Hypothesis: Ten sessions of customized preoperative PR will significantly reduce the number of postoperative pulmonary complications.

2.2.2 To prospectively determine the effect of a 10-session preoperative PR on the trajectory of quality of life at 3 and 6 months after the curative resection compared to a matched control group.

Hypothesis: Ten sessions of customized preoperative PR will significantly and meaningfully (more than the minimal clinically important difference) improve quality of life after surgery compared to a control group.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should recognize that the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit this page.

___ **3.2.1** Patient is scheduled to undergo NSCLC resection: video assisted thoracoscopy (VATS) or open thoracotomy for: limited resection, lobectomy, or pneumonectomy. Surgery must not be scheduled to take place < 3 weeks after registration.

___ **3.2.2** Patient has a doctor diagnosis of COPD.

___ **3.2.3** Patient is a current or ex-smoker with a smoking history of ≥ 10 pack years. (Calculated by multiplying the number of **packs** of cigarettes smoked per day by the number of years the person has smoked. For example, 1 **pack-year** is equal to smoking 20 cigarettes (1 **pack**) per day for 1 **year**, or 40 cigarettes per day for half a **year**, and so on).

___ **3.2.4** Age ≥ 18 yrs.

4.0 PATIENT REGISTRATION

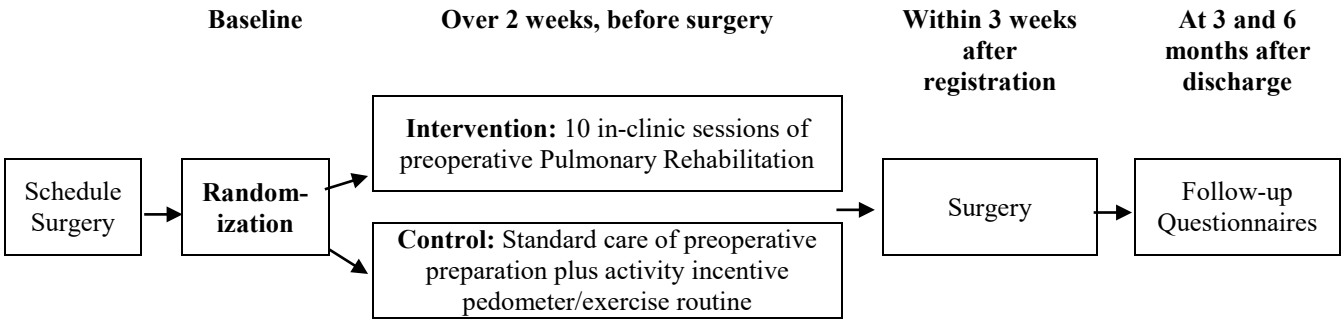
4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

Human Subject Protection (HSP) training certificate

7.0 STUDY INTERVENTION



7.1 Intervention group procedures

Patients who are randomized to the intervention group will start the Pulmonary Rehabilitation (PR) within 7 days after randomization. The PR will consist of 10 sessions with the interventionist lasting less than 2 hours each. Patients will receive a Participant Manual demonstrating and explaining the rehabilitation process. Patients will also receive a log for recording their efforts and notes for every day until the day of surgery. We will consider 6 sessions as the minimum to be deemed a complete intervention (for analysis purposes). The patients should not be asked to come only 6 times to the clinic. In case of missing sessions, the patient should be encouraged to do the sessions at home, however, they will not be counted as intervention sessions.

Using the video recording during Pulmonary Rehabilitation sessions:

A video recording of the intervention from start to finish will be provided to all patients in the intervention arm. The recording will be an mp3 file that can be played from any device (e.g., phone, computer). Alternatively a CD that has the breathing practice may be used. Patients may keep the DVD/CD. The DVD should be used during the intervention with the participant. The patient and interventionist should both follow the video. This ensures that the same intervention is being delivered.

The video recording should be played in all 10 sessions at the registering site. Following the video recording will add uniformity to the intervention across sites. The interventionist can stop the video recording any time during the session to give instructions or answer questions.

Modifications may be made if needed. For example, if the patient has shoulder injury and cannot lift arms over head, then the exercise may be modified to accommodate the patient.

PR sessions will include the following components:

The patient will document in a log that they completed each component of the rehabilitation. The patients will be asked to return the log to the registering site at the end of their last PR session.

7.1.1 Breathing Awareness (in clinic): Before and after each session, the patient will do a 3-minute mindful breathing awareness exercise guided by an audio recording provided either as a CD or mp3 file. We provided also an ultra-short 10 Breath Practice that can be used during the day and at times when there are worsening symptoms (i.e. pain after surgery).

7.1.2 Upper and lower extremity exercise (in clinic): Strength and stretching exercises (goal of at least 20 minutes per session), treadmill or hallway walking (preferred) with a goal of total 24 minutes per session (not less than 18 minutes). The sites and patients will be provided a DVD that demonstrates the rehabilitation session from start to finish.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

If surgery is cancelled after registration, the participant will be considered a screen failure.

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), baseline and off-treatment notice data submission is required. See the Data Submission Schedule accompanying the All Forms Packet.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Overview

Prospectively, 194 patients will be randomized to either ten sessions of preoperative pulmonary rehabilitation vs. standard care at a number of healthcare centers throughout the United States.

11.2 Sample Size, Accrual Time, and Study Duration

11.2.1 Sample Size

A total of 194 patients (97 in each group) will be accrued to this study. This sample size includes a 10% adjustment to account for attrition and will provide at least 80% power for testing each aim of the study. Based on estimates from the pilot study, this sample size will provide 80% power to detect a 25% difference in complication rates, a 3-day difference in chest tube days, 3 day difference in length of stay, and a half standard deviation difference in QOL endpoints.

11.2.2 Accrual Rate and Accrual Duration

This study will be open for 36 months. We expect to close the study to accrual at month 30 to allow time for statistical analysis and publication. About 7 patients a month need to be recruited to meet the 30 month proposed time line.

11.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purposes of ClinicalTrials.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least 6 months.

11.3 Statistical Design and Analysis for the Primary Endpoint

11.3.1 Primary Endpoint

End point that will address AIM 1: hospital length of stay. The coordinator at each site will be responsible for sending complete de-identified hospital records from each patient to Dr. Benzo's staff, where a nurse blinded to the study arm will abstract the main outcome (length of stay and postoperative complications). See Section 6.3.

The primary endpoint will be assessed at Dr. Benzo's office (Mayo Clinic) with the complete admission hospital records in order to extract the length of stay. The records will be mailed from the sites to [redacted] in a pre-stamped envelope. See Section 6.3.

11.3.2 Analysis Plan

Differences in length of stay between arms will be tested using a two-sample, two-sided t-test. Wilcoxon nonparametric testing will be used for analyzing continuous outcomes that are skewed and not approximately normally distributed. Fisher's exact tests will be used to test for differences in categorical variables between arms. All tests will be two-sided with a 0.05 significance level. Linear models will be created to test the effects of treatment after adjusting for the baseline characteristics of age, gender, and lung function.

11.4 Supplementary Analysis Plans

11.4.1 Secondary Endpoints

End points that will address AIM 2 (baseline and at 3 and 6 months after hospital discharge):

Post-Operative Pulmonary Complications: The following events will be considered post-operative pulmonary complications: pneumonia (new infiltrate + either fever (>38.5 C) and white cell count >11,000 or fever and purulent secretions), severe atelectasis (requiring bronchoscopy), prolonged chest tubes (>6 days), and respiratory failure (intubation or prolonged mechanical ventilation (>24 hours). These outcomes will be obtained by chart review by a nurse trained in the abstraction of the desired outcomes from the medical records and blinded to treatment assignment.

Chronic Respiratory Questionnaire (CRQ) (four domains: dyspnea, fatigue, emotional function and mastery). This instrument will be the primary tool to assess QoL given that it was specifically designed for COPD. Specifically, the CRQ represents one of the most well-known, widely-applied, and psychometrically-sound patient reported outcomes for use in clinical trials involving patients with COPD. The CRQ has been validated and has demonstrated a reliable quality of life measures for patients with chronic airflow limitations. .A 0.5 point will be considered significant and was considered in the sample size calculation as that difference as is the well-established MCID (minimally clinically important difference) for the instrument. Analysis for the QOL outcomes will be identical to that for the primary endpoint. We include the scores from the dyspnea questionnaire under the generic umbrella term as a domain of QOL.

LASA (single-item numerical analogue quality of life Questionnaire) individual QOL domain scores. All of these questionnaires have been validated previously for lung cancer patient populations and for assessment of patient-reported outcomes in similar trials. LASA items have been validated as general measures of global QOL dimensional constructs in numerous settings and have been constructed and validated at Mayo Clinic for use in cancer patients. These single-item assessments have become the most used assessments in all NCI-sponsored cancer control studies.[28]

11.4.2 Secondary Analysis

Longitudinal analysis for the relationship between QOL and the intervention will be handled by repeated measures analysis of variance modeling and multiple regressions. Finally, a logistic regression model will be used to identify which variables are most closely associated with the dependent variable of patients who experience either clinically significant deficits in QOL (one regression model). The modeling processes will include the aforementioned covariates to control for spurious correlations.

4.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at [redacted]. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at [redacted].

4.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.3.1 Downloading Site Registration Documents:

Site registration forms may be downloaded from the A221502 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen

It is acknowledged that it could be "boring to have a recording" or follow a movie every time but that will provide consistency of the intervention across sites. Patients are expected to engage in walking once daily and complete the IMT routine and upper extremity exercises.

7.1.3 Instructions for Inspiratory Muscle Training (IMT) performed using the PFlex valve (Philips Healthcare Andover, MA) (in clinic): Patients will be instructed to inhale deeply and forcefully for 2 seconds and exhale normally. Repeat for one minute and rest for 30 seconds for a total of 10 complete cycles (training plus resting time). Patients are asked to adjust their trainer (there is a selector with different levels of effort) to a level of perceived exertion of "Somewhat Hard to Hard" (11-13 on the 6-20 BORG scale) when they breathe through the device. When patients note perceived exertion less than "Somewhat Hard", the next IMT setting is increased to achieve the desired effort. The rationale to include routine use of inspiratory muscle training, not recommended as a routine in the current PR guidelines, is based primarily on a recent large randomized study which showed decreased postoperative complications.[20-22]

The table below lists the exercises that are part of the PR sessions.

Exercise	Time	Description
Breathing Awareness	3 Minutes	3 minute breathing practice at start of session
Upper Extremity	20 Minutes	Neck, Shoulder, Arm Movements
Lower Extremity	18-24 Minutes	Goal is 4 six Minute Walks, but not less than 3
P-Flex	15 Minutes	10 one minute repetitions with 30 second breaks in-between
Breathing Awareness	10 Breaths	10 Breath practice at end of session

7.1.4 Practice at home:

One-on-one revision of the IMT technique will be completed every session in the lab, and patients will be asked to do 10 repetitions of IMT twice a day when not in the lab, which includes the weekend. Twice a day training is the minimum required.

Upper and lower extremity training: Once a day training of one set of ten repetitions of upper extremity exercises, and two 6 minute walks in a safe place in the home is the minimum required.

This is a critical step in the process. Patients will be encouraged to practice every day and record their practice into a log that will be reviewed by the interventionist every session.

7.1.5 Goal setting

The patients are encouraged to set goals, a post-operative goal and post hospital discharge goal. The patients do not record the goals.

Post-operative goals will be to do at least one six minute walk, one upper arm series every day while still in the hospital. Patients will also be asked to set a goal to practice the breathing awareness, ten breaths, at least two times a day, particularly when in pain or stressed.

Post hospital discharge goals the same as post-operative goals.

7.2 Control Group Procedures

Patients randomized to the control arm will receive a pedometer to monitor their daily steps and a pamphlet with exercises plus the standard course of care for patients undergoing lung resection

11.5 Study Monitoring

11.5.1 Adverse Event Stopping Rule

Not applicable.

11.5.2 Accrual Monitoring Stopping Rule

Slow Accrual: Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

11.5.3 This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every month as per NCI guidelines.

11.6 Study Reporting

At study activation, this study will have been registered within the "ClinicialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

11.7 Descriptive Factors

None.

11.8 Inclusion of Women and Minorities

Inclusion of Women: Based upon the gender distribution of patients from past studies and the gender distribution with ICD-9 codes for COPD/ lung cancer, we anticipate a female to male ratio of 5/6 ratio.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	0	0	2
Asian	5	3	1	1	10
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	14	9	1	1	25
White	80	57	4	4	145
More Than One Race	4	3	2	1	10
Total	105	74	8	7	194