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Remote Therapy to Improve Outcomes in Lung Transplant Recipients: Design of the INSPIRE-III Randomized Clinical Trial

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Background. Impaired functional capacity and emotional distress are associated with lower quality of life (QoL) and worse clinical outcomes in post lung transplant patients. Strategies to increase physical activity and reduce distress are needed. **Methods.** The Investigational Study of Psychological Interventions in Recipients of Lung Transplant-III study is a single site, parallel group randomized clinical trial in which 150 lung transplant recipients will be randomly assigned to 3 months of telephone-delivered coping skills training combined with aerobic exercise (CSTEX) or to a Standard of Care plus Education control group. The primary endpoints are a global measure of distress and distance walked on the 6-Minute Walk Test. Secondary outcomes include measures of transplant-specific QoL, frailty, health behaviors, and chronic lung allograft dysfunction-free survival. **Results.** Participants will be evaluated at baseline, at the conclusion of 3 months of weekly treatment, at 1-year follow-up, and followed annually thereafter for clinical events for up to 4 years (median = 2 y). We also will determine whether functional capacity, distress, and health behaviors (eg, physical activity, medication adherence, and volume of air forcefully exhaled in 1 second (FEV1), mediate the effects of the CSTEX intervention on clinical outcomes. **Conclusions.** Should the CSTEX intervention result in better outcomes compared with the standard of care plus post-transplant education, the remotely delivered CSTEX intervention can be made available to all lung transplant recipients as a way of enhancing their QoL and improving clinical outcomes.

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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.¹ Due to the growing number of individuals with advanced lung disease, the frequency of transplantation has increased exponentially during the past 2 decades, with nearly 42 000 patients having been transplanted; >2500 individuals were

transplanted in 2016 and is projected to continue to increase in the future.²

Despite the increasing acceptance of lung transplantation as a treatment resulting in improved short-term survival, the median overall survival remains ~6 years,³ with only 26% of patients surviving to 10 years, which is markedly less than other solid organ transplants.⁴ Greater post-transplant

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mortality is primarily due to chronic lung allograft dysfunction (CLAD) as defined by a progressive decline in lung function. Even early post-transplantation has high morbidity, with as many as 4 out of 5 patients being rehospitalized within a year after transplant.^{5,6} This high health resource utilization results in compromised QoL and a significant economic burden to the patient, family, and healthcare system. Indeed, the importance of patients' QoL has received growing attention as a marker of transplant success beyond just survival.⁷⁻⁹ Psychological distress can adversely affect recovery and impair QoL,¹⁰ while lack of regular exercise after lung transplantation is common, despite improved lung function.^{11,12}

While lung transplantation extends survival and improves functional capacity for most patients, surprisingly, mental health QoL does not necessarily improve after transplant and actually may worsen over time.¹³ 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 post-traumatic stress disorder.¹⁴ Indeed, a recent systematic review found that psychological QoL declines over time.¹⁵ Moreover, in a systematic review of psychological functioning following cardiothoracic transplantation, Dew and DiMartini¹⁶ 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.

Indeed, few predictors of long-term clinical outcomes among lung transplant recipients have been identified.¹⁷ Lung allocation scores, which are used to prioritize candidates for donor lungs, are based on risk of death without a transplant and short-term survival after transplant; however, the lung allocation score only uses objective pretransplant factors including age, native disease, and disease severity, which are poorly predictive of longer-term outcomes after transplant.¹⁸ Recent evidence suggests that biobehavioral factors, particularly physical activity (PA) and psychological distress, may offer important prognostic information and may be modifiable with treatment.¹⁹⁻²¹

Physical Activity

Poor 6-minute walk distance (6MWD) before transplant is one of the strongest predictors of pulmonary-related hospitalization²⁰ and post lung transplant mortality,^{22,23} and objectively measured, leisure-time PA is more strongly associated with all-cause mortality among patients with pulmonary disease than traditional prognostic indices.²⁴ Although regular aerobic exercise is recommended for lung recipients in the first year after transplant, most patients discontinue regular exercise on returning home following transplant, averaging 50% lower PA compared with healthy controls.²⁵

There is now good evidence that greater functional status and higher levels of PA are associated with improved survival among patients with end-stage lung disease, including lung transplantation.^{22,26-29} Despite the importance of PA in patients with pulmonary disease, relatively few studies have examined PA after lung transplantation.^{30,31} 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,³² with a continued decline at 1 year, placing

their PA level well below population norms.²⁵ In addition, PA has been associated with preserved graft functioning in other transplant populations,^{33,34} and physical inactivity appears to worsen lung function,³⁵⁻³⁷ increasing the risk of poorer clinical outcomes.^{38,39} Moreover, evidence from small, pilot studies suggests that exercise can improve functional capacity in lung transplant recipients.⁴⁰ Taken together, these data provide a strong rationale for the importance of regular aerobic exercise and increased PA as a way to improve long-term outcomes in lung transplant recipients.

Psychological Distress

There is also growing evidence that many patients experience significant psychological distress and poor psychological QoL following transplant, despite improvements in physical QoL.^{9,13,41} Lung transplant recipients exhibit a slower return to normal psychological functioning compared with other solid organ transplant recipients,⁴² and, surprisingly, it has been reported that psychological QoL fails to improve significantly following transplant,¹³ particularly among older patients.⁹ These data are important because elevated levels of psychological distress are associated with a variety of adverse events in transplant recipients, including CLAD⁴³ and all-cause mortality,⁴⁴ even after accounting for other clinical predictors. For example, in a study of 155 transplant recipients followed up to 15 years after transplant, Rosenberger et al⁴³ found that depression assessed 1 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. Similar findings in a sample of 132 lung transplant recipients assessed 6 months following transplantation demonstrated that greater psychological distress and depression, even at subclinical levels, were predictive of elevated mortality rates.⁴⁵ 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.⁴⁴ These findings were confirmed in a small prospective study of 66 lung transplant recipients: greater depressive symptoms assessed 2 weeks after transplantation were strongly predictive of survival over a 3-year follow-up, independent of perioperative medical outcomes (eg, length of hospital stay and primary graft dysfunction).⁴⁶ Similar results have been reported in other solid organ recipients. For example, DiMartini et al reported that depression following liver transplant more than doubled the risk of mortality,⁴⁷ and found that 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 with nondepressed patients.²¹

Previous trials have demonstrated that behavioral interventions are effective in reducing distress and improving psychological QoL in patients with lung disease,⁴⁸⁻⁵¹ including pretransplant patients.⁵² For example, coping skills training (CST), delivered to waitlisted prelung transplant candidates, has been shown to be effective in reducing psychological distress and depression, as well as to improve psychological QoL; further, improved coping and reduced distress mediated the beneficial effects of treatment.⁵²

Exercise interventions also have been shown to reduce distress and improve depressive symptoms in a variety of clinical populations,⁵³⁻⁵⁷ including individuals with cardiovascular

disease,⁵⁸ heart failure,⁵⁹⁻⁶¹ and chronic obstructive pulmonary disease.⁶² Furthermore, there is growing evidence that exercise may be comparable to the benefits of antidepressant medications in reducing depressive symptoms^{56,58} and has the additional benefit of improving physiological biomarkers,^{58,63-65} which also may contribute to long-term survival.⁶⁶

Despite evidence that exercise improves muscle strength and functional capacity in post lung transplant patients,^{40,67} to our knowledge, few studies have examined the impact of exercise on distress, psychological QoL, and clinical outcomes in lung transplant recipients.³⁸ In a study of chronic obstructive pulmonary disease patients, higher levels of PA were associated with lower levels of depression, and the relationship between elevated depressive symptoms and greater risk of adverse clinical events was mediated by low levels of PA.¹⁹ In addition, improvements in functional status and PA were associated with improved event-free survival, independent of traditional clinical risk markers.²⁰ These findings suggest that exercise may play an important role in improving functional capacity, increasing PA, and reducing distress.

Surprisingly, there have been few studies that have attempted to reduce distress and improve functional capacity in lung transplant recipients. The mobile Pocket Personal Assistant for Tracking Health trial was a 1-year mobile health intervention randomized clinical trial (RCT) in post-transplant patients.⁶⁸ While results showed that the mobile health participants initially performed self-monitoring more frequently, were more adherent to their medical regimens, and reported abnormal indicators more often to the clinical staff compared with usual care controls, group differences in self-management behaviors were not maintained and there was no difference in mortality or hospitalizations.^{68,69} 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. Investigational Study of Psychological Interventions in Recipients of Lung Transplant-III (INSPIRE-III) employs a RCT design, but also embraces proof-of-concept trial philosophy in which comprehensive pretreatment and post-treatment evaluations of distress, functional status, and QoL measures, as well as health behaviors targeted by the CST combined with exercise (CSTEX) intervention are performed. Figure 1 displays a conceptual model by which CSTEX aims to reduce distress and increase functional capacity, thereby improving key prognostic factors that independently impact QoL and clinical outcomes.

Promoting regular exercise and enhancing coping skills are 2 approaches that have been shown to reduce psychological distress, improve QoL, and increase functional capacity in patients with a variety of chronic conditions.^{48,52,61,70-72} However, despite data showing that psychological distress and physical inactivity are common in post-transplant patients, and are independently predictive of worse clinical outcomes, these strategies have not been integrated into the management of transplant recipients and, to our knowledge, no studies have targeted distress, low functional capacity, and physical inactivity in post lung transplant recipients. The resulting gap in our knowledge represents an important, unmet need to evaluate interventions designed to reduce psychological distress, improve functional capacity, and increase regular exercise in lung transplant recipients, to improve their psychological QoL, functional capacity, and ultimately, clinical outcomes.

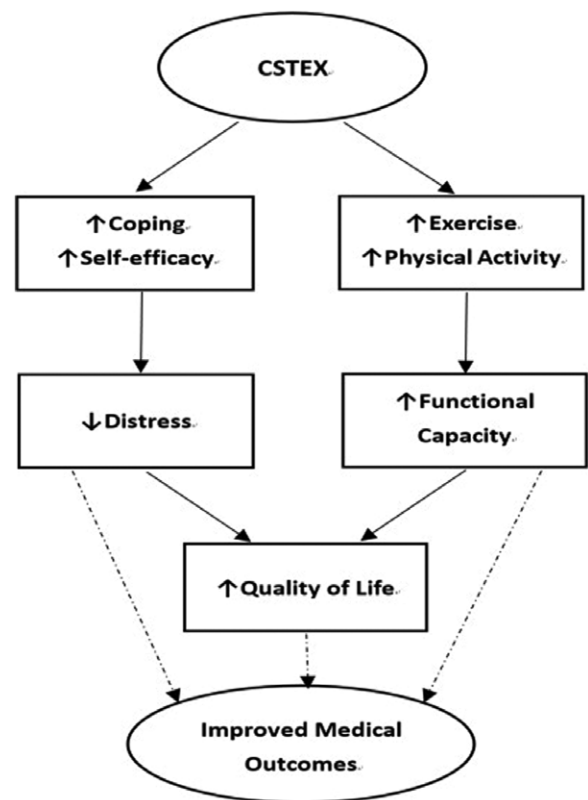


FIGURE 1. A conceptual model illustrates how CSTEX may reduce distress and increase functional capacity, resulting in improved quality of life and better clinical outcomes. CSTEX, Coping Skills Training combined with Exercise.

CLINICAL TRIAL DESIGN

INSPIRE-III is a single site, parallel group RCT in which 150 lung transplant recipients will be randomly assigned with equal allocation to 12 weeks of CSTEX or to Standard of Care plus Education (SOC-ED). Native Disease (cystic fibrosis versus non-cystic fibrosis) and sex (male versus female) will be used as stratification variables. The CSTEX protocol will have 2 integrated components: the CST component will systematically train patients in the use of coping skills for stress reduction (eg, training in relaxation, imagery, cognitive restructuring, etc) and promote key transplant-specific health behaviors (eg, monitoring of pulmonary function, medical adherence, etc). The EX component of the intervention will progressively increase participants exercise and promote daily PA through motivational interviewing (MI) strategies used previously.⁶¹ Patients in the SOC-ED condition also will receive 12 weekly sessions that will provide support and enhanced post-transplant education. The primary endpoints will be a global measure of distress and 6MWD to quantify functional capacity. Secondary outcomes will include measures of frailty, PA, sleep and health behaviors, and medical outcomes (ie, CLAD), the latter of which will be documented by annual medical record review for up to 4 years (median >2 y).

Patient Selection

The study sample will consist of 150 recent (<1 y) lung transplant recipients from a single center. All patients who have undergone a lung transplant within the past year will be contacted by e-mail and invited to participate in the trial.

Inclusion Criteria

Men or women aged 18 years or older; single or bilateral first lung transplant recipient; discharged from the hospital for a minimum of 6 weeks; completed post-transplant PR within the past year; and on a stable medication regimen.

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 (eg, due to dementia); multiorgan transplant recipient or repeat lung transplant.

Interventions

CST Combined With Home-Based Exercise

The CSTEEX intervention will consist of 12 weekly sessions, delivered remotely, and conducted by respiratory therapists knowledgeable about lung transplantation and trained in MI, cognitive behavior therapy, and exercise therapy (Table 1). Remote or distance therapy refers to the use of telemedicine or e-health approaches to treating patients outside the conventional in-person office-based visit. The CSTEEX intervention will be delivered over the telephone in patients' home environment. Remote therapy 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. The theoretical underpinnings of the CSTEEX intervention reflect prior work grounded in social cognitive theory,⁷³⁻⁷⁶ self-management strategies,⁷⁷⁻⁸³ and MI techniques^{61,77} that have been adapted for post lung transplant recipients to address our proximal goals of (1) increasing functional capacity and (2) reducing psychological distress. The CSTEEX intervention will use MI principles, using client-centered, collaborative engagement with reflective listening, validation, and elicitation of change talk.^{78,79,84} Consistent with social cognitive theory,^{74,75} 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 (ie, exercise prescription), identification and management of barriers to exercise, and assessment and reinforcement of exercise participation from real-time Fitbit monitoring. Fitbit data will be used to guide individually tailored goals, calibrated to maximize early success and adoption of exercise. Fitbit data will be reviewed during each session and any issues will be addressed before addressing the scheduled topic area.

As participants demonstrate self-mastery of exercise-related behavioral goals, the intervention focus will shift to emphasize elements of self-management theory.^{81,85-87} Coping skills to aid in the management of distress include training in relaxation techniques, cognitive restructuring, and problem solving.

Exercise Prescription

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 (eg, walking), 3–5 d/wk for at least 150 minutes each week, flexibility exercises, and muscle-strengthening activities that involve all major muscle groups 2 or more days a week.⁸⁸ This is an aspirational goal that may not be realistic for all participants, so that exercise prescriptions will be individualized based on their baseline PA levels, 6MWD, and resting heart rate (HR). For most participants, the aerobic exercise prescription will consist of 30 minutes of aerobic exercise at least 3 d/wk 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.

Use of Fitbit Technology

Participants will be provided with a Fitbit Inspire HR (Fitbit Group Health, San Francisco, CA) fitness wristband activity and HR monitor. 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. Participants will be instructed to perform the data-sync process at least once daily. While this commercially available device lacks the precision of the Actigraph GT9X Link, the more user-friendly Fitbit will provide reasonable estimates of bouts of moderate to vigorous PA (MVPA) and overall daily PA. Importantly, it has been shown to successfully strengthen PA interventions,⁸⁹ encourage the use of theory-driven self-regulation skills,⁹⁰ and will serve to increase participant motivation by providing feedback and enhancing participants' accountability. The interventionists will be able to monitor participants' daily MVPA exercise (of bouts >10 min) and PA 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.

TABLE 1.
INSPIRE-III weekly topics for the CSTEEX and SOC-ED interventions

Week	CSTEEX topic	SOC-ED topic
1	Introduction and overview	Introduction and overview
2	Exercise and physical activity	Infection prevention
3	Adherence: pulmonary function, medications, and diet	General medication guidelines
4	Stress	Importance of medication adherence
5	Relaxation training I	Monitoring pulmonary function
6	Relaxation training I and imagery	Post-transplant complication and management
7	Cognitive strategies I	Management of possible transplant-related medical issues
8	Cognitive strategies II	Stress
9	Values clarification and time management	Sleep
10	Communication and social support	Nutrition and transplant patients
11	Problem solving	Maintaining your exercise program and an active lifestyle
12	Review and summary	Review and summary

CSTEEX, Coping Skills Training combined with Exercise; INSPIRE-III, Investigational Study of Psychological Interventions in Recipients of Lung Transplant; SOC-ED, Standard of Care plus Education.

Training and Supervision of Respiratory Therapists

The training protocol integrates skills practice with real-time constructive feedback. The training of the respiratory therapists will be trained and supervised by experienced clinical psychologists (D.C.M. and F.J.K.). Interventionists will summarize the progress of therapy during weekly supervision sessions and specific problems will be addressed. In addition, clinical competence and adherence will be monitored by weekly review of contact logs and by regular review of audio-taped intervention sessions. Similarly, the SOC-ED sessions delivered by the health educators will be audiorecorded for review by our medical team to confirm that the intervention adheres to the manualized protocol.

Standard of Care and Education Comparison Group

Patients in the standard of care and lung transplant education condition (SOC-ED) will receive their standard medical care and, in addition, will receive twelve 30 minutes weekly calls for support and enhanced education about transplantation. During these calls, patients will be given detailed educational information about post-transplant care, the importance of medication adherence, and maintenance of PA (see Table 1 for list of educational topics). Participants randomized to the SOC-ED intervention also will be provided with a Fitbit to self-monitor their PA. Health educators will deliver the education module and assist patients with self-management but they will not instruct patients in coping strategies or provide PA feedback. Previous study has shown that self-management interventions alone may improve self-care, but do not reduce distress or improve survival.⁶⁸

Assessments

Assessments will include the 6-Minute Walk Test (6MWT), PA using actigraphy, pulmonary function, and a psychometric and behavioral battery consisting of a global measure of distress including stress, depression, anxiety, and anger; transplant QoL, frailty, coping, and self-efficacy. The psychological measures will be administered at 3 time points: baseline, 12 weeks, and 1-year follow-up. Participants will receive a link to complete the questionnaires online through Research Electronic Data Capture (REDCap). REDCap is a secure, web-based application designed to support data capture. At each time point, study participants receive a link to complete the questionnaires online. Through this web-based application, study staff are able to monitor the participants progress, send reminders to complete the questionnaires as needed, as well as verify when the questionnaire battery is complete. Because medical adherence is a critical aspect of patient management and ultimately clinical outcomes, both general medical adherence and medication adherence will be assessed. Specifically, adherence to medical regimen will be assessed using the Health Habits Survey.^{91,92} The Health Habits Survey is a self-report measure of behavioral compliance that uses an ordinal response format to determine post-transplant adherence such as taking medications in general and primary immunosuppressants, attending clinic appointments, performing home spirometry, and abstaining from tobacco use and limiting alcohol consumption. Following convention,⁹¹ 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).

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. 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 (eg, CsA: 100–150 ng/mL and FK: 5–10 ng/mL for most patients). Consistent with previously established methods,^{93,94} trough blood level results will be combined using the nontherapeutic blood assay variability of FK and CsA, in which the percentage of subtherapeutic or suprathreshold 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, to allow for individual variability in initial metabolic adaptation to post-operative medication changes.

The primary endpoints for INSPIRE-III include (1) psychological distress and (2) functional capacity (6MWD).

1. Psychological distress: The global measure of distress will consist of a combined score from 5 separate instruments, which have been found to (a) capture different aspects of distress, (b) predict clinical events, and (c) be modifiable with treatment.⁹⁵
 - a. 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.⁹⁶
 - b. 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.⁹⁷ The GHQ has been shown to be modifiable with treatment and predictive of adverse events.^{98,99}
 - c. 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.¹⁰⁰ The items on the PSS tap the degree to which individuals feel that events in their lives are unpredictable and uncontrollable.
 - d. Anxiety will be measured by the State Trait Anxiety Inventory-State (20-item) version of the STAI.¹⁰¹ The STAI was developed as a tool for investigating anxiety in normal (nonpsychiatric) adults, but has been used in assessing anxiety in neuropsychiatric, medical, and surgical patients.
 - e. Patient-Reported Outcomes Measurement Information System (PROMIS) Anger will be used to assess anger, which may be an important aspect of distress.¹⁰² The 8-item PROMIS Anger scale assesses several dimensions of anger with higher scores indicating greater anger.
2. Functional capacity: Functional capacity will be quantified as the distance walked on the 6MWT.^{23,103} 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 and is a reliable and sensitive index of change in functional ability following

treatment that is prognostic of clinical outcomes.¹⁰⁴ The 6MWT is a self-paced, timed test of the total distance that a patient is able to walk in 6 minutes.

We will have several secondary endpoints, including a measure of CLAD-free survival (CLAD and all-cause mortality). Patients' medical records will be reviewed semiannually and within 3 weeks following the anniversary of their baseline study assessments. Events will be adjudicated by our pulmonologists using standard criteria for CLAD.¹⁰⁵ Data with regards to survival, retransplant, and CLAD are routinely obtained as part of regular clinic follow-up. Records of outside hospitalizations will be incorporated into the electronic record and information from a range of sources to populate a centrally managed Redcap database (<https://redcap.duke.edu/redcap/>).

PA will serve as another secondary endpoint and will be assessed using the Actigraph GT9X Link (Actigraph 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 days prerandomization, and again for 7 days postintervention. The total weekly minutes of MVPA will be the primary GT9X-based outcome measure, with secondary outcome measures including average daily cumulative step count and average daily energy expenditure (kcal/d), derived using the Actigraph Actilife software.^{106,107}

The actigraph also will be used to assess sleep quality, derived from the wrist-worn GT9X actigraphy data obtained during the nighttime sleep periods over the 7-day preintervention/postintervention PA assessment protocol described above. The sleep parameters of primary interest will be average daily sleep duration (calculated by subtracting all periods of wakefulness from the time spent in bed) and sleep efficiency (defined as the ratio of total sleep time divided by time spent in bed).^{108–110} Additional measures will include sleep fragmentation index (a measure of the restlessness of sleep, defined as the sum of 2 percentages: the percentage of the sleep period spent moving, and the percentage of the number of immobile phases that were ≤ 1 min long). Scoring of actigraphy sleep data will follow the guidelines set forth by the Society of Behavioral Sleep Medicine.¹¹¹ 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.¹¹² The Pittsburgh Sleep Quality Index, a widely used and reliable measure of global sleep quality,¹¹³ also will be administered prerandomization and postintervention.

The Lung Transplant Quality of Life Survey^{114,115} is a 60-item survey that measures 10 transplant-specific QoL domains including physical symptoms, functioning, emotional well-being, and health perceptions.¹¹⁶

Frailty will be assessed by the Fried Frailty Index including self-reported exhaustion, weak grip strength, slow walking speed, and low PA, and unintentional weight loss.¹¹⁷

The COPE Inventory,¹¹⁸ a measure of functional and dysfunctional coping styles, will be used to assess coping. Self-efficacy for emotional distress will be obtained from the 10-item General Self-efficacy scale.¹¹⁹

OUTCOME ANALYSIS

All analyses will follow the intention-to-treat principle, including all patients who were randomized. Patterns of

missing data will be characterized using Rubin's¹²⁰ criteria and managed accordingly using Harrell's multiple imputation (mult.impute) procedure in R. Intention-to-treat analysis will be supplemented with an examination of the treatment effect among completers using Rubin's Complier Average Causal Effect model.¹²¹ The primary hypotheses (ie, that the CSTEM intervention will be superior to SOC-ED in reducing distress and improving functional capacity) will utilize the "gatekeeper" approach,¹²² 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^{123–131} as a parsimonious strategy to control type-I error within the first (ie, "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 family-wise error rate can then be propagated to the second analysis stage, examining individual components. In contrast, error correction to individual components of the composite measure often over-controls for type-I error when the purpose is explanatory. To mitigate type-I error with multiple outcomes, we will partition the conventional $\alpha = 0.05$ to test treatment effects on global distress and functional capacity each at $\alpha = 0.025$. Thus, for our examination of changes in global distress, an experiment-wise P value of 0.025 will be used to assess significance. If this test fails to be rejected at $P \leq 0.025$, 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.¹³² Consistent with contemporary recommendations,^{133–138} secondary outcomes will be considered as potentially supportive and therefore examined at the $\alpha = 0.05$ for each domain.

The effect of treatment on global distress will be assessed using the procedure recommended by O'Brien¹³⁹ as a way to control for type 1 error with multiple endpoints across related domains. The general approach is to combine the multiple endpoints into a global score within a domain of interest. Before combining outcomes, each scale is transformed into ranks, which are then averaged. The global distress score will be comprised of the BDI-II, GHQ, PSS, STAI-S, and PROMIS Anger. Changes in global distress following treatment will be assessed using general linear modeling framework with treatment assignment (CSTEM versus SOC-ED) as a between-subjects factor, and pretreatment global distress, age, native disease, gender, type of transplant (bilateral versus unilateral), primary graft dysfunction, donor age, and total number of days hospitalized following transplant as covariates. Following the statistical principles section from the International Conference on Harmonization,¹⁴⁰ we have selected the covariates for the primary models a priori, but we also will conduct auxiliary sensitivity analyses that evaluate whether potential group imbalances might have biased the treatment effect estimate. These analyses will be performed using conventional testing for confounding.¹⁴¹ A parallel approach will be used to examine changes in 6MWD using the same covariates and pretreatment 6MWD in lieu of global distress. Secondary outcomes will be examined using the same analytic strategy, with separate models for each outcome and a correction for multiple testing using Benjamini and Hochberg's¹⁴² false discovery rate. Secondary outcomes will include PA during daily life, QoL, sleep quality, frailty, coping, and self-efficacy.

As an exploratory aim, CSTEM will be compared with SOC-ED on CLAD-free survival. Special consideration will be given to the high mortality (55% at 5 y) and frequency of CLAD (45% at 4 y)¹⁴³ among lung transplant recipients. A clustered event approach will be used following the Wei-Lin-Weissfeld methodology,^{144,145} a recurrent time-to-event modeling approach in which multiple clinical outcomes can be aggregated into a unified criterion. We have previously used this approach,⁶¹ as the Wei-Lin-Weissfeld has been shown to improve power by up to 50% to detect group differences among clinical populations with high event rates.¹⁴⁵ Specifically, separate Cox proportional hazards models will be aggregated into a composite outcome of (1) diagnosis of CLAD and (2) retransplantation or death. Patients who have not died or who have not been hospitalized will be managed as censored as of the time of last contact. This model will utilize the same covariates as above. In addition to examining the standard regression assumptions, assumptions specific to the Cox model will be assessed using techniques suggested by Schoenfeld.¹⁴⁶ We will use Harrell's Design and Hmisc libraries¹⁴⁷ in the R software package (<http://cran.r-project.org>) to conduct these analyses.

Additional exploratory analyses will examine factors that may have mediated any observed treatment improvements in distress, functional capacity, or CLAD-free survival. Specifically, improvements in PA, medical adherence, and reduced distress will be examined as possible mediators of treatment-related improvements following the bootstrap procedures described by MacKinnon¹⁴⁸ using the mediation package available in R for time-to-event outcomes¹⁴⁹ and the PROCESS MACRO in SAS for continuous outcomes.¹⁵⁰ We also will consider the persistence of benefit by examining the treatment effects at the 1-year follow-up using a repeated measures, mixed model approach (PROC MIXED in SAS).

Power Considerations

With respect to changes in global distress, we estimated power using a correlation of 0.53 between covariates and the outcome,⁴⁸ an initial sample size of 150 participants, attrition of 15%, and an α of 0.025. Based on these assumptions, we will have 80% power to detect a small-to-moderate treatment size difference ($d = 0.44$). 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 CSTEM on clinical outcomes. Power for our exploratory clinical event models was estimated assuming a conservative event rate of 75% in the SOC-ED 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 α of 0.05, and 75 patients per group, we will have 80% power to detect a 64% event rate reduction.

DISCUSSION

INSPIRE-III is a RCT that, if shown to be effective in improving functional capacity and QoL and potentially improving clinical outcomes, the CSTEM intervention could be adopted in the routine management of post-transplant recipients. The trial is unique in that few studies have examined the impact of behavioral interventions in post-transplant patients,^{151,152} and to our knowledge, none have

done so among lung transplant recipients, despite the high prevalence of post-transplant psychological distress and its prognostic relationship with adverse clinical outcomes. Previous studies have focused on pretransplant psychological functioning, which is only weakly associated with post-transplant levels of distress and are not prognostic of poor clinical outcomes after surgery. In addition, by focusing on pretransplant candidates, studies have not accounted for clinically relevant, post-transplant medical factors and fail to target psychological factors at a time when behavioral aspects of care (eg, medical adherence, PA) are critical for optimal longer-term outcomes. Our examination of intervention effects on post-transplant clinical events is unique in that we will be targeting psychological distress and physical inactivity at a critical time for improving behavioral aspects of care.¹⁵³ Our examination of long-term CLAD-free survival is also innovative in that we will test the premise that improving both psychological and physical well-being will lead to reduced lung transplant complications, admissions, improved medication compliance, and improved long-term CLAD-free survival.

We believe that the timing of the intervention is an important design feature insofar as the intervention will be delivered at a critical time in which patients, who are medically stable, have been transitioned from the security of an outpatient transplant PR program to their own home environment. This transition period is when patients are more likely to discontinue their exercise routines²⁵ and often experience increased distress.^{16,45} As such, this transition period represents a window of opportunity in which patients may be especially receptive to behavioral interventions.¹⁵⁴ Once patients leave the PR center and return home, they may be apprehensive about exercising on their own without supervision. CST teaches individuals to become aware of and change cognitions that contribute to anticipatory anxiety and avoidance of activity. Although previous trials have examined the impact of intervening among waitlisted lung candidates,^{52,155} no studies have targeted this important transition period, when patients need to maintain important health behaviors such as daily exercise and medication adherence, and are most vulnerable to depression, distress, and adverse medical events.

Previous studies have relied on the use of mental health professionals to deliver CST, which is often impractical and costly. Moreover, mental health professionals often are not familiar with the unique needs of transplant patients. Respiratory therapists, with specific knowledge and experience working with this patient population, are especially attuned to the issues these patients encounter on a daily basis. INSPIRE-III will engage respiratory therapists to deliver the CSTEM intervention, providing a translatable framework for "real-world" implementation of the intervention. Further, INSPIRE-III utilizes accelerometry assessment tools with Bluetooth capability and cloud-based data access, providing therapists with data-driven feedback on participants' daily exercise and activity levels that will be incorporated in the weekly CSTEM therapy sessions. If successful, results of the INSPIRE-III could serve as a model for extending care of post lung transplant recipients by remotely delivering training in coping skills and exercise to promote enhanced psychosocial functioning, reduced distress, improved functional capacity, and potentially better clinical outcomes.

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