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A mobile health technology enabled home-based intervention to treat frailty in adult lung transplant candidates: a pilot study

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Abstract

Background—Frailty is prevalent in lung transplant candidates (LTC) and is associated with waitlist delisting or death. We performed a pilot study to assess the safety and feasibility of a home-based, mobile-health technology facilitated intervention to treat frailty in LTC.

Methods—We performed an 8-week, non-randomized, home-based exercise and nutrition intervention in LTC with Short Physical Performance Battery (SPPB) frailty scores of 11. The intervention utilized a customized, mobile device application ("app") enabling monitoring and progression of the intervention in real-time. We aimed to evaluate key process measures. Secondarily, we tested whether the intervention could improve frailty scores quantified by the SPPB and Fried Frailty Phenotype (FFP).

Results—15 subjects enrolled were 63 ± 5.7 years old; oxygen requirements ranged from 3-15LPM. Thirteen subjects completed the intervention. Over 108 subject-weeks there were no adverse events. Subjects found the app engaging and easy to work with. SPPB frailty improved in 7 (54%) and FFP improved in 8 (62%). There was a strong trend towards improved frailty scores (SPPB change 1.0 ± 1.9 ; p=0.08; FFP change -0.6 ± 1.0 ; p=0.07).

Conclusion—In this pilot study, we found that a home-based pre-habilitation program that leverages mobile health technology to target frailty in LTC is well received, safe, and capable of improving physical frailty scores.

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CONFLICT OF INTEREST AND FUNDING SOURCE: Allan Bruun is CEO of AidcubeTM. This pilot study was funded by a Nina Ireland Program in Lung Health award (JPS); other funding was provided by the National Heart, Lung, and Blood Institute (K23 HL11115 and R01 HL134851; JPS)

Keywords

frailty; lung transplant candidates; rehabilitation; exercise; pilot study

INTRODUCTION

A 2005 overhaul in the U.S. donor lung organ allocation system aimed to reduce an unacceptably high waitlist mortality (1). While achieving its primary aim, a consequence of the Lung Allocation Score (LAS) system is that older and sicker candidates are prioritized for transplantation. Despite advances in medical and surgical pre-operative management, 20% of patients listed for lung transplantation die or become too ill for surgery before receiving a suitable donor offer – a rate that has been increasing since 2010 (2). After transplant, mortality remains high and perioperative morbidity is increasing (3–5). To maximize the individual and societal benefit of lung transplant, there is a critical need to identify and intervene upon modifiable risk factors for poor waitlist and perioperative outcomes.

Frailty, originally a geriatric construct, reflects accumulated deficits across physiologic systems that attenuate the body's physiologic reserve. We recently demonstrated that frailty is prevalent in lung transplant candidates and is independently associated with disability and delisting or death on the waiting list, as well as with death after lung transplantation (6, 7). Recent studies in community-dwelling and institutionalized older adults suggest that frailty may be reversible through exercise-based intervention (8–11). For those with lung disease, traditional hospital-based pulmonary rehabilitation may achieve similar goals, but many patients cannot access these programs due to geography or insurance limitations (12–14). Thus, a home-based intervention targeting at-risk frail patients *before* lung transplantation could overcome these limitations and, if successful, could potentially reduce frailty-attributable waitlist disability and mortality. Further, it might allow patients to undergo surgery in a more optimized physical and nutritional state (*i.e.*, "pre-habilitated"), potentially reducing postoperative complications, disability, and mortality (15).

Although home-based pulmonary rehabilitation is common elsewhere, it is rare in the U.S. and a program to treat frailty in patients awaiting lung transplantation at home has never been attempted (16, 17). Herein, we report the results of a pilot home-based intervention that leverages mobile health technology to treat frailty in adults awaiting lung transplantation.

METHODS

Study rationale

Our primary aim was to determine the feasibility of treating frailty in adult candidates for lung transplantation using a home-based program leveraging mobile health technology. If successful, such an intervention could be an inexpensive option not bound by geography or insurance to test whether reducing frailty reduces wait-list mortality and/or perioperative complications.

Study design, participants, and setting

We performed an 8-week non-randomized home-based exercise intervention in patients aged 50 who were listed or soon to be listed for lung transplantation for either Chronic Obstructive Pulmonary Disease (COPD) or pulmonary fibrosis (PF) at the University of California, San Francisco. Additional inclusion criteria were the ability to understand and speak English, home oxygen equipment capable of delivering the required supplemental oxygen determined during in-person assessment (see below), a Short Physical Performance Battery (SPPB) frailty score of 11 (SPPB range 0 - 12, lower scores reflect increasing frailty), and outpatient status. We excluded patients who were already enrolled or planned on soon enrolling in a traditional hospital based pulmonary rehabilitation program or those with pulmonary hypertension (pulmonary arterial mean pressure 30 mmHg on right heart catherization or a pulmonary arterial systolic pressure > 50mmHg or a report of moderate right ventricular dysfunction or worse on transthoracic echocardiogram). We excluded those who lived alone based on concerns for safety. Based on two years of funding, the timeframe for recruitment was December 2015 through November 2017.

Our primary goal was to test the key process measures needed to inform the design of a randomized controlled trial (*i.e.*, safety, attrition, adherence; Table 1). Nevertheless, we aimed to recruit 26 subjects based on sample size calculations needed to identify a withinperson improvement in the SPPB derived from prior studies (α set at 0.05, β set at 0.2). We previously found a one-point change in the SPPB to be associated with increased risk of disability and waitlist mortality. The study was registered at ClinicalTrials.gov (Protocol ID: 15-17503) and was approved by our Institutional Review Board (CHR #15-17503). All subjects provided written informed consent after the intervention was explained.

Mobile(m) Health Interface—We customized a commercially available mobile device application ("app") platform (Aidcube[™]) to deliver our intervention. Aidcube[™] was initially developed to enable the delivery of home-based pulmonary rehabilitation for patients with COPD. On the patient-facing side, patients can view their daily exercise prescription, descriptions and videos demonstrating correct execution of the exercises, document completion of exercises, and message their health-care provider (Figure 1A). On the provider-facing side, providers can develop a customized exercise prescription from >150 available exercises, surveys, and activities (Figure 1B). Based on real-time patient feedback, the exercise prescription can be progressed (*i.e.*, advanced and/or modified) by adding repetitions or time to existing prescribed exercises or by adding new exercises. The provider can also message the patient from within the Aidcube environment. The app also allows for linking of Fitbit activity trackers. For this pilot, we solicited guidance from experts in pulmonary rehabilitation (Anne Holland, BAppSc, PhD; Martijn Spruit, PT, PhD; Richard ZuWallack, MD PhD). Based on this guidance, we worked with Aidcube[™] to modify the platform for a U.S. audience and include exercises focused on the treatment of frailty based on the Strong For Life and Weight Bearing Exercise for Better Balance programs (18, 19). A video illustrating the intervention is available: www.aidcube.com/ucsfdemo

Intervention Phase 1: In-person assessment, training and baseline exercise prescription

The intervention consisted of two-phases: an in-person assessment and training phase, followed by a home-based exercise phase. For the in-person phase, baseline measures of frailty, grip strength quantified with a handheld dynamometer (Jamar hydraulic hand dynamometer; Stoelting, Wood Dale, IL) and a 6-minute walk test (6MWT) were performed in a research exercise laboratory setting. The 6MWT was performed in a 40 meter hallway, with markings every 3 meters and 8'' orange traffic cones marking the turnaround point in accordance with American Thoracic Society guidelines (20). The 6MWT was performed once and participants were encouraged to use the same amount of oxygen they normally used for other exercise activities. A structured survey to assess disability and functional capacity was also administered (Lung Transplant Valued Life Activities [LT-VLA] and Duke Activity Status Index [DASI] (21, 22)). Participants were provided tablets preloaded with the Aidcube[™] app or the app was installed on their smartphones, if preferred. To improve adherence, we developed a menu of potential exercises allowing participants to choose those exercises that they found most interesting for certain muscle groups. Once selected, participants were taught how to safely perform the exercises at home and were asked to demonstrate "teach-back" until correct performance was confirmed. We utilized techniques to address both the motivational and volitional phases of behavior change. For example, we asked patients to recall earlier experiences when exercising and eating well made them feel that they had endurance and energy. After selecting exercises, they goal set in a collaborative way with the study coordinator. The coordinator helped patients adopt phrases to improve their sense of self-efficacy (e.g., "I know I can do this [the prescribed exercises]". All exercises, except daily aerobic exercise (*i.e.* walking), were to be completed thrice weekly. Participants were instructed to give muscle groups at least one day to recover before training the same group again. We advised alternating the days that they completed upper and lower body exercises to allow for adequate recovery time. The exercise training was followed by education in how to titrate oxygen during exertion as well as dyspnea control techniques such as pursed-lip breathing and recovery positions.

During this training, participants were shown how to operate the Aidcube[™] app that served as the home-based exercise prescription interface. Participants were also provided Fitbit activity trackers, Therabands and Theraband door anchors, and, if needed, portable oximeters. Finally, a registered dietitian met with the participant for an individualized nutrition counseling session. Participants were provided general healthy eating guidelines based on the 2015–2020 Dietary Guidelines for Americans, which include increasing fruit and vegetable consumption and choosing lean protein sources, whole grains, and low fat dairy products (23). Limited intake of foods and beverages containing saturated fats, trans fats, added sugars, and sodium was encouraged. Recommended foods and meal patterns were tailored based on participants' reported allergies, cultural food preferences, and comorbidities such as hypertension, hyperlipidemia, and diabetes. Recommended nutrient intake was adjusted based on weight loss or weight gain goals to achieve an acceptable pretransplant body mass index (BMI). Diet and activity goals were set with each patient.

Participants were assigned five core exercises frequently used in pulmonary rehabilitation (walking, sit to stands, tandem walking, wall push-ups, and pursed-lip breathing) and five

stretches. We used the provider interface of Aidcube[™] (below) to create and adjust the participant's exercise diaries. The initial aerobic exercise prescription was set at 65–75% of each participant's maximum exercise capacity which was estimated from the 6MWT. The initial strength prescription was based on each participant's baseline SPPB frailty score. Participants without access to a home treadmill were prescribed a daily step count goal based on their diagnosis. Those participants with access to a treadmill were prescribed a walking recommendation based on speed in addition to a daily step count goal. Participants' grip strength was used to select which color (intensity) Theraband was appropriate; those with grip strengths falling below the lowest quintile cutoff for gender and BMI based norms or self-reported wrist, hand, or finger pain were provided red Therabands (24). Participants with grip strengths falling above the lowest quintile cutoff tested the green and blue Therabands during the in-person training and selected the color that felt safest and most appropriate for their needs.

Intervention Phase 2: Home based exercise and nutrition intervention

Once home, participants utilized the patient interface of Aidcube to view and log the completion of their prescribed exercises. Before beginning their exercises, they were provided a pop-up safety guideline message. In addition to logging their exercises, participants indicated their level of motivation to exercise and their mood for the day. They also reported their maximum heart rate and lowest oxygen saturation observed during the exercise prescription. Progress was monitored in real-time through the provider interface of Aidcube. This interface was also used to progress the exercise prescription over time by an expert in pulmonary rehabilitation (CG).

A trained coordinator conducted weekly phone checkins. These calls utilized semistructured interview techniques to evaluate subject compliance with safety guidelines, to identify any problems with exercise equipment, to assess the usability of AidcubeTM, and to solicit general impressions of the intervention. Diet and dietary goals were reviewed and input from the dietitian was solicited if modifications to the diet or new goals were needed. Additionally, subjects were provided support and feedback using motivational interviewing techniques. For example, for participants who were progressing as expected with no reported problems, we used positive reinforcement and also asked them to set goals for the upcoming week. For participants who were not progressing or engaging in the exercise program as prescribed, we asked them first to identify barriers (e.g., time, energy, dyspnea, concern about harming themselves, sense of self-efficacy, etc...). We used positive reinforcement techniques to improve volitional self-efficacy (e.g., "I am capable of overcoming these barriers [lack of energy/motivation, severe dyspnea]") and reinforced compliance. Additionally, we continued to ask them to recall that the program was intended to help them have a smoother perioperative course. After eight weeks, participants returned to the study center where measures of frailty, disability, and exercise capacity were repeated. At this visit we also conducted semi-structured interviews to debrief them on their experiences over the course of the intervention. In the early phase of the study, the intervention was designed to last 12 weeks. One of the early participants underwent transplant prior to the end of the intervention. Based on this early experience and literature supporting improvement in frailty in as little as six-weeks, we reduced the intervention duration to eight weeks (25).

Analyzed measures

Process measures—Given the pilot nature of this study, the primary outcomes of interest were those process measures needed to inform the design and execution of a randomized controlled trial. The measures included consent rates, attrition, safety, adherence, and subject feedback (Table 1).

Outcome measures—Although we anticipated being underpowered to detect statistically significant changes in outcome measures, we were interested in determining whether the intervention was capable of improving measures of frailty, functioning, and patient-reported outcomes in order to generate point estimates of change for future sample size calculations. We evaluated within subject changes over the course of the intervention. We evaluated the Short Physical Performance Battery (SPPB) and the Fried Frailty Phenotype (FFP) as our measures of frailty (24, 26). The SPPB is a 3-component battery that includes gait speed, chair stands, and balance. Each component is scored from 0-4, yielding an aggregate score ranging from 0–12. Lower SPPB scores reflect increased frailty and a threshold 7 has been used in lung transplantation to define the frail state (7, 27). Other studies have used different thresholds to define frailty by SPPB (e.g., 6, 8, 9, 10) and prior work in COPD used a threshold of 9 (28). The FFP is an aggregate score of five constructs: low physical activity, slowness, weakness, shrinking, and exhaustion (24). We used a modified version of the FFP that has better construct and predictive validity in lung transplant candidates than the original measure that was developed in a community dwelling older population (29). Each construct is assigned "1" if present or "0" if absent, standardized to sex, height, and weight. The FFP ranges from 0–5 and a score of 3 has been used to define the frail state. In contrast to the SPPB, higher scores reflect increased frailty. We previously demonstrated that a one-point worsening in either measure is associated with increased risk of disability and wait-list mortality in lung transplant candidates. Disability was quantified by the Lung Transplant Valued Life Activity (LT-VLA) and Duke Activity Status Index (DASI), both patient-reported measures of functional capacity validated in lung transplant candidate populations (21, 22). The LT-VLA has a range of 0–3 with higher scores reflecting worse disability; a change of 0.3 reflects the minimally clinically important difference. Other outcome measures included grip strength, 6MWD, and weekly step count quantified by Fitbit.

Analysis Approach

Analyses were performed using Stata (15.1, StataCorp, College Station, TX). For tests of change, we used paired t-test or paired-Wilcoxon rank sum tests, as appropriate. A p-value of < 0.05 was used as the threshold for statistical significance.

RESULTS

Over 22 months, 45 candidates were screened (Figure 2). Of these, 13 were excluded; pulmonary hypertension was the predominant reason (n=8, 62%). An additional nine candidates either had SPPB scores of 12 on reexamination or consented but underwent transplant before they were able to attend the in-person evaluation. Of the remaining 23 potential candidates, eight declined to participate (31%), yielding 15 participants who

enrolled in the intervention. These 15 subjects were aged 62.9 years (standard deviation $[SD] \pm 5.7$), 33% female, and 66% had COPD (Table 2). At baseline, SPPB and FFP frailty scores were 9.7 (SD \pm 1.0) and 2.4 (SD \pm 1.1), respectively. By SPPB, no participants were frail using the 7 threshold (2 were frail using a 8-point threshold, and 7 were frail using a 9-point threshold). By FFP, 7 participants were frail.

Process Measures

We found that the majority of eligible candidates (23/26; 89%) did not have access to a traditional pulmonary rehabilitation program defined as either insurance coverage or geographic proximity of <1.5 hour drive each way. Of the eight candidates who declined to participate in the study, reasons included lack of interest (n= 5), poor timing in relation to other life responsibilities (n= 2), a safety monitor convinced a candidate not to participate after undergoing in person evaluation (n= 1), and indecision on whether to pursue transplant (n= 1). After the in-person evaluation and training, one participant failed to initiate the home-based exercise phase of the intervention despite multiple phone calls and was dropped. One additional participant underwent transplant before completing the initial 12-week intervention; the remaining 13 participants completed the intervention.

We found that the intervention was safe. Over 108 subject-weeks of intervention, there were no falls, injuries, or serious adverse events. There were 36 documented episodes of desaturation to a SaO2 of <85% during exercise, of which 70% of the desaturation episodes occurred in one subject. Overall, the group demonstrated moderate adherence, completing an average of 60% to the prescribed exercise regimen. Of note, the variation in adherence was large (range: 31% - 94%). Despite weekly phone call reminders, adherence to wearing the FitBit device was surprisingly poor to the point where the data could not be analyzed. Only four participants wore them as prescribed. A 63-year old male with COPD provided the following feedback,

"The Fitbit is fun, but I have trouble remembering to wear it. It's also small and I lose track of where I put it." – Subject 13

The participant experience in the intervention was nearly uniformly positive. Even older participants found the app interface intuitive and user friendly. Table 3 details specific quotes. A 69-year-old male with COPD commented,

"The app [Aidcube] is so easy to use. I was really scared about using it; I'm not good with phones and things, but it's actually a lot easier than I expected it to be. Very straightforward." - Subject 2

Further, participants found exercising at home while awaiting lung transplantation to be convenient. A 68-year-old male with IPF remarked,

"My exercises are doable. It took some time for me to get used to them since I have never regularly exercised, but I got used to them and now that I have a routine, it's easy for me to keep going" – Subject 7

Overall, the intervention ended up being a rewarding experience for most of the participants during the challenging time of waiting for a donor offer. A 57-year-old woman with COPD reflected,

"This study has really helped me and my family. I'm so tired of just sitting around waiting while I get sicker. I feel like I have control of something for a change." – Subject 6.

Secondary outcome measures

Amongst 13 participants, SPPB frailty scores improved in 7 (54%) and FFP frailty scores improved in 8 (62%) subjects, respectively. We found a strong trend towards improvement in SPPB frailty scores from before (9.7 ±1.1) to after the intervention (10.8 ±1.5) with a within-person change of 1.0 ± 1.9 (p = 0.08) (Table 4). No subjects were frail by SPPB using the 7 point threshold; using a 9 point threshold, 5 participants were frail before the intervention. At the end of the intervention frailty had resolved in 3 participants (Table 5). Similarly, there was a trend towards improved FFP frailty scores from before (2.4 ±1.1) to after the intervention (1.7 ±1.4) with a within-person change of -0.6 ± 1.0 (p = 0.07). Of the 6 participants who were frail by FFP at the beginning of the intervention (*i.e.*, FFP score of 3), 4 were no longer frail after the intervention (Table 5). We did not identify overall improvements in 6MWD, grip strength, LT-VLA, or DASI (all p 0.26).

DISCUSSION

In this pilot study utilizing customized commercially available mobile health technology, we found that a home-based exercise and nutrition intervention is feasible, safe, and capable of improving frailty in adult lung transplant candidates quantified by two validated physical phenotype measures. The data generated from this pilot can provide important information needed to conceptualize and design future interventions focused on "pre-habilitation" of lung transplant candidates with the goal of reducing morbidity and mortality both before and after lung transplantation.

Given the older and sicker candidates increasingly prioritized for lung transplantation, rising wait-list mortality rates, and increasing peri-operative morbidity and cost after lung transplantation, new strategies to improve transplant candidacy are needed (2, 4, 30). A robust existing literature supports that some drivers of physical frailty such as physical inactivity, poor nutrition, body composition, and others, may be modifiable. These potentially modifiable drivers of frailty, as well as frailty itself, are associated with increased risk of mortality before and after lung transplantation (27, 31–36).

In addition to achieving our primary aims of demonstrating feasibility and safety, our most notable finding was that frailty can be improved through a targeted intervention consisting of escalating doses of exercise and nutrition counseling, even in end-stage lung disease. Of the participants who completed the intervention, over half improved their frailty scores by the minimally clinically important difference and an equal proportion transitioned from frail to not-frail states. Interestingly, the proportion of participants who improved in our pilot study is similar to the few interventional studies aimed at treating frailty in other populations. In a prospective observational study of 91 institutionalized older adults prescribed a standardized exercise program combined with nutritional supplementation, 53% improved their SPPB scores by at least one point by six weeks (25). Cameron, *et al*, performed a 12-month randomized controlled trial of a multifactorial intervention targeting each component of the

FFP frailty criteria in 241 community-dwelling older subjects meeting 3 FFP criteria. In those randomized to the intervention, SPPB improved by 0.52 points (SD \pm 2.47) and FFP frailty improved by 0.8 points (SD \pm 1.19) (8). Finally, in a prospective observational study of 816 adults with COPD attending a traditional pulmonary rehabilitation program, of the 117 frail subjects who completed pulmonary rehabilitation, 62% improved their FFP frailty scores by at least one point (14).

Despite our promising early findings, our pilot study has limitations that should be considered. First, our focus on process measures such as safety and feasibility involved weekly phone calls with a research coordinator. In addition to collecting process measure data, our coordinator provided participants encouragement and strategies to maintain engagement in the intervention. As a result, the intervention was not entirely contained within the app and it is possible that the effect size we observed would have been smaller if an intervention were conducted without weekly checkins. In addition, the behavioral intervention in both Phase 1 and Phase 2 of the study included several different components. Anecdotally, at least one participant commented on the value of each of the different components. Our limited sample size and survey structure, however, did not enable us to determine which of the behavioral intervention components were most helpful nor the ways in which they interacted to impact our secondary outcomes. Second, given limited time and funding, we aimed for a relatively homogenous population of patients aged 50 years with either COPD or IPF. Although there is no biologic or physiologic reason to suggest our intervention would be less effective in younger subjects with other lung diseases, we lack primary data in these groups. Additionally, given the theoretical risks accompanying unsupervised exercise in advanced lung disease, we restricted the intervention to adults without severe pulmonary hypertension. The prevalence of pulmonary hypertension is high in wait-listed candidates and safety data in this large group of patients would be helpful for future studies. Finally, since the primary aims of the study were to establish safety and feasibility, we used a liberal SPPB inclusion criterion of a score <12. It is unknown whether patients with worse SPPB frailty scores would be more or less responsive to our intervention.

Despite these limitations, our study has notable strengths. First, our pilot study is the first to demonstrate that a mobile health supported home-based, unsupervised exercise and nutrition intervention in lung transplant candidates is safe, feasible, and effective. We also found that frailty scores can improve over a short time frame, supporting the investigation of a pre-habilitation program near the time of listing for transplant. Finally, this study also provides early data to inform future intervention or randomized controlled trial sample size calculations, recruitment and retention strategies, and potential outcome measures.

In conclusion, our findings suggest that a home-based pre-habilitation program that leverages mobile health technology may be an inexpensive intervention not bound by geography or insurance that can safely and effectively improve frailty in lung transplant candidates. Whether this intervention can improve waitlist and longer-term outcomes in lung transplantation is worthy of additional study.

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References

- Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, Coke MA, Garrity ER, Sweet SC, Heiney DA, Grover FL. Development of the new lung allocation system in the United States. Am J Transplant. 2006; 6:1212–1227. [PubMed: 16613597]
- Valapour M, Skeans MA, Smith JM, Edwards LB, Cherikh WS, Uccellini K, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2015 Annual Data Report: Lung. Am J Transplant. 2017; 17(Suppl 1): 357–424. [PubMed: 28052607]
- Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Goldfarb SB, Levvey BJ, Lund LH, Meiser B, Stehlik J, Lung T. International Society for H. The Registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. J Heart Lung Transplant. 2014; 33:1009– 1024. [PubMed: 25242125]
- Maxwell BG, Mooney JJ, Lee PH, Levitt JE, Chhatwani L, Nicolls MR, Zamora MR, Valentine V, Weill D, Dhillon GS. Increased resource use in lung transplant admissions in the lung allocation score era. Am J Respir Crit Care Med. 2015; 191:302–308. [PubMed: 25517213]
- Maxwell BG, Levitt JE, Goldstein BA, Mooney JJ, Nicolls MR, Zamora M, Valentine V, Weill D, Dhillon GS. Impact of the lung allocation score on survival beyond 1 year. Am J Transplant. 2014; 14:2288–2294. [PubMed: 25208599]
- 6. Singer JP, Diamond JM, Gries C, McDonnough J, Blanc PD, Shah R, Dean YM, Hersch B, Dolan J, Arcasoy S, Ramphal K, Greenland JR, Smith N, Patterson S, Shah L, Golden JA, Blumenthal N, Huang D, Sonett J, Hays S, Oyster M, D'Ovidio F, Katz PP, Robbins H, Brown M, Leard L, Kukreja J, Bacchetta M, Bush E, D'Ovidio F, Rushefski M, Raza K, Christie JD, Lederer DJ. Frailty phenotypies, disability, and outcomes in adult candidates for lung transplantation. Am J Respir Crit Care Med. 2015
- 7. Singer JP, Diamond JM, Anderson MR, Katz PP, Covinsky K, Oyster M, Blue T, Soong A, Kalman L, Shrestha P, Arcasoy S, Greenland JR, Shah L, Kukreja J, Blumenthal NP, Easthausen I, Golden JA, McBurnie A, Cantu E, Sonett J, Hays SR, Robbins H, Raza K, Bacchetta M, Shah R, D'Ovidio F, Venado A, Christie JD, Lederer DJ. Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. Am J Transplant. 2018
- Cameron ID, Fairhall N, Langron C, Lockwood K, Monaghan N, Aggar C, Sherrington C, Lord SR, Kurrle SE. A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. BMC Med. 2013; 11:65. [PubMed: 23497404]
- Fairhall N, Langron C, Sherrington C, Lord SR, Kurrle SE, Lockwood K, Monaghan N, Aggar C, Gill L, Cameron ID. Treating frailty--a practical guide. BMC Med. 2011; 9:83. [PubMed: 21733149]
- Fairhall N, Sherrington C, Lord SR, Kurrle SE, Langron C, Lockwood K, Monaghan N, Aggar C, Cameron ID. Effect of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail older people: a randomised controlled trial. Age Aging. 2014; 43:616–622.
- 11. Latham NK, Harris BA, Bean JF, Heeren T, Goodyear C, Zawacki S, Heislein DM, Mustafa J, Pardasaney P, Giorgetti M, Holt N, Goehring L, Jette AM. Effect of a home-based exercise program on functional recovery following rehabilitation after hip fracture: a randomized clinical trial. JAMA. 2014; 311:700–708. [PubMed: 24549550]
- Brooks D, Sottana R, Bell B, Hanna M, Laframboise L, Selvanayagarajah S, Goldstein R. Characterization of pulmonary rehabilitation programs in Canada in 2005. Canadian Respiratory Journal: Journal of the Canadian Thoracic Society. 2007; 14:87–92.

- Hayton C, Clark A, Olive S, Browne P, Galey P, Knights E, Staunton L, Jones A, Coombes E, Wilson AM. Barriers to pulmonary rehabilitation: Characteristics that predict patient attendance and adherence. Respiratory Medicine. 107:401–407.
- Maddocks M, Kon SS, Canavan JL, Jones SE, Nolan CM, Labey A, Polkey MI, Man WD. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax. 2016; 71:988– 995. [PubMed: 27293209]
- Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med. 2000; 133:253–262. [PubMed: 10929164]
- 16. MaltaisFo, BourbeauJ, , ShapiroS, , LacasseY, , PerraultHln, BaltzanM, , HernandezP, , RouleauM, , JulienM, , ParenteauS, , ParadisB, , LevyRD, , CampP, , LecoursR, , AudetR, , HuttonB, , PenrodJR, , PicardD, , BernardS. Effects of Home-Based Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease A Randomized Trial. Annals of Internal Medicine. 2008; 149:869–878. [PubMed: 19075206]
- Holland AE, Hill CJ, Rochford P, Fiore J, Berlowitz DJ, McDonald CF. Telerehabilitation for people with chronic obstructive pulmonary disease: feasibility of a simple, real time model of supervised exercise training. J Telemed Telecare. 2013; 19:222–226. [PubMed: 23666438]
- Jette AM, Lachman M, Giorgetti MM, Assmann SF, Harris BA, Levenson C, Wernick M, Krebs D. Exercise--it's never too late: the strong-for-life program. Am J Public Health. 1999; 89:66–72. [PubMed: 9987467]
- Weight Bearing Exercise for Better Balance (WEBB)2018Available from: http://www.webb.org.au/ attachments/File/WEBB_draft_19.pdf
- 20. Society AT. ATS Statement: Guidelines for the Six-Minute Walk Test. American journal of respiratory and critical care medicine. 2002; 166:111–117. [PubMed: 12091180]
- 21. Singer JP, Blanc PD, Dean YM, Hays S, Leard L, Kukreja J, Golden J, Katz PP. Development and validation of a lung transplant-specific disability questionnaire. Thorax. 2014; 69:445–450.
- 22. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989; 64:651–654. [PubMed: 2782256]
- 23. Agriculture USDoHaHSaUSDoAgriculture USDoHaHSaUSDo2015–2020 Dietary Guidelines for Americans8. 2015Internet
- 24. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001; 56:M146–156.
- 25. Abizanda P, Lopez MD, Garcia VP, de Estrella JD, da Silva Gonzalez A, Vilardell NB, Torres KA. Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older Adults: The ACTIVNES Study. Journal of the American Medical Directors Association. 2015; 16:439.e439– 439.e416.
- 26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994; 49:M85–94. [PubMed: 8126356]
- 27. Singer JP, Diamond JM, Gries C, McDonnough J, Blanc PD, Shah R, Dean YM, Hersch B, Dolan J, Arcasoy S, Ramphal K, Greenland JR, Smith N, Patterson S, Shah L, Golden JA, Blumenthal N, Huang D, Sonett J, Hays S, Oyster M, D'Ovidio F, Katz PP, Robbins H, Brown M, Leard L, Kukreja J, Bacchetta M, Bush E, D'Ovidio F, Rushefski M, Raza K, Christie JD, Lederer DJ. Frailty phenotypies, disability, and outcomes in adult candidates for lung transplantation. Am J Respir Crit Care Med. 2015; 192:1325–1334. [PubMed: 26258797]
- 28. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, Vaes B, Legrand D, Verghese J, Wang C, Stenholm S, Ferrucci L, Lai JC, Bartes AA, Espaulella J, Ferrer M, Lim J-Y, Ensrud KE, Cawthon P, Turusheva A, Frolova E, Rolland Y, Lauwers V, Corsonello A, Kirk GD, Ferrari R, Volpato S, Campo G. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. BMC medicine. 2016; 14:215. [PubMed: 28003033]

- 29. Baldwin MR, Singer JP, Huang D, Sell J, Gonzalez WC, Pollack L, Maurer MS, D'Ovidio FF, Bacchetta M, Sonett JR, Arcasoy SM, Shah L, Robbins H, Hays SR, Kukreja J, Greenland JR, Shah RJ, Leard L, Morrell M, Gries C, Katz PP, Christie JD, Diamond JM, Lederer DJ. Refining Low Physical Activity Measurement Improves Frailty Assessment in Advanced Lung Disease and Survivors of Critical Illness. Ann Am Thorac Soc. 2017
- 30. Bentley TS. 2014 U.S. organ and tissue transplant cost estimates and discussion. 2014
- Grimm JC, Valero V 3rd, Kilic A, Crawford TC, Conte JV, Merlo CA, Shah PD, Shah AS. Preoperative performance status impacts perioperative morbidity and mortality after lung transplantation. Ann Thorac Surg. 2015; 99:482–489. [PubMed: 25528724]
- 32. Castleberry AW, Englum BR, Snyder LD, Worni M, Osho AA, Gulack BC, Palmer SM, Davis RD, Hartwig MG. The Utility of Preoperative Six-Minute Walk Distance in Lung Transplantation. Am J Respir Crit Care Med. 2015
- Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006; 174:659–664. [PubMed: 16778159]
- 34. Baldwin MR, Arcasoy SM, Shah A, Schulze PC, Sze J, Sonett JR, Lederer DJ. Hypoalbuminemia and early mortality after lung transplantation: a cohort study. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012; 12:1256–1267.
- 35. Lederer DJ, Wilt JS, D'Ovidio F, Bacchetta MD, Shah L, Ravichandran S, Lenoir J, Klein B, Sonett JR, Arcasoy SM. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med. 2009; 180:887–895. [PubMed: 19608717]
- 36. Singer JP, Peterson ER, Snyder ME, Katz PP, Golden JA, D'Ovidio F, Bacchetta M, Sonett JR, Kukreja J, Shah L, Robbins H, Van Horn K, Shah RJ, Diamond JM, Wickersham N, Sun L, Hays S, Arcasoy SM, Palmer SM, Ware LB, Christie JD, Lederer DJ. Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med. 2014; 190:1012–1021. [PubMed: 25233138]

 Tittage 18 sagere suitate Shoulder exercise Briefly about the activity UCSF Patient's dia This exercise strengthens the muscles in your arms etied last 7 days Description 5 - Sit on a chair or stand with some distance between your feet. + Grab the water bottles and stretch your arms above your head. Stretch them as high + a cklist before exercise · Lower them again Take a break after 10 repetitions Do 30 repetitions in total + 9 Sit to Stand: 5 reus Video + 9 Push-ups Steps I Push-ups: 5 rep: + 9 + a ises 5-8 repl + Q ler Shrug Stretch: 5 repr

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ŧ	Heel Raises, 5-8 reps	Q 8 ++ I
ŧ	Shoulder Shrug Stretch: 5 reps	Q 8 ++ I
ŧ	Knee bends: 5 reps	Q 8 +4 I
ŧ	Walking	Q 8 +4 I
J	Exercise Bike	Q 8 ++ I

UCSF Patient

Figure 1.

Figure 1A. Patient-facing interface for mobile health frailty intervention platform. When a subject opens the AidcubeTM app, he or she is presented first with his/her exercise prescription for the day. S/he inputs the number of repetitions performed for a particular exercise and then selects the "Next" button to automatically load the next exercise.

Incorporating "gamification" for motivation, a white unsmiling cartoon face is located at the top of left of the screen. As activities are completed, the face the moves to the right and transitions from white to yellow to green and smiles. If the patient needs to, s/he can view a description and video of the exercise by clicking on the magnifying glass to the right of each exercise name.

Figure 1B. Provider-facing interface for mobile health frailty intervention platform.

Based on documented progress and responses to the weekly checkins with the study coordinator, the provider can advance the exercise prescription in the provider portal by adding time for aerobic activities, repetitions and/or sets for strength exercises, or adding new exercises. Exercises can also be re-ordered or replaced using simple commands to the right of each exercise name.

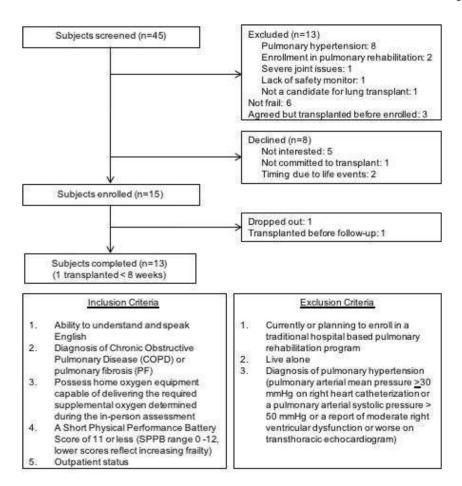


Figure 2. Consort Diagram, Inclusion and Exclusion Criteria

Table 1

Measures	
Process	

CONTENT	Outcome	Method of assessment	Rationale
Subject enrollment	 Number of eligible subjects who do not have access to traditional pulmonary rehabilitation (PR) program 2) Consent rates 	 Patients listed for transplant over study period enrolled in PR Percent of subjects screened that consent to participate 	Traditional PR programs may achieve similar goals as a home- based intervention; assess willingness to travel to participate; data will inform sample size calculations and recruitment strategies.
Subject attrition	 Completion of intervention prior to lung transplantation 	1) Percent of subjects enrolled that complete the intervention	The time from listing to transplant is unpredictable. At UCSF, median wait-time is 3.2 months.
Safety	 SaO2 < 85% during exercise. Falls/injuries 	 Home-oximetry monitoring reported in Aidcube Weekly phone calls 	Establishing safety will be needed for a RCT of home-exercise in subjects with progressive lung disease
Adherence	 Percent of activities completed per day Percent of days exercised per week 	 Aidcube Fitbit activity tracker 	Determine whether additional strategies to encourage adherence are needed.
Subject input	 Was Aidcube. Fitbit easy to use? Were there problems completing home-exercises? What were the most difficult parts of the study to complete? 	Weekly phone checkins and semistructured interview at study completion	Identify whether additional education or modifications to Aidcube and Fithit activity monitor are needed and identify problems in the home-exercise program overall from the perceptive of the study subject

Table 2

Initial cohort demographics and clinical characteristics. n = 15

Age (years)	62.9 ± 5.7
Female	5 (33.3%)
White, non-Hispanic	15 (100%)
Diagnosis	
Pulmonary fibrosis	10 (66.7%)
COPD	5 (33.3%)
BMI (kg/m ²)	28.4 ± 3.5
FEV ₁	1.3 ± 0.8
FEV ₁ % predicted	41.5 ± 25.7
FVC	2.8 ± 1.1
FVC % predicted	65.7 ± 22.7
mPAP	19.9 ± 4.4
O ₂ (L/min) with exertion	5.4 ± 2.9 (range: 3 – 15)
6MWD (m)	287.5 ± 83.8
SPPB	9.7 ± 1.0
FFP	2.4 ± 1.1

Data presented as n (%) or mean \pm SD. COPD = Chronic Obstructive Pulmonary Disease; BMI = body mass index; FEV = forced expiratory volume in one second; mPAP = mean pulmonary arterial pressure measured from right heart catheterization; 6MWD = distance walked in six minutes; SPPB = Short Physical Performance Battery (range 0–12, lower scores denote worse frailty; FFP = Fried Frailty Phenotype (range 0 – 5; higher scores denote worse frailty)

Subject quotes			
Topic	Subject quotes		
Were Aidcube and Fitbit easy to use?	"I think the app [Aideube] is wonderful. I'm an app developer myself and I think this can work for a lot of people who have various levels of technological knowledge." (Subject 4, M, age 65, IPF)	"I was excited about using the Fithit, but I just kept misplacing it. My daughter got me the Flex device after I lost the Zip and that was a bit better, but still hard to remember to wear it." (Subject 6, F, age 57, COPD)	"I ve had no trouble using the app [Aidcube] and I'm not good with the stuff. I like that there are videos available if I forget how to do an exercise." (Subject 9, M, age 63, IPF)
Were there problems completing home- exercises? What did you like about your exercises?	"It's nice being able to use exercise equipment that I can adjust to however I'm feeling that day. Weights are unforgiving, but the Therabands are much easier to use." (Subject 7, M, age 66, IPF)	"It's hard to be motivated to exercise when you're not feeling well. Half the issue is just getting myself up and going. I like that I can do my exercises in my kitchen or in my bedroom. Doesn't take as much effort." (Subject 3, F, age 55, COPD)	"I find that I do strain to stay with my program. I'm doing the progressions like I should; It's just difficult to get into it on the days when I'm not feeling great. I know that this is good for me though so it makes me want to try." (Subject 2, M, age 69, COPD)
Overall feedback of the study	"The idea that I'm doing something makes me feel good. I like having a schedule of something concrete I can do to help myself rather than just waiting for my next appointment and worrying about my next breathing test." (Subject 4, M, age 65, IPF)	"I liked participating in this study. The exercises were fun and easy and I lost weight during the study. The weekly calls were nice. It felt good to have someone checking on me." (Subject 1, F, age 58, COPD)	"This was really helpful. I worked hard to keep up with the program and it felt good. That made me want to keep at it even more. I hope that more patients can use this. It was so helpful for me." (Subject 6, F, age 57, COPD)

Table 3

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	Baseline	8 week	8 week Within-person change from baseline to 8 week P-value ¹ Improved 1× MCID Improved 2× MCID Improved 3× MCID	P-value ^I	Improved 1× MCID	Improved 2× MCID	Improved 3× MCID
SPPB	9.7 ± 1.0	10.8 ± 1.5	1.0 ± 1.9	0.08	1 (7.7%)	3 (23.1%)	3 (23.1%)
FFP	2.4 ± 1.1	1.7 ± 1.4	-0.6 ± 1.0	0.07	7 (58.3%)	1 (8.3%)	0 (0%)
6MWD (m)	287.5 ± 83.8	279.7 ± 74.8	-7.8 ± 77.7	0.73	$2 (16.7\%)^2$	ł	I
Grip strength	32.8 ± 10.6	33.7 ± 11.9	1.5 ± 7.3	0.48	ł	1	I
LT-VLA	1.1 ± 0.7	1.1 ± 0.7	0.1 ± 0.4	0.26	I	1	I
DASI	19.1 ± 13.2	19.1 ± 13.2 21.5 ± 12.3	-0.1 ± 5.8	0.94	1	1	I

Outcome measures (n = 13 subjects who completed the intervention)

P-value by paired t test.

²Defined as six-minute walk distance increase 30 meters.

SPPB = Short Physical Performance Battery (range 0–12, lower scores denote worse frailty; MCID = 1); FFP = Fried Frailty Phenotype (range 0 – 5; higher scores denote worse frailty; MCID = 1)

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Table 5

Change in frailty scores and states over the course of the intervention by participant

	Shc	Short Physical Performance		Battery (Frailty Defined as Score 9)		Fried Frailty Ph	Fried Frailty Phenotype (Frailty Defined as Score 3)	ed as Score 3)
Participant	Baseline	Intervention end	Frailty resolved [*]	Change in score (positive score = improved frailty)	Baseline	Intervention end	Intervention end Frailty resolved*	Change in score (negative score = improved frailty)
1	Not frail (10)	Not frail (10)		0	Frail (3)	Not frail (2)	Yes	-1
2	Frail (9)	Not frail (12)	Yes	+3	Not frail (2)	Not frail (1)		-
3	Frail (9)	Frail (9)	No	0	Not frail (2)	Not frail (1)		-
4	Not frail (10)	Not frail (12)		+2	Frail (3)	Not frail (2)	Yes	-
S	Not frail (11)	Frail (8)		- 3	Frail (3)	Frail(5)	No	2
9	Not frail (10)	Not frail (12)		+2	Not frail (1)	Not frail (0)		-
7	Not frail (11)	Not frail (12)		+1	Not frail (1)	Not frail (1)		0
8	Frail (9)	Frail (9)	No	0	Not frail (1)	Not frail (2)		1
6	Not frail (11)	Not frail (10)		- 1	Not frail (1)	Not frail (1)		0
10	Not frail (11)	Not frail (11)		0	Not frail (1)	Not frail (0)		-1
11	Frail (9)	Not frail (12)	Yes	+3	Frail (3)	Frail(3)	No	0
12	Not frail (10)	Not frail (12)		+2	Frail (3)	Not frail (1)	Yes	-2
13	Frail (8)	Not frail (12)	Yes	+4	Frail 4	Frail(3)	No	-1

^{*}Cells populated only if participant was frail at baseline assessment.