Improving Lung Transplant Outcomes with Coping Skills and Physical Activity

INSPIRE III

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Purpose of the Study

The study will aim to evaluate the effectiveness of the Coping Skills Training plus Exercise (CSTEX) intervention in reducing distress. It is hypothesized that compared to Standard of Care plus Education (SOC-ED), the CSTEX intervention will result in greater reductions in global distress measured by an established psychometric test battery. Additional secondary outcomes will include measures of functional capacity assessed by distance walked on a standard Six Minute Walk test (6MWT), physical activity (PA) during daily life, QoL, sleep quality, coping and self-efficacy, measures of frailty, and clinical outcomes defined as CLAD-free survival, a well-established clinical outcome following lung transplantation. We also will explore possible mechanisms by which the CSTEX intervention may reduce distress, increase functional capacity, and improve medical outcomes, including enhanced coping skills, increased self-efficacy, greater PA, and better adherence to prescribed medical therapies (including immunosuppressant medications, regular exercise, and monitoring of pulmonary function).
We will test the hypothesis that CSTEX, a post-transplant intervention combining CST and exercise, will reduce distress. We also hypothesize that CSTEX will promote such health behaviors as increased functional capacity, daily PA and medication adherence, enhance psychological QoL, and potentially improve clinical outcomes

Background & Significance

For patients with end-stage lung disease, lung transplantation is now a viable treatment option to improve their quality of life (QoL) and extend their survival. With the growing number of individuals with advanced lung disease, most commonly idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), the frequency of transplant has increased exponentially over the past 20 years, with nearly 42,000 patients having been transplanted; more than 2,500 individuals were transplanted in 2016, which is projected to continue to increase in the future. Public health expenditures due to chronic lung diseases are estimated to reach $832 billion in 2021.

Despite the increasing acceptance of lung transplantation as a treatment and improvements in short term-survival, the median overall survival remains ~6 years, with only 26% of patients surviving to 10 years, which is markedly less than other solid organ transplants. Greater post-transplant mortality is primarily due to chronic organ rejection, termed chronic lung allograft dysfunction (CLAD). CLAD encompasses both the older term of obstructive chronic rejection, i.e., Bronchiolitis Obliterans Syndrome (BOS), as well as the more recent definition of restrictive CLAD. As many as 4 out of 5 patients will be re-hospitalized within a year after transplant, which results in compromised QoL and a significant economic burden to the patient, family, and health care system. Indeed, the importance of patients' self-evaluations of their QoL has received growing attention.Psychological distress can impair QoL and lack of regular exercise after lung transplantation is common, despite improved lung function.

While lung transplantation extends survival for most patients, surprisingly, mental health QoL does not necessarily improve after transplant and may actually worsen over time. Prospective studies following lung transplant recipients during the first year of recovery suggest that 30% of patients experience major depression, 18% experience panic disorder, and 15% meet criteria for posttraumatic stress

disorder. Indeed, a recent systematic review found that psychological QoL declines over time. Moreover, in a systematic review of psychological functioning following cardiothoracic transplantation in adults, Dew and DiMartini found that post-transplant depressive and anxiety disorders are not only common, but that psychological distress following transplant was independently associated with worse clinical outcomes. Interventions to reduce psychological distress may have the potential to not only improve QoL, but also to extend survival.

Few predictors of long-term clinical outcomes among lung transplant recipients have been identified. Lung allocation scores (LAS), which are used to prioritize candidates for donor lungs, is based on risk of death without a transplant and short-term survival after transplant; however, the LAS uses only pre-transplant factors including age, native disease, and disease severity, which are poorly predictive of longer-term outcomes after transplant. Recent evidence suggests that biobehavioral factors may offer important prognostic information and may be modifiable with treatment. The proposed RCT will aim to improve exercise tolerance and functional capacity and reduce psychological distress in lung transplant recipients.

There is now good evidence that greater functional status and increased physical activity (PA) are associated with improved survival among patients with end-stage lung disease, including lung transplant. Despite the importance of PA in patients with pulmonary disease, few studies have examined PA after lung transplantation. Available evidence suggests that patients tend to engage in regular PA shortly after hospital discharge following lung transplant when participating in supervised pulmonary rehabilitation (PR), but exhibit a decrease in PA as early as 3 months following surgery,with a continued decline at one year, placing their PA level well below population norms. In addition, PA has been associated with preserved graft functioning in other transplant populations, and physical inactivity appears to worsen lung function, increasing the risk of poorer clinical outcomes. Moreover, evidence from small, pilot studies suggests that exercise can improve functional capacity in lung transplant recipients.Taken together, these data provide a strong rationale for the importance of regular aerobic exercise and PA as a way to improve long-term outcomes in lung transplant recipients.

There also is growing evidence that depression and psychological distress following transplant are associated with increased risk of CLAD, graft loss, and mortality. In a study of 155 transplant recipients followed up to 15 years after transplant, Rosenberger and colleagues found that depression assessed one year after transplant was associated with nearly twice the risk of chronic rejection, a 75% increase in the likelihood of graft loss, and a 65% increase in the risk of death. Our group reported similar findings in a sample of 132 lung transplant recipients assessed 6-months following transplantation, demonstrating that greater psychological distress and depression, even at subclinical levels, were predictive of elevated mortality rates. These prognostic relationships also persisted when patients were assessed 18-months following transplant, with elevated depressive symptoms predicting a greater likelihood of death in the 10 years following transplant.We recently confirmed these findings in a prospective study of 66 lung transplant recipients: greater depressive symptoms assessed two weeks after transplantation were strongly predictive of survival over a three-year follow-up (HR = 2.17), independent of perioperative medical outcomes (e.g., length of hospital stay and primary graft dysfunction). Similar results have been reported in other solid-organ recipients: for example, DiMartini and colleagues reported that depression following liver transplant more than doubled the risk of

mortality, and that adequate treatment of depression during the post-transplant period mitigated this risk. Importantly, individuals who exhibited depressive symptoms that were subsequently treated exhibited no greater risk of mortality compared to non-depressed patients.

In sum, the present study is based upon compelling evidence that heightened psychological distress and low functional capacity are common after lung transplant, impairing QoL, and reducing longer-term event-free survival.

Previous RCTs have demonstrated that behavioral interventions are effective in reducing distress and improving psychological QoL in patients with lung disease, including pre-transplant patients. We previously demonstrated that coping skills training (CST), delivered to wait-listed, pre-lung transplant candidates was effective in reducing psychological distress and depression, as well as improving psychological QoL, and that improved coping and reduced distress mediated the beneficial effects of treatment. Similar benefits from CST were observed for COPD patients.

Exercise interventions also have been shown to reduce distress and improve depressive symptoms in a variety of clinical populations, including individuals with cardiovascular disease, heart failure, and COPD. Furthermore, there is growing evidence that exercise may be comparable to the benefits of antidepressant medications in reducing depressive symptoms and has the additional benefit of improving physiological biomarkers, which may improve long-term survival.

Despite evidence that exercise improves muscle strength and functional capacity in post-lung transplant patients, to our knowledge, no study has examined the impact of exercise on distress, psychological QoL, and medical outcomes in lung transplant recipients. In a study of COPD patients, we reported that greater levels of PA were associated with lower levels of depression, and that the relationship between elevated depressive symptoms and greater risk of adverse clinical events was mediated by low levels of PA. In addition, we found the improvements in functional status and PA were associated with improved event-free survival, independent of traditional clinical risk markers. These findings suggest that exercise may play an important role in improving functional capacity, increasing PA, and reducing distress, and that these improvements may result in clinical benefits among individuals with advanced lung disease.

Surprisingly, there have been few studies that have attempted to reduce distress and improve functional capacity in lung transplant recipients. The mPATH (Pocket Personal Assistant for Tracking Health) trial was a 1-year mobile health intervention RCT in post-transplant patients. While results showed that the mHealth participants performed self-monitoring more frequently, were more adherent to their medical regimens, and reported abnormal indicators more often to the clinical staff compared to usual care controls, there was no difference in mortality or hospitalizations and group differences in self-management behaviors were not maintained. Moreover, changes in psychological functioning or PA were not measured. These findings suggest that careful monitoring of self-management behaviors alone is not effective in sustaining behavior change or in improving medical outcomes.

The CST and exercise intervention (CSTEX) described in this protocol is a cognitive-behavioral approach to disease self-management that encourages more adaptive coping behaviors, promotes exercise and PA, and facilitates adherence to medical treatment recommendations. The study employs a RCT design,

but also embraces proof-of-concept trial philosophy in which we include comprehensive pre- and post-treatment evaluations of distress, functional status, and QoL measures, as well as health behaviors targeted by the CSTEX intervention.

Design & Procedures

This study is a parallel group randomized clinical trial in which up to 180 lung transplant recipients recruited from Duke University Medical Center will be randomly assigned with equal allocation to 12 weeks of Coping Skills Training combined with Exercise (CSTEX) or to Standard of Care plus Education (SOC-ED).

The CSTEX condition has two integrated components: the CST component will systematically train patients in the use of coping skills for stress reduction (i.e., training in relaxation, imagery, calming self-statements, cognitive restructuring, etc.) and promote key transplant-specific health behaviors (e.g., monitoring of pulmonary function, medical adherence, etc.). The EX component of the intervention will progressively increase participants exercise and promote daily physical activity (PA) through motivational interviewing strategies.

The CSTEX intervention will consist of 12, 30 min weekly sessions conducted by respiratory therapists knowledgeable about lung transplantation and trained in motivational interviewing (MI), Cognitive Behavioral Therapy (CBT), and exercise therapy. Consistent with social cognitive theory, initial sessions are designed to target daily exercise and focus on improving exercise self-efficacy by providing a rationale for exercise, instruction and goal setting (i.e., exercise prescription), identification and management of barriers to exercise, and assessment and reinforcement of exercise participation.

Each weekly session will be delivered via a telephone call to the study participant from the interventionist. This method decreases the burden associated with in-person appointments, eliminates travel expenses for patients living in rural areas, and permits outreach to individuals who may be less receptive to traditional mental health services.

Patients in the CSTEX group will also receive a Fitbit fitness wristband to self-monitor their activity levels. They will be asked to wear the Fitbit daily during the 12-week intervention, from rising in the morning until bedtime, when they will recharge the device overnight. Patients will download the Fitbit app onto their smartphone, allowing the Fitbit to transfer each patient's daily activity data to the Dashboard on the app. The interventionist will be able to monitor participants' exercise and physical activity remotely through the Fitbit Dashboard portal and will incorporate this information in their weekly sessions. Participants also will have access to the Dashboard so they will be able to self-monitor their performance. Fitbit data will be reviewed during each session and any issues will be addressed before addressing the scheduled topic area.

The standard home-based exercise prescription for post-transplant patients is identical to the current recommendations for adults and includes frequency, intensity, and duration – 30 minutes of moderate-vigorous intensity aerobic exercise (e.g., walking), 3-5 days/week for a total of 150 minutes each week.

This may be an aspirational goal that may not be realistic for all participants, so exercise prescriptions will be individualized based on their baseline activity levels, 6-minute walk distance, and resting heart rate (HR). For most participants, the aerobic exercise prescription will consist of 30 minutes of aerobic exercise at least 3 days/week at an intensity of 4-6/10 ('sort of hard' to 'hard') on the Modified Borg Rating of Perceived Exertion Scale, corresponding to a HR >60% max. These 30 min bouts of moderate-vigorous (MVPA) intensity exercise can be partitioned into several 10-15 min bouts per day or a single 30-min session.

As participants demonstrate self-mastery of exercise-related behavioral goals, the intervention focus will transition to emphasize elements of self-management theory. Coping skills to aid in the management of distress include training in relaxation techniques, cognitive restructuring, and problem solving. When indicated, relaxation and cognitive restructuring will be applied to the management of unpleasant physiological responses to exercise and problem solving strategies will be used to address barriers to exercise.

The SOC-ED condition provides support and enhanced post-transplant education. Patients in SOC-ED will also receive 12, 30 minute weekly telephone calls between the study participant and study educator. Patients in this group will be given detailed educational information about post-transplant care, the importance of medication adherence, and maintenance of physical activity. The calls will be conducted by trained staff knowledgeable about transplantation and skilled in educational instruction. The study educator will assist patients with self-management but they will not instruct patients in coping strategies or provide physical activity feedback. However, participants randomized to the SOC-ED intervention also will be provided with a Fitbit fitness wristband to self-monitor their own activity levels.

The telephone calls may be audio-recorded for training and quality control. The recorded sessions will be stored on a secure Duke server and only accessible to study key personnel. The recordings will be erased at the earliest possible time or by the end of the study.

Patients in both groups will be able to keep the Fitbit activity monitor. Randomized participants will also receive a t-shirt with the study logo.

All patients enrolled in this study will have completed 6 weeks of supervised exercise as part of mandatory post-transplant Pulmonary Rehabilitation before returning home and continue their standard medical care.

All participants will complete assessments at baseline, 12-weeks (post-intervention) and again at 1-year for a follow-up visit. Additionally, participants will be followed for up to 4 years for medical record review in which chronic lung allograft dysfunction, re-transplantation, and all-cause mortality will be assessed.

Specifically, assessments will include medical and medication adherence, a global measure of distress including stress, depression, anxiety and anger, functional capacity, frailty, activity levels, sleep, quality of life, coping, self-efficacy and health behaviors.

Patients will also be asked for their permission to have their photograph taken, allowing study staff to better remember each participant. The photos will be stored on a secure Duke server and only accessible to study key personnel.

Study participants will also receive a holiday card from study staff. These cards are intended to acknowledge the participants' continued study participation and to aid with retention. All participants who receive cards are consented and have willingly provided their contact information. The messages within the cards will be standard holiday greetings, "Best wishes for a joy-filled holiday season", "Season's Greetings", "Happy Holidays", "May every joy of the holiday season be yours", "A warm holiday wish for peace, cheer, and happiness and all the best for the coming new year".

Demographic, Medical history information, and Adherence

We will characterize each patient according to background and medical characteristics. Background information will include age, native disease, duration of illness, employment status prior to transplant, education, marital status, and history of substance use. Medical characteristics will assess both current level of functioning and data from the transplant-hospitalization, which have been associated with differential risk of clinical events. Current medical status variables are routinely collected through clinical care and will be obtained from electronic medical records. These will include pulmonary function testing, gas exchange, 6MWD at the completion of pulmonary rehabilitation, and body-mass index. Pulmonary function testing procedures are performed in accordance with guidelines established by the American Thoracic Society. Transplant-related data will include type of transplant (bilateral, unilateral), presence of grade 3 primary graft dysfunction at 72 hours following transplant, length of transplant-hospitalization, use of mechanical ventilator support, perioperative use of extracorporeal membrane oxygenation (ECMO), and neutrophil count from bronchoalveolar lavage (BAL) fluid.

Medical adherence is a critical aspect of patient management and ultimately clinical outcomes. Therefore, we will assess both general medical adherence and medication adherence:

1) Medical Adherence. Adherence to medical regimen will be assessed using the Health Habits Survey (HHS). The HHS is a self-report measure of behavioral compliance that uses an ordinal response format to determine post-transplant adherence in 10 areas: (i) taking medications in general; (ii) taking the primary immunosuppressant (IS; cyclosporine or tacrolimus); (iii) attending clinic appointments; (iv) completing blood work; (v) monitoring home blood pressure, (vi) following a prescribed diet; (vii) following the prescribed exercise plan; (vii) abstaining from tobacco use; (ix) limiting alcohol consumption; and (x) performing home spirometry. Responses for each element will be adjudicated based on the minimum level acceptable according to programmatic guidelines set forth by our study pulmonologists. To estimate overall adherence, elements are summed for a total score (range 0-10).

2) Medication Adherence. Because medication adherence is critical to the success of solid organ transplantation, we will rely on biologic markers of medication adherence. In addition to our self-report assessment of medication adherence, we will validate participants' self-reported adherence levels using blood assays, which are routinely obtained in our transplant clinics. Blood assay markers for tacrolimus (FK) and cyclosporine (CsA) are performed at each clinic visit using a therapeutic range for each drug based on clinical guidelines (e.g., CsA: 100–150 ng/mL and FK: 5–10 ng/mL for most patients). Trough blood level results will be combined using the non-therapeutic blood assay variability of FK and CsA, in which the percentage of sub- or supra-therapeutic FK / CsA assays are calculated by dividing the number

of assays outside individually determined, recommended levels divided by the total number of FK / CsA assessments taken. Blood levels assessed >3-months following transplant will be used for baseline assessments, in order to allow for individual variability in initial metabolic adaptation to postoperative medication changes.

No blood will be drawn as part of the study.

Global psychological distress will be measured using a battery of questionnaires composed of composed of BDI-II, GHQ, STAI, PSS, and PROMIS Anger;
1. Depression will be measured using the Beck Depression Inventory (BDI-II). The BDI-II is a 21-item self-report inventory of depression that assesses the current degree of depression through items pertaining to affective, cognitive, motivational, and physiologic areas of depressive symptomatology.
2. General Distress will be measured using the General Health Questionnaire (GHQ). The GHQ is a 60-item screening questionnaire for nonpsychotic psychiatric disorders. It assesses somatic symptoms, anxiety, social dysfunction, and depression. The GHQ has been shown to be modifiable with treatment and predictive of adverse events.
3. Perceived Stress will be measured by the Perceived Stress Scale (PSS). The PSS consists of 10 items that are evaluated on a 5-point Likert scale. The items on the PSS tap the degree to which individuals feel that events in their lives are unpredictable and uncontrollable.
4. Anxiety will be measured by the State Trait Anxiety Inventory-State (20-item) version of the STAI. The STAI was developed as a tool for investigating anxiety in normal (non-psychiatric) adults, but has been used in assessing anxiety in neuropsychiatric, medical, and surgical patients.
5. Patient-Reported Outcomes Measurement Information System (PROMIS) Anger will be used to assess anger, which may be an important aspect of distress. The 8-item PROMIS Anger scale assesses several dimensions of anger with higher scores indicating greater anger.

Functional capacity will be measured by performance (i.e., distance walked) on the Six Minute Walk Test (6MWT). This procedure is a commonly performed test of functional capacity and is a functional measure of disease severity in patients with moderate to severe respiratory impairment. The 6MWT is a self-paced, timed test of the total distance that a patient is able to walk in 6 minutes. A trained technician will ensure the test is administered in a reproducible manner per the American Thoracic Society Guidelines. Pulse oximetry also will be utilized to provide a measure of oxygen saturation (SpO2) during the procedure. Although distance achieved at 6 min is the primary measure in the 6MWT, we will also record symptoms and heart rates at rest and at 6 minutes and record oxygen utilization and desaturations throughout the procedure.

Frailty will be measured by performance on the Fried Frailty Index. This assessment includes the following criterion: patient's weight, exhaustion level, physical activity, walking speed, and hand grip strength. Patients will be asked if they have experienced unintentional weight loss of more than 10 lbs, in the past year. Patients will rate the following 2 statements from 0-3; "I felt that everything I did was effort" and "I could not get going". Additionally, patients will be asked "How often in the last week did you feel this way?". Patients will answer questions regarding which activities that participated in within the last month. Patients will complete a 15-second 'get up and go' test in which their walking speed will be measured. Lastly, patients will complete a hand grip strength test using a hand held dynamometer.

Additional assessments will include measures of clinical outcomes, physical activity, sleep, quality of life, and coping and self-efficacy, social support and health habits.

1. The main clinical/medical endpoint will be a composite measure of CLAD-free survival (CLAD and all-cause mortality). Patients' medical records will be reviewed semi-annually and within 3-weeks following the anniversary of each patient's baseline study assessments. Patients are followed closely by each of the enrolling transplant centers for their lifetime after lung transplantation facilitating accurate assessment of these medical events. Events will be adjudicated by our pulmonologists using standard criteria for CLAD. Data with regards to survival, re-transplant, and CLAD are maintained accurately at each center and reported regularly to the United Network of Organ Sharing (UNOS). Records of outside hospitalizations are incorporated into the electronic record of the enrolling center. We will use information from a range of sources to populate a secure Redcap database (https://redcap.duke.edu/redcap/) with clinical follow-up forms. If the patient is no longer being seen at Duke, we will acquire their records from their local pulmonary provider; death data are available to the respective transplant programs through the UNOS. Documentation of patient mortality will include verification through the acquisition of hospital and Emergency Medical Services records.
2. Physical activity will be assessed using the Actigraph GT9X Link (ActigraphTM Corp., Pensacola, FL). The GT9X is a small, lightweight, rechargeable device that uses a 3-axis accelerometer, with motion sampled at a frequency of 30-100 Hz. It will be worn on the wrist, with time-of-day display active (but activity data display inaccessible) for 24 hours per day, over 7 consecutive day's pre-randomization and again 7 days post-intervention, as well as 7 days as part of the 1-year follow-up. Self-reported physical activity will be measured with the Godin Leisure-Time Exercise Questionnaire.
3. Sleep quality will be assessed with the Actigraph watch over the same 7-day periods as described above. The sleep parameters of primary interest will be average daily sleep duration, sleep efficiency, and sleep fragmentation index. In addition, to these objective measures of sleep quality, we also will assess subjective sleep times and quality over the 7 days of actigraphy monitoring, using the Consensus Sleep Diary Core and participants will also complete the Pittsburgh Sleep Quality Index (PSQI).
4. Quality of Life (QoL) will be assessed using the Lung Transplant Quality of LIfe Survey. This questionnaire assesses symptoms, health perceptions, functioning, and well-being of patients post lung transplantation.
5. Coping and Self Efficacy will be measured using the COPE Inventory and General Self-Efficacy Scale, respectively. The COPE Inventory is composed of five scales that measure problem-focused coping, five scales that measure emotion-focused coping, and three scales that measure less useful coping responses. The General Self-Efficacy Scale is a 10-item scale which measure emotional distress.
6. Social Support will be measured through the Perceived Social Support Scale (PSSS). The PSSS is a 12-item questionnaire.
7. Health habits post transplant will be assessed by the Health Habits Assessment Questionnaire which is a 23-item scale designed to measure follow-up treatment post lung transplantation.
8. Post-intervention, participants will complete a 12-item survey assessing their perceived changes in mood and behavior as a result of completing the study intervention.
9. Concurrent therapy will be assessed with a brief 3-item questionnaire assessing medication use and/or any counseling the participant may receive while participating in the study. This questionnaire will be administered post-intervention and at the 1-year follow up.

All assessments will be completed by study staff. Patients will complete questionnaires online via RedCap. No study scheduling with occur through Maestro Care.

Selection of Subjects

Inclusion Criteria: Men or women aged 18 years or older; single or bilateral first lung transplant recipient; discharged from the hospital and at least 6 weeks post-transplant; completed post-transplant pulmonary rehabilitation within the past 18-months; on a stable medication regimen; and proficient in the English language.

Exclusion Criteria: Illness such as malignancies that are associated with a life-expectancy of < 12 months; current pregnancy; inability to read or to provide informed consent (e.g., due to dementia), multi-organ transplant recipient or repeat lung transplant. Patients >80 yrs are typically ineligible for transplant.

A waiver of inclusion criteria was requested for a single patient who completed post-transplant pulmonary rehab on March 1, 2019. The participant lives out of state and his next visit to Duke is scheduled for March 9, 2020. If approved, this patient's schedule would then allow them to enroll in our study and complete assessments on March 9, 2020, 8 days past the 1-year window.

The participant appears to meet all other study inclusion criteria and their participation in a study designed to determine the effectiveness of an exercise and coping skills intervention for post-lung transplant recipients would likely only be beneficial and not place the patient at any increased risk or harm. Additionally, this protocol is minimal risk.

Subject Recruitment and Compensation

As described above, patients will be recruited from the pulmonary programs at Duke University Medical Center within 18 months of completing the post-transplant rehabilitation program. The study will initially be introduced to potential participants through the pulmonary rehab staff at each medical facility, their collaborating transplant coordinator or pulmonologist in-person/verbally or with an informative IRB approved letter mailed to the patient inviting them to contact study staff and learn more.

The Duke patient population is predominantly Caucasian, due to underlying disease leading to transplant, with over half the recipients having IP and last year Duke completed 104 lung transplantations. Thus, there will be an ample recruitment base for potential participants.

Participant compensation will total $300 each for the 180 randomized participants. Payments will occur in installments and include the following: $25 for screening, $75 for completion of baseline assessments, $100 for completion of the 3-month intervention, and $100 for the 1-year follow-up visit.

Risk/Benefit Assessment

The primary risks of this study are minimal and are primarily associated with confidentiality. There is some risk attendant to confidentiality of self-report data. In order to ensure confidentiality of data, all records will be identified by the patient's identification number, not by name. All raw data will be kept in a locked file cabinet. Although several previous psychosocial interventions may be associated with increased risk, we believe that it is unlikely that this treatment will be harmful to patients. Nevertheless, we will carefully monitor symptoms and refer those patients with high levels of depression or distress for treatment.

All patients enrolled in the study will continue to take all of their prescribed medications. The risk of serious injury due to study participation is negligible. All measurement techniques have been used extensively by the investigative team without a single adverse event. Nonetheless, we are aware that the lung transplant recipient can be characterized by unstable health. Procedures for protecting subjects against potential risks include screening procedures, a brief physical examination by the study pulmonologist who also will be available to attend to any acute medical issues when patients are in treatment with the interventionists. Patients possibly requiring immediate medical care will be contacted for further evaluation by members of the research team who also may be their healthcare providers at the transplant clinics in the DUMC. However, study personnel will not be involved in the ongoing medical care of participants. Patients will be referred to their local physicians when needed.

We also will take special precautions to ensure the safety of patients with clinically significant depression, i.e., patients with BDI-II scores >29 (moderate-severe depression) or who are actively suicidal. Although we are not pre-selecting transplant recipients based upon their level of distress or depressive symptoms, our assessments may determine the presence of significant clinical depression. In the unlikely event that patients are determined to be actively suicidal, they will be queried for suicidal plans, intent and past suicidal behaviors. Those with current active suicidal ideation, history of suicidal acts within the past 12 months, or bipolar disorder or psychosis will not be enrolled in the study and appropriate referral or admission procedures will be initiated. If a patient exhibits moderate-severe depression (e.g., BDI-II >29) at baseline, we will inform the participant and, with his or her permission, notify the treating pulmonologist. During the 12-week treatment phase, any patient who is determined to be actively suicidal over the course of the trial will be referred for psychiatric evaluation and possible hospital admission. If they are found to be at immediate risk, emergency procedures will be followed including requesting an ambulance to take the patient to the emergency department (ED) for immediate evaluation and treatment.

This study has several potential benefits. First, patients receiving CSTEX may learn coping skills that may significantly decrease symptoms of distress, improve their quality of life, and potentially reduce their pulmonary-related hospitalizations and increase their survival. Second, patients in SOC-ED may benefit from a better understanding of their condition and its management. Third, this study will also explore individual differences that may be related to improvements in distress and clinical outcomes. For example, older patients, women, or patients with a particular native disease may be more likely to benefit from treatment. This may make it possible to identify lung transplant patients who are most likely to respond well to CSTEX.

If a potential participant chooses to not participate, information on exercise and coping mechanisms can be acquired through their pulmonologist or staff from the PR program.

Data Analysis & Statistical Considerations

The primary endpoint will be a global measure of distress. Secondary outcomes will include measures of functional capacity, coping, self-efficacy, PA, health behaviors, frailty, and medical outcomes (i.e., CLAD), the latter of which will be documented by annual follow-up visits of up to 4 years (median >2 years).

All analyses will follow the intention-to-treat (ITT) principle, including all patients who were randomized. Patterns of missing data will be characterized using Rubin's criteria and managed accordingly using Harrell's multiple imputation (mult.impute) procedure in R. We will supplement the ITT analysis with an examination of the treatment effect among completers using Rubin's Complier Average Causal Effect (CACE) model.

We will test our primary hypotheses using the "gatekeeper" approach, which has been shown to maintain the experiment-wise error rate while maximizing power when testing multiple endpoints. This type of methodology has been widely advocated in RCTs involving medical populations as a parsimonious strategy to control type-I error within the first (i.e. "gatekeeper") step, because a favorable result on any individual component observed by chance is unlikely to be overly influential to the composite as a whole. Because the type-I error is minimized at this stage of analysis, the familywise error rate can then be propagated to the second analysis stage, examining individual components. In contrast, error correction to individual components of the composite often over-controls for type-I error when the purpose is explanatory. In order to mitigate Type-I error with multiple outcomes, we will partition the conventional alpha = .05 to test treatment effects on Global distress and Functional capacity each at alpha = .025. Thus, for our examination of global distress changes, an experiment-wise p-value of .025 will be used to assess significance. If this test fails to be rejected at p-value < .025, then tests of individual components are not interpreted. However, if improvements in global distress are found, examination of changes in individual components of distress are carried out in a secondary, explanatory step. Consistent with contemporary recommendations, secondary outcomes will be considered as potentially supportive and therefore examined at the alpha = .05 for each domain.

With respect to changes in global distress, we estimated power using a correlation of 0.53 between covariates and the outcome, an initial sample size of 150 participants (amended to up to 180 participants), attrition of 15%, and an alpha of 0.025. Based on these assumptions, we will have 80% power to detect a small-to-moderate treatment size difference (d = 0.44), comparable to what we observed in our prior work among pre-transplant candidates. For changes in functional capacity and PA, we should have 80% power to detect even small differences in 6MWD (d = 0.21) and total daily actigraphy steps (d = 0.32). As an exploratory aim, we also will examine the impact of CSTEX on clinical outcomes. Power for our exploratory clinical event models was estimated assuming a conservative event rate of 75% in the control group, 42 months for patient accrual, a median follow-up of 30 months and a minimum follow-up time of 6 months. At an alpha of 0.05, and 75 patients per group, we will have

80% power to detect a 64% event rate reduction. We will carefully examine all model assumptions and reparameterize as indicated. All analyses will be carried out using SAS (Cary, NC) or R (http://cran.r-project.org/) software.