home, with a supplementary video on breathing techniques to reduce atelectasis from pain. Virtual synchronous home-based PR will be offered to patients who have barriers to in-center PR.

Smoking Cessation Intervention
Regarding smoking cessation, patients will be offered and prescribed the gold standard therapies in an attempt at smoking cessation, including a one-hour individual counseling session with a mental health therapist trained in smoking cessation therapy, varenicline treatment, dual acting NRT, and referral to the state smoking cessation program. Education modules on the benefits of smoking cessation will also be created for participants to review in the education portion of prehab. None of these interventions will be required, but offered as is standard of care.

Assessments Post-Prehab and Visit 3, 30 Days Post-Surgery/Treatment
Following completion of prehab, Pulmonary Rehabilitation standard of care assessments and research-based assessments will be repeated. This will include interim health history, healthcare resource utilization, and medication usage, assessment for adverse events and COPD exacerbations, substance use and smoking status including recall of average cigarettes per day, carbon monoxide measurements, Fagerström nicotine dependence scale, readiness to change, GAD-7 and the study evaluation. 30 days following completion of prehab, or surgery for those who qualify, the study team will review the participants medical record for any adverse events and smoking status. Post-prehab assessments will be repeated, including interim health history, healthcare resource utilization, medication usage, assessment for adverse events and COPD exacerbations, substance use and smoking status including recall of average cigarettes per day, carbon monoxide measurements, Fagerström nicotine dependence scale, readiness to change, SGRQ, PHQ-9, GAD-7, mMRC and a 6-minute walk test. The 6-minute walk test performed at this timepoint for research purposes only will be compared to those performed for standard of care as a component of the PREHAB program. Every attempt will be made to conduct visit in person; if patient cannot attend visit in-person, CO and 6MWD will not be collected.

Schedule of Study Visits and Assessments

	Visit 0 (V0)	Visit 1 (V1)	Prehab (16 total sessions: 2 sessions/day, 4 days/week for 2 weeks)	Visit 2 (V2)	Visit 3 (V3)
Timeline (days)	-1 (± 7)	0 (-3, ≤ 3 days prior to PR start)		± 7, ≤ 3 days from PR end	30 days +14 from PR end
Visit Duration	1-1.5 hrs	1-1.5 hrs		1-1.5 hrs	1 hr
Informed Consent	*				
Demographics	*				
Brief Medical and Smoking History	*				
Physician assessment	*				
Eligibility Criteria	*				
Sociodemographic and economic characteristics		*			
Full Medical and Surgical History		*			
Interim Health and COPD History				*	*
Medication Review		*		*	*
Substance Use and Smoking History		*		*	*
Height and Weight		*			
Questionnaires		*		*	*
Prehab Initiation		*			
6MWT					*
Pulmonary Rehab SOC Assessments (6MWD,		*		*	

SGRQ, PHQ-9, etc.)					
Pulmonary Rehab participation			*		
Smoking Cessation Counseling, NRT and varenicline			*		

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)

Check all that apply

X	Survey (mail, telephone, in-person, on-line)		Blood drawing:	Vol.		Over days, weeks?	
X	Medical exams/history					Type & Amt.	
	Deception ***see below**		Surgery			Collection of Urine and/or Feces	
X	Observation		Drug Administration			Communicable Disease Testing	
	Photographs		Device Use			Ultrasound (e.g., echocardiogram)	
	Audio Recording	X	Exercise			Imaging (e.g., CT scan, DEXA, mammogram, PET scans, SPECT)	
	Video Recording		Diet			Use of Radiation treatment	
	Interviews in person or by phone		Pathology Specimens (retrospective)			Use of Radioactive substances (e.g., radiolabeled antibodies, drugs, or contrasts)	
	Focus Groups		Genetic Materials (DNA)** **see below**			MRI (for treatment studies)	
X	Review of prospective data	X	Questionnaires			MRI (not for treatment studies)	
X	Review of retrospective data		Diaries			Tissue (obtained for clinical purposes)	
X	Recording of Identifiable Data		Pregnancy Tests			Tissue (obtained solely for research)	
	Electrocardiograms						
	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)			(specify):			

****If genetic information is being collected, GINA language must be added to the consent form.**

*Deception typically involves withholding information from the potential subject and would require an alteration to the consent process.

If you are requesting Radiology services (equipment and professional needs) you will need to contact the Radiology Research Coordinator John.Little@uvmhealth.org and complete this form.

Statistical Considerations: Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.

Given that this is a pilot feasibility study, we will use a convenience sample size based on prior studies that will inform feasibility of proceeding with a larger study. The feasibility of the study will be based on the ability to enroll 20 participants and their ability to attend 50% of sessions (8 out of 16 sessions) of the PR program. Barriers to enrollment and adherence will be monitored throughout the study. Adverse events will be monitored from the start of the study through 30 days after lung cancer treatment.

Reporting of results will include feasibility and acceptability data noted above along with patient demographics and sociodemographic and economic characteristics, anthropometrics, respiratory and other relevant medical history, medication use, smoking cessation and abstinence, compliance with NRT and varenicline if utilized, results from questionnaires/surveys including respiratory symptoms and quality of life etc, 6MWD, PR program adherence, adverse events and COPD exacerbations, complications from treatment, and healthcare resource utilization.

For analysis of secondary outcomes, we will initially compare change in continuous variables (i.e. 6MWD) using appropriate parametric and non-parametric testing. We will also generate effect size and variability estimates for future studies.

Risks: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks (including breach of confidentiality, which is always a risk when collecting identifiable information). Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.

Carbon Monoxide Measurement
There are no known risks or discomforts associated with this procedure.

Questionnaires
The questionnaires/surveys are not tests. There are no right or wrong answers. Some people may feel uncomfortable answering some questions. Participants will not be required to complete questionnaires or questions that make them feel uncomfortable or do not want to answer. Responses to questionnaires/surveys will be kept confidential.

Psychological
Although unlikely, there may be unforeseen psychological or financial risks for participants in this trial. For example, patients may have unrealistic expectations of benefit from Pulmonary Rehab, or may have psychological distress from having a diagnosis of lung cancers or other concomitant diseases, discomfort during Pulmonary Rehab and potential complications from treatment unrelated to the research study. Many patients, however, have psychological benefit from participating in pulmonary rehab and research in general, when there is potential to help others based on the results of the study.

Prehab
The potential risks to participants are based on the two interventions of this study. Regarding participating in PR, we assess and monitor the risks of the following occurring during exercise. Respiratory exacerbation is a rare complication of PR, although some patients may experience bronchospasm. Patients are assessed for symptoms, monitored by pulse oximetry during exercise, auscultated by stethoscope if having distress, and provided oxygen as needed. If warranted, patients are advised to use their rescue inhaler for relief, and exercise would be discontinued for the day or transitioned to less intense exercise (i.e., seated exercises). Hypertension is a normal response during exercise, however if a participant presents with elevated blood pressure prior to exercise, they will not be allowed to exercise for the day. The primary care physician and medical director will intervene as needed to control blood pressure so that PR can be resumed as soon as possible. Vital signs are obtained before, during, and after exercise. Symptoms for hypertension are assessed by a respiratory therapist (RT) or physical therapist (PT) during exercise, as is standard of care during PR. The risk of arrhythmia is low in participants who do not have a preexisting diagnosis. For any participant experiencing palpitations, light-headedness, or chest discomfort, they will be instructed to stop exercising and additional vital signs and examination will be performed, and medical director is notified for further work-up and evaluation. Musculoskeletal injuries can occur, however patients are monitored by a PT during exercise to ensure that exercises are performed correctly. Exercise is modified based on patient safety and pre-existing medical problems. For participants with diabetes and on medication that can induce hypoglycemia, they are asked to measure glucose prior to exercise with their glucometer and monitored for signs of hypoglycemia. High glycemic drinks are available should hypoglycemia occur.

6-Minute Walk Distance
This test will be performed according to standard ATS guidelines by trained members of the Pulmonary Rehab and research team. Participants will be asked to walk at their own comfortable, but brisk pace. As such, they may experience dyspnea on exertion, fatigue, or other symptoms associated with exercise and COPD. Participants are monitored by heart rate and pulse oximetry and may be stopped at any time.

Smoking Cessation Intervention
Regarding smoking cessation, risks include withdrawal symptoms, including urges to smoke, irritability, difficulty

concentrating, difficulty sleeping, increased hunger, or increased feelings of depression or anxiety. Symptoms will be explained and mitigated by pharmacologic and nicotine replacement therapy. There are also known side effects of NRT and varenicline. Participants will be queried about potential side effects throughout the prehab program. The most common side effects of NRT are skin irritation and difficulties sleeping. These will be mitigated by encouraging rotation of patch side and adjusting timing and dosing of NRT. The most common side effects of varenicline are nausea, insomnia, and vivid dreams. These will be managed by encouraging patients to take the medication with food and adjusting timing of doses. Intervention will be offered remotely if the patient elects.

Confidentiality
This study includes a risk of loss of confidentiality. We will follow Health Insurance Portability Accountability Act guidelines on confidentiality and minimize these risks by assigning unique identifiers to health information and study records, whenever possible. All physical records will be stored in the locked Vermont Lung Center in locked areas restricted to research personnel. All electronic records will be maintained on password protected electronic devices and on the Vermont Lung Center UVMMC shared drive with limited access to Vermont Lung Center and institution research personnel.

Benefits: Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Potential Benefits
Benefits of the study include immediate access to PR, which currently has a long wait list and few locations in Vermont and New York. Additionally, they will be provided multiple smoking cessation therapies, including varenicline, nicotine replacement therapy, and education and behavioral therapy to aid in smoking cessation.

Therapeutic Alternatives: List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.

☐ Not Applicable

Patients could elect to not participate in the study and proceed directly to treatment. They can also seek alternative forms of rehabilitation and education on lung disease. All patients are offered smoking cessation strategies regardless of inclusion in the study.

Data Safety and Monitoring: *Please note that this is not the same as the Data Management and Security Plan that will be uploaded as a separate document.*
Describe the data and safety monitoring plan (DSMP). This should provide for a regular review of accrued research data and other relevant information to ensure the validity and integrity of the data and that there is no change to the anticipated benefit-to-risk ratio of study participation. In addition, there should be an ongoing review of study procedures to ensure that the privacy of research subjects and the confidentiality of research data has not been violated.

The specific design of a DSMP for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.

Data Safety Monitoring Board
We will invite 3 physicians who are knowledgeable in rehabilitation medicine to participate in the Data and Safety Monitoring Panel (DSMP), who will include Drs. David Kaminsky, Renee Stapleton, and Charlotte Teneback. The panel will convene biannually primarily to review safety data including AEs/SAEs and protocol deviations, review integrity of the data being collected, any potential conflicts of interest and will ultimately provide recommendations regarding continuation of the study. Changes to the protocol will be reviewed at these biannual meetings and any significant changes to the protocol that may affect patient safety, as determined by the investigator/study physician/study team, will be reviewed by at least one members of the DSMP prior to initiation.

Safety
The treatment and LMDC physicians, pulmonary rehab staff/clinicians, and the investigator/study physician and

study team will monitor study participants for adverse events and any other potential safety concerns continuously throughout the study. Participants will also be encouraged to notify the study team in the event of any safety concerns they may have or adverse events they may experience including urgent health care needs between study visits.

During Pulmonary Rehab, patients/participants are monitored by PR staff/clinicians and the Medical Director is available by real-time audio-visual communication as is dictated by CMS while PR is in session.

Reporting
Adverse event reporting for this protocol will be as follows:

- The Investigator/Study Physician/Study Team will submit a completed serious adverse event report to the IRB in the form of an RNI, and as necessary to the grant funding agency/Sponsor, when applicable, and to the Chair or at least one member of the DSMP within 48 hours after becoming aware of any serious adverse events (SAEs) possibly, probably or definitely related to the study.
- The Investigator/Study Physician/Study Team will submit a completed adverse event report to the IRB in the form of an RNI, and as necessary to the grant funding agency/Sponsor, when applicable, and to the Chair or at least one member of the DSMP within 48 hours after becoming aware of any Grade 3: Severe, adverse events (AEs) possibly, probably or definitely related to the study.
- The Investigator/Study Physician/Study Team will report any other event or condition regardless of grade, which in their judgment represents an event reportable to the IRB in the form of an RNI, and as necessary to the grant funding agency/Sponsor, when applicable, and to the Chair or at least one member of the DSMP within a reasonable timeframe of becoming aware of the event.
- A summary of all adverse events, serious adverse events, protocol deviations and any other applicable safety concerns will be reported to the DSMP biannually, the IRB annually at continuing review, and as necessary to the grant funding agency/Sponsor, when applicable.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. “stopping rules).

Discontinuation
During the study period if there is any reason to stop the entire study or discontinue intervention for one or more participants due to safety concerns, the protocol will be temporarily or permanently discontinued. This will be based on the discretion of the Investigator/Study Physician, IRB, DSMP, or grant funding agency/Sponsor, when applicable. However, the stopping rules are intentionally broad given the nature of this feasibility study.

Serious Adverse Events (SAEs)
The protocol will be temporarily stopped if three or more serious adverse events (SAEs) that meet the reporting requirements noted above (any serious adverse events (SAEs) possibly, probably or definitely related to the study) until adequate safety review and possible protocol modifications have been completed. Re-instatement will require written formal approval by the IRB, DSMP, and/or grant funding agency/Sponsor.

Adverse Events (AEs)
The protocol will be temporarily stopped if five or more adverse events (AEs) that meet the reporting requirements noted above (any Grade 3: Severe, adverse events (AEs) possibly, probably or definitely related to the study) until adequate safety review and possible protocol modifications have been completed. Re-instatement will require written formal approval by the IRB, DSMP, and/or grant funding agency/Sponsor.

DSMP Stopping Rules
The protocol may be permanently or temporarily stopped at any time at the recommendation of the DSMP via unanimous decision or grant funding agency/Sponsor as a result of any reasonable concerns related to the protocol, for example safety and data integrity in consultation with the Investigator/Study Physician, Study Team and Director of the Vermont Lung Center.

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. These reviews must be conducted at the frequency indicated below and must be documented in the regulatory binder or files.

Forward copies of data and safety monitoring board reports to the IRB via a modification.

☐	Monthly	☐	Annually
☐	Quarterly	☐	Other (e.g., by dosing level, no. of subjects enrolled):
☒	Bi-annually		

Will the sponsor be conducting data monitoring visits for this study?

☐ Yes ☒ No ☐ NA

If yes, how often?

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in "Section 18: Reportable New Information" of the IRB Policies and Procedures will be followed.

Evaluation of Events

Definition of an Adverse Event (AE)
An adverse event (AE) is any unanticipated or unintended medical occurrence or worsening of a sign or symptom (including any clinically significant abnormal physical finding as determined by the study physician) or disease in a study participant, which does not necessarily have a causal relationship with the study condition, procedures or study intervention, that occurs after the informed consent is obtained throughout participation in the study.

Pre-existing conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events. Symptoms of the disease under study, COPD and Lung Cancer, and events which are unequivocally related to the disease under study are not considered adverse events. Such events, for example COPD exacerbations, will not be considered adverse events unless it meets SAE criteria, results in discontinuation of Pulmonary Rehab, or the sign or symptom is new to the participant or not consistent with participant's pre-existing COPD history.

Definition of a Serious Adverse Event (SAE)
Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following outcomes:

- Death
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event as determined by the investigator/study physician)
- Inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

AE/SAE Grading and Relationship Assignment

Intensity (severity) Scale
Each adverse event will be assessed by the site investigator for severity and classified into one the categories below:

- **Grade 1 (Mild)**: event requires minimal or no treatment and do not interfere with the patient's daily activities.
- **Grade 2 (Moderate)**: event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)**: event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Life threatening)**: Any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it

occurred in a more severe form, might have caused death.
- **Grade 5 (Death)**

Relationship Assessment
For all collected AEs, the site investigator who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:
- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study visit.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study visit, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possibly Related:** There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study visit makes a causal relationship improbable (e.g., the event did not occur within a reasonable time) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated:** The AE is completely independent of study, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.
- **Expected Events Related to Disease Process:** Expectedness refers to the awareness of adverse events related to study.

Action Taken
The site investigator will classify the action towards intervention taken with regard to the AE. The action taken will be classified according to the categories below:
- **Intervention not changed:** intervention not changed in response to an AE
- **Intervention reduced:** intervention frequency reduced in response to an AE
- **Intervention interrupted or delayed:** intervention interrupted in response to an AE
- **Intervention withdrawn:** intervention permanently discontinued in response to an AE
- **Not applicable**: Action taken regarding intervention does not apply. "Not applicable" will be used in circumstances such as when the intervention been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

Adverse Event Outcome
An AE will be followed until the site investigator has determined and provided the final outcome or the participant has completed the study.
- **Recovered/resolved:** resolution of an AE with no residual signs or symptoms
- **Recovered/resolved with sequelae**: resolution of an AE with residual signs or symptoms
- **Not recovered/not resolved (continuing):** either incomplete improvement or no improvement of an AE, such that it remains ongoing
- **Fatal:** outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE
- **Unknown:** outcome of an AE is not known (e.g. a subject lost to follow-up)

Withdrawal Procedures: Define the precise criteria for PI withdrawal of subjects from the study. Include a description of study procedures for when a subject withdraws themself from the study.

Participation is voluntary. Participants may withdraw from the study at any point in time. Participants may elect to withdraw from Pulmonary Rehab but will be encouraged to continue with study visits including assessments and follow-up. Study visits, assessments and procedures may be modified in the above instance to meet the participant's needs and reduce research burden in order to adequately capture acceptability, feasibility and other safety and outcomes data.

DRUG INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] **Not applicable**

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source.

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also, adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.
2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.
3. for the intended action?

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

Participants may experience financial loss from their occupation to attend pulmonary rehab and research visits. Financial risks are mitigated by reasonable research compensation. Some participants may have a copay for pulmonary rehab, which is standard of care, if it is not covered in full by insurance.

Compensation for participation: Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.

[ ] Not applicable

Participants will be compensated $25 via pre-paid debit card for each of the follow-up assessments (Visit 1, Visit 2, and Visit 3). Patients who are ≥20 miles from in-center PR will be offered transportation stipend of $200 to participate in the trial.

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.