Study Protocol and Statistical Analysis

Official Title: Lung Transplant G0 (LTGO): Improving Self-Management of Exercise After Lung Transplantation

ClinicalTrials.gov ID (NCT number): NCT 03728257

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Scientific Background

Lung transplantation is one of the fastest growing solid organ transplant procedures in the United States.[1] Over the past four decades, notable progress has been made in the success of lung transplantation due to advances in organ preservation, surgical techniques, availability of bridge treatments (e.g., ventilator support, extracorporeal membrane oxygenation), and new immunosuppressive regimens.[2] According to the most recent report from the International Society for Heart and Lung Transplantation (ISHLT), the overall 5-year survival rate for LTR is 53%.[2] Lung transplantation leads to extended survival and quality of life in persons limited by advanced lung disease[3-5] and, therefore, has become an established treatment option.

After transplant, lung function typically returns to near normal levels. [6-8] However, reduced physical function and an inactive lifestyle compromise this benefit. Prior to transplant, end-stage lung disease reduces ventilatory capacity.[9] Disabling dyspnea limits physical activity and exercise, causing low muscle mass and qualitative changes in large exercising skeletal muscle groups.[10] Thus, LTR are severely deconditioned when they come to transplant surgery. After transplant, skeletal muscle changes persist.[11] Side effects of immunosuppressive agents further reduce lean muscle mass, increase fatigue, and decrease motivation to stay active.[12] A systematic review of 18 studies evaluating loss of skeletal muscle mass, strength and function in LTR reported that quadriceps strength was reduced in the pre-transplant period (range, 49%-86% predicted; n = 455 patients), further reduced immediately after transplant (51%-72% predicted, n = 126), with variable improvement at 3 months after transplant (58%-101% predicted, n = 164).[13]

While improved lung function after transplant has the potential to improve physical function, there is consistent evidence of limitations in reaching this goal.[6, 14-16] To promote rehabilitation goals, LTR are advised to attend a PR program.[17-19] Whereas post-transplant medical management requires following an established protocol, participation in PR is elective to LTR's individual decision. Studies documenting PR outcomes in other populations, [20, 21] consistent with our experience, report that PR is underused. It enrolls about a half of those referred [20] and loses > 25% of those who enroll to attrition.[21] Attrition of LTR in our PR clinic was greater than 50%. Barriers include scheduling and travel requirements,[18] perceptual disincentives and, of concern to LTR on immunosuppressive regimens, group participation which risks exposure to infection. Further, and of primary interest to this study, we pose that characteristics inherent to PR programs impact long-term adherence to exercise in LTR. During PR, exercise occurs under close clinician supervision but, afterward, LTR are expected to continue exercise unsupervised at home while not feeling confident. Consequently, LTR have little opportunity to establish behavior patterns that promote continued, independent self-management of exercise. Importantly, behavioral strategies, essential to achieve exercise goals and sustain self-management of exercise and active lifestyle, are not the main focus of traditional PR programs.

Telerehabilitation (TR) offers a flexible and sustainable alternative with the potential to promote and sustain self-management of exercise in LTR. Defined as an application of tele-health to rehabilitation,[22] TR uses telecommunication and computing technology to assess patients and deliver interventions in remote locations.[23-25] RCTs have evaluated TR-focused interventions in other populations, e.g., knee arthroplasty, stroke, and supported benefits of TR.[26-28] No

RCT has evaluated the use of the TR in LTR nor have exercise interventions for LTR incorporated behavioral strategies for self-management of exercise.

Study Objectives

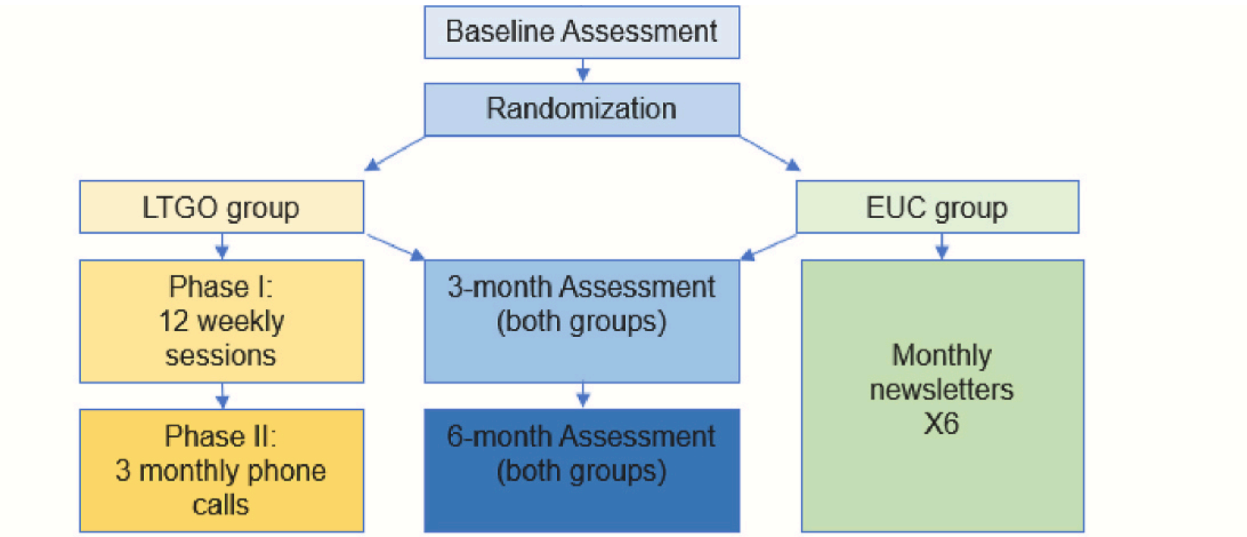
The study aims to evaluate efficacy of a behavioral exercise intervention, Lung Transplant Go (LTGO) compared to enhanced usual care (EUC) in improving physical function, physical activity and blood pressure (BP) control in lung transplant recipients.

Primary Aim: Evaluate efficacy of LTGO in improving physical function and physical activity from baseline to 3 and 6 months post-randomization.

Secondary Aim: Evaluate efficacy of LTGO on BP control from baseline to 3 and 6 months post-randomization.

Study Design & Methods

After completing a baseline assessment, lung transplant recipients (LTRs) were randomized 1:1 to either the LTGO or Enhanced Usual Care group. To achieve balance between groups for known differences in exercise capacity, a blocked randomization scheme stratified by sex, and length of transplant-hospital stay (≤2 weeks or >2 weeks) was used as an indicator of hospital-associated deconditioning. The statistician was responsible for randomization.



After the start of Covid, all study activities were performed remotely for both groups, including intervention delivery, recruitment, consenting, assessment, and data collection. Outcome assessors were blinded to group assignments. Data collectors were trained to perform study assessments until they demonstrated competency. Quality control checks of inter-rater reliability between assessors were repeated every quarter and remediation was instituted to remedy any drift from the assessment protocol less than (r = .97). Assessors were trained to abstract data

from the electronic health record using established code books. Inter-rater reliability was determined between two raters for every 10 records. Data safety and intervention fidelity were monitored regularly. Surveys and semi-structured interviews were used to determine the usability and acceptability of the LTGO intervention. Performance of all assessments and delivery of intervention sessions and phone calls were audio or video-recorded. Intervention fidelity was monitored for 10% of phase 1 exercise sessions per subject and all phase 2 phone calls. Data safety monitoring (DSM) meetings were held monthly by the PI and PD, and annually by PI, PD and medical monitor.

Eligibility Criteria

Inclusion Criteria:

- 18 years of age or older

  ->4 weeks after the participant had lung transplant surgery

- Discharged from the hospital after your lung transplant surgery
- MD report of difficulty walking ¼ mile or climbing 10 steps without resting
- Medical monitor approves patient eligibility for participation

Exclusion Criteria:

- concurrent participation in a formal exercise program, e.g., pulmonary rehabilitation, during the active eligible study period with no plans to stop formal exercise
- having other chronic conditions that may severely limit participation in exercise training, i.e., cardiac, musculoskeletal or cognitive impairments
- does not have home internet or smart device with Bluetooth capabilities
- medical issue precluding participation
- declining to be asked screening questions, or declining an introduction to the research team to hear about research
- greater than 18 months post-transplant hospital discharge (time/scheduling delays, transportation issues, etc.)

Protocol changes to primary outcomes due to COVID

1. Primary Outcome: Physical function-Walking, Change is being assessed from baseline to 3 months

* Protocol modification 06-24-2020: since COVID, alternate measures for 6MWT due to inability to conduct in-person outcome assessments were the 30 Second Chair Stand Test (see primary outcome 5 and 6) and Average Steps per Day

2. Primary Outcome: Physical function- Walking, Change is being assessed from baseline to 6 months using Avg Steps per Day

*Protocol modification 06-24-2020: since COVID, alternate measures for 6MWT due to inability to conduct in-person outcome assessments were the 30 Second Chair Stand Test (see primary outcome 5 and 6) and Average Steps per Day

3. Primary Outcome: Physical function- Balance-Change is being assessed from baseline to 3 months using the Berg Balance Scale

4. Primary Outcome: Physical function- Balance-Change is being assessed from baseline to 6 months using the Berg Balance Scale

5. Primary Outcome: Physical function- Lower Body Strength-Change is being assessed from baseline to 3 months using the 30 Second Chair Stand Test

6. Primary Outcome: Physical function- Lower Body Strength-Change is being assessed from baseline to 6 months using the 30 Second Chair Stand Test

Primary outcome: Physical function- maximal exercise watts per Kg, Change is being assessed from baseline to 3 months during the Cardio Pulmonary Exercise Test (CPET)

*Protocol modification- since COVID, the max ex watts per KG test was excluded from outcomes due to inability to conduct in-person outcome assessments and no alternative measure was available for the CPET. This modification does not appear in the primary outcomes change history.

* Protocol modification-Physical function- Quadriceps Muscle Strength-outcome was never assessed as it was deemed redundant with the 30 Second Chair Stand Test. This modification does not appear in the primary outcomes change history.

7. Primary Outcome: Physical function- Respiratory-related quality of life, Change is being assessed from baseline to 3 Months using the St. George Respiratory Questionnaire (SGRQ

8. Primary Outcome: Physical function- Respiratory-related quality of life, Change is being assessed from baseline to 6 Months using the St. George Respiratory Questionnaire (SGRQ)

9. Primary Outcome: Physical Activity-Minutes of Moderate to Vigorous Physical Activity Per Day, Change from Baseline to 3 Months using Actigraph

*Protocol modification 06-24-2020: since COVID, due to inability to conduct in-person outcome assessments, the Actigraph or the International Physical Activity Questionnaire-S (IPAQ-S) were approved measures of physical activity. The actigraph devices were mailed to participants thus preluding the need to administer the IPAQ.

10. Primary Outcome: Physical Activity-Minutes of Moderate to Vigorous Physical Activity Per Day, Change from Baseline to 6 Months using Actigraph

    *Protocol modification 06-24-2020: since COVID, due to inability to conduct in-person outcome assessments, the Actigraph or the International Physical Activity Questionnaire-S (IPAQ-S) were approved measures of physical activity. The actigraphs were mailed to participants thus preluding the need to administer the IPAQ.

11. Secondary outcome: Blood Pressure Control, Change in stage of hypertension from baseline to 3 months

12. Secondary outcome: Blood Pressure Control, Change in stage of hypertension from baseline to 6 months

Statistical Considerations

An intent-to-treat (ITT) design was used wherein all participants were analyzed in the groups to which they were randomly assigned, regardless of treatment received or protocol deviations. The projected sample size was 112 participants a priori to reach a final sample of 80 randomized subjects (40 per group) to achieve 80% power to detect an effect size as small as 0.64, α=0.05, two-tailed, for measures of the difference between LTGO and EUC groups in change in physical function, physical activity, and blood pressure control between baseline and 3 and 6 months.

Phases of data analysis involved an initial screening of data followed by the primary analysis to address each specific aim. All the analyses, including exploratory data analysis and linear mixed model, will be conducted by using SAS (v. 9.4, SAS Institute, Inc., Cary, NC).

Standard descriptive summaries (e.g., means, standard deviation, percentiles, range) and graphical techniques (e.g., histograms, scatter plots) were generated. The distribution of key variables was examined to ensure that the proposed modeling techniques were suitable. The assumptions underlying planned analysis methods were checked, and appropriate data transformation were performed, if necessary. The two groups were compared with respect to baseline variables using Student t-test or Mann-Whitney U test for continuous variables; categorical variables were compared between two groups by using Chi-square test or Fisher's exact test to ensure that randomization resulted in equal distribution of important variables.