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LAM*Fit*: A Digital Fitness Program for Individuals with Lymphangioleiomyomatosis

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Abstract

LAM*Fit*: A Digital Fitness Program for Individuals with Lymphangioleiomyomatosis

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Background: Daily physical activity is reported to be substantially reduced in individuals with the rare lung disease lymphangioleiomyomatosis (LAM). This important modifiable risk factor can be reduced using proven behavioral change and exercise interventions. Using a digital health platform with remote monitoring to deliver a structured exercise regimen in the home setting may be feasible and safe for individuals with LAM that are medically appropriate to participate. **Methods:** In this dissertation, we describe the design and pilot testing of 'LAM*Fit,*' a fully remote, digital fitness program for individuals with LAM living in the United States. First, we convened a group of experts in LAM and conducted a 2-round, modified Delphi study to develop an expert consensus LAM*Fit* exercise preparticipation screening tool for providers to use to determine medical appropriateness prior to patient enrollment in LAM*Fit.* Next, we conducted a retrospective analysis of in-person clinical exercise testing during two prior exercise studies our research team as conducted among patients with interstitial lung disease (ILD) [n=15 LAM and

n=15 idiopathic pulmonary fibrosis (IPF)]. To determine the utility of using peak heart rate (HR) on six minute walk test (6MWT) for exercise prescription in higher-functioning individuals with ILD in the absence of maximal cardiopulmonary exercise test (CPET), we evaluated the agreement between peak HR on 6MWT and HR at the first ventilatory threshold on CPET, the criterion standard for aerobic exercise prescription. We identified a 'cutoff' threshold at or above 85% pred. 6MWT distance where it becomes inappropriate to use of peak HR on 6MWT to estimate aerobic exercise threshold in ILD. Lastly, we pilot tested LAM*Fit* over a period of 6 months using LAM medical provider prescreening, a custom digital health platform with a fitness tracker, a medical-grade pulse oximeter, a novel, in-app remote 6MWT, and patient-reported outcome measures administered during baseline, midpoint, and final remote study visits.

Results: All 25 participants with LAM (100%) completed the first 12-week exercise program of the LAM*Fit* pilot study, including baseline, and midpoint study visits. Twenty-two participants (88%) completed the second 12-week exercise program and final study visit, with 3 discontinuations for reasons unrelated to the study intervention. No serious or non-serious study-related adverse events occurred. High adherence to aerobic exercise during the two 12-week intervention periods of LAM*Fit* was achieved (intervention period 1: 81±18%; intervention period 2: 79±18%). In the first 12 weeks of the exercise program, the mean daily minutes of moderate-to-vigorous physical activity (MVPA) increased by an average of 51% (25.6 ± 32.6 min to 52.5 ± 59.2 min; p=0.0318) compared to the run-in period. Distance achieved in 6MWT increased by an average of 7.1% (36.2 ± 9.1m, p=0.0021) from baseline to midpoint, and continued benefit was seen after completion of the second exercise intervention, with an average increase of 8.5% distance walked on 6MWT (43.4 ± 10.9, p=0.0021) at final study visit compared to baseline. Significant improvements in fatigue, health-related quality of life, and

dyspnea were observed after participation in the first 12 weeks. Participants expressed a high level of satisfaction and acceptability of the LAM*Fit* digital fitness program.

Conclusion: A fully-remote approach to delivering a home-based exercise program in LAM is feasible and safe. The pilot feasibility study of LAM*Fit* was a noteworthy success. Stakeholder interest in the LAM community is very high for continuing to scale access to the LAM*Fit* program nationally and internationally.

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To Toni, my mother

You taught how to do hard things.

To Henry and Alice, my children

You can do hard things.

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Plain Language Summary

This dissertation summarizes the design and pilot testing of 'LAM*Fit*,' a digital fitness program to increase access to the health benefits of exercise for individuals with lymphangioleiomyomatosis (LAM). We built a custom digital health platform and used remote monitoring to pilot test the LAM*Fit* program's ability to safely deliver a home exercise regimen to patients with LAM living in the United States. As a first step, we brought together experts in LAM to develop a tool to medically screen patients with LAM for safety to participate in exercise outside of medically-supervised settings. Next, we invited patient representatives with LAM to serve as equal partners on the design team and co-designed a LAM*Fit* program logo, a study recruitment website, exercise program training materials, and an online, LAM-specific community forum. The private LAM*Fit* community forum served as a place where participants could share insights into overcoming barriers related to exercise and LAM and celebrate activity goal achievements. The use of fitness watches, activity goal setting, automatic reminder messages, and community engagement also helped encourage participants to be physical active and achieve their goals. Finally, we evaluated LAM*Fit* program in a testing period of 6 months. Program adherence and completion were high, no study-related health events occurred, fatigue, dyspnea, and health-related quality of improved, and participants expressed a high level of satisfaction and acceptability of the LAM*Fit* digital fitness program. Research findings will be used inform any necessary changes to the program, before invitations to enroll in LAM*Fit* are extended to all patients with LAM that are medically appropriate to participate.

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Chapter 1 – Introduction

1.1 Background

Lymphangioleiomyomatosis (LAM) is a rare, female-predominant disease of the lung parenchyma characterized by burdensome dyspnea, fatigue, and reduced quality of life.[1] LAM is caused by abnormal growth of smooth muscle cells in the lung vasculature, lymphatics, and alveoli, leading to the development of cysts in the lungs bilaterally.[2] Pulmonary manifestations include cystic lung destruction, slow annual forced expiratory volume (FEV_1) decline, and progressive gas exchange impairment.[3,4] LAM can also have extrapulmonary manifestations in the lymphatic system (e.g., thoracic duct dilatation, chylothorax, chylous ascites), the kidneys (e.g., renal angiomyolipomas), and other visceral organs, including the brain, heart, skin, eyes, and liver.[2] LAM presents sporadically (S-LAM) or can be associated with tuberous sclerosis complex (TSC-LAM), a rare genetic disease; pathologically, these two subtypes are indistinguishable, with dysfunction of the mTOR Complex 1 (mTORC1) pathway.[2] The true prevalence of LAM is unknown; however, one study completed in 7 countries estimated a prevalence of 3 to 7 cases per million in adult women.[5] Another study estimated that the sporadic form affects 1 in 400,000 adult women.[2] Patients with LAM are generally younger than patients with other respiratory diseases, with an average age of onset of symptoms of 38.9 ± 0.73 years.[6] At time of diagnosis, many patients are heavily involved in career and family responsibilities.

LAM is theorized to be estrogen-dependent as it primarily affects women; it also tends to progress more rapidly during premenopause.[7] LAM cells are estrogen receptor-positive.[8] Women with LAM can become pregnant and bear children, and some women have little to no complications during pregnancy; however, recent cohort studies suggest that pregnancy in LAM is associated with increased complications like maternal pneumothorax and reduction in lung

function, especially among women with moderate or advanced disease.[9] Pneumothorax during pregnancy and subsequent imaging sometimes precede a diagnosis of LAM.[10] Spontaneous pneumothorax is very common in LAM; the incidence of pneumothorax in LAM is about 1000 times higher than in the general female population.[11] Many pneumothoraces in LAM occur at the time of diagnosis (~36%) and are treated with chemical or surgical pleurodesis, which can reduce the risk of pneumothorax recurrence.[10] Even after pleurodesis, the rate of recurrence is high in LAM with an average of 3-4 pneumothoraces over one's lifetime.[6]

Presently, there is no published literature or expert opinion to suggest an increased risk for pneumothorax during aerobic exercise training beyond the natural risk associated with the disease. One study evaluated the incidence of pneumothorax in patients with LAM after pulmonary function testing (PFT) and maximal cardiopulmonary exercise testing (CPET) during admissions to the National Institutes of Health (NIH) Clinical Research Center between 1995 and 2015, and showed that the risks were extremely low (incidence during PFTs: 0.14 to 0.29 of 100 patients, or 0.02 to 0.04 of 100 tests; incidence during CPET: 0.14 to 0.28 of 100 patients, or 0.05 to 0.10 of 100 tests).[12] Gloeckl et al reported that one patient with LAM experienced a pneumothorax during their 4-week pulmonary rehabilitation (PR) program and was transferred to a hospital for treatment, but this event was interpreted to be part of the natural course of LAM and not related to any interventions during PR.[13] Recently, our study team reported on another patient with LAM that experienced a pneumothorax during recreational mountain biking that was outside of her prescribed walking regimen as part of the 'Exercise & Fatigue in LAM' study; this event was deemed to be non-study related and likely part of the natural course of LAM.[3]

Some literature does support an increased risk of pneumothorax in LAM after air travel,[10,11] but a larger retrospective cohort study of 449 patients with LAM and other interstitial

lung diseases (ILD) that were admitted to the NIH Clinical Research Center showed that the risk of pneumothorax after air travel remained relatively low in LAM and is more likely related to the naturally high incidence of pneumothorax in LAM compared to other lung diseases, instead of air travel itself.[14] Upon arrival to the NIH, the frequency of a new pneumothorax for LAM patients who traveled by airplane was 2.9% (1.1 per 100 flights) and by ground transportation, 1.3% (0.5 per 100 trips), compared to no patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis that presented with a pneumothorax.[14]

Otherwise, known risks of adverse event(s) during exercise in LAM are similar to those experienced by other individuals living with ILD. Individuals with ILD are especially at risk for exercise-induced desaturation, particularly as their interstitial disease progresses.[3] The 2023 American Thoracic Society (ATS) clinical practice guideline on "Pulmonary Rehabilitation for Adults with Chronic Respiratory Disease" advises that people with ILD, including LAM, often experience profound exertional oxygen desaturation, and consideration should be given to delivering pulmonary rehabilitation and structured exercise training in a setting in which necessary levels of supplemental oxygen can be administered.[15] Other age-related factors that should be screened for in ILD prior to initiating an exercise program include cardiovascular disease-related impairments and balance.[16,17]

A strong commitment to research in the LAM community has led to the formation of a leading rare disease patient advocacy group, The LAM Foundation (TLF), an engaged clinician and researcher network with international, specialized pulmonary clinic designations as "LAM Centers of Excellence," and successful FDA-approval of the drug sirolimus for the treatment of LAM in 2015. TLF is a registered 501(c)3 non-profit organization that was founded in 1995 as a grassroots effort, and has evolved into an organization that is described by the National Heart,

Lung, and Blood Institute (NHLBI) of the NIH as a "model for voluntary health agencies."[18] In 2015, the MILES trial, cosponsored by TLF and the NIH Division of Rare Diseases, showed that sirolimus, a commonly used drug to prevent rejection of transplanted organs, reduces the growth rate of lung cysts, preserves lung function, increases life expectancy, and delays the onset of end-stage lung disease (ESLD) in LAM.[19]

Even with the availability of sirolimus, some individuals with LAM still progress to ESLD necessitating consideration for lung transplantation. Positively, lung transplantation for LAM is associated with markedly better survival as compared to lung transplantation for other lung disease indications, including other ILDs, with a median survival after transplantation of 12 years.[20] Despite strong documented outcomes after lung transplantation in LAM, individuals with LAM do not have easy access to exercise interventions known to improve quality of life, reduce comorbidities, and prevent frailty that can limit eligibility for lung transplantation.

1.2 Pulmonary Telerehabilitation and Exercise Training

Traditionally, individuals with chronic respiratory diseases like LAM are referred to outpatient pulmonary rehabilitation (PR) centers after initial diagnosis, after acute exacerbation(s), after changes in functional status, or prior to listing for lung transplantation.[21] PR is a standardized program consisting of aerobic exercise, peripheral muscle strengthening, medication management, psychological support, patient education, and smoking cessation as needed.[15] The COVID pandemic has had lasting implications on access to center-based physical therapy and PR for individuals with chronic respiratory diseases, including individuals with LAM. Many PR centers closed or reduced their in-person capacity,[22] creating an access problem of unprecedented scale. Circumstances expedited a rapid expansion of telehealth services to restore access.[23] Numerous centers have not reopened, and those that have reopened have long

waitlists to start.[22] Even in non-pandemic times, center-based PR is challenged by co-pays and transportation barriers,[24–26] which are removed in a home-based exercise approach. A growing body of literature demonstrates comparable effectiveness between home-based telerehabilitation and traditional center-based PR in chronic obstructive pulmonary disorder (COPD).[27] Fewer studies are available to inform home-based, hybrid, and remote telerehabilitation programming in ILD,[11] and more research is needed. All of the components of traditional, comprehensive PR may not be necessary for the majority of individuals with ILD. The core components of aerobic exercise and resistance training on their own are shown to add significant value towards health promotion and risk reduction for health complications, hospitalizations, and death.[28,29,16]

Smartphone uptake and advances in health monitoring technologies have made remote, asynchronously monitored exercise programs much more feasible to safely deliver to individuals living with chronic diseases in the United States. According to the Pew Research Center, the vast majority of Americans – 98% – now own a cellphone of some kind. Ninety-one percent of adults own a smartphone, up from just 35% in the Pew Research Center's first survey of smartphone ownership conducted in 2011.[30] Widely adopted technology platforms, including mobile devices and wearable health monitors, can be leveraged to help improve patient access and health outcomes. The provision of care and exercise programs via telerehabilitation platforms is likely to be a lasting disruptive innovation to traditional health care delivery models. As technology-enabled telerehabilitation programs become more ubiquitous, more research is needed to optimize the design of technology platforms and exercise interventions that are feasible and safe for individuals with interstitial lung diseases (ILD), including LAM.

1.3 A Patient-Centered Approach to Exercise Programming

Tailored exercise interventions are shown to be more effective than generalized solutions.[25,31] The patient-centered, or person-centered care movement in health care encourages tailoring of interventions to individual needs and incorporates patient preferences into care delivery.[32–34] We hypothesize that each ILD needs a slightly different approach to telerehabilitation due to unique disease-specific factors. For example, patients with LAM are generally younger (mean age of symptom onset = 38.9 years)[6] and tend to have lower comorbidities than other chronic lung diseases like COPD.[24] However, physical activity (PA) in daily life is reduced in patients with LAM compared to healthy controls and patients with COPD.[35] This disease-specific impact may be associated with low energy levels, also described as "extreme exhaustion" and "absolutely crushing fatigue" by patients with LAM.[1] Patients with another rare type of ILD, idiopathic pulmonary fibrosis (IPF), are typically older (mean age of diagnosis = 68 years old)[36] than patients with LAM, and are thus likely to have lower technology literacy[37] and other age-related health changes.

We also hypothesize that person-level factors should be incorporated to optimize the feasibility, acceptability, effectiveness of a community-based exercise intervention. Some individuals with ILD are at risk for oxygen desaturation during exertion, but not all. Some intervention participants may prefer to cross train on different modalities of aerobic exercise (e.g., alternating upright cycling and walking on a treadmill), while others tend to choose one preferred exercise modality each session (e.g., walking outside only). Patient-level and disease-specific factors must be considered when weighing intervention accessibility and risk for adverse event(s) during home-based, non-medically supervised exercise. If these factors are not designed

for *a priori*, efforts to disseminate our exercise intervention will instead *augment* digital divides, *increase* risks during exercise, and *exacerbate* access problems.

1.4 Leading Up to LAM*Fit*

In November 2017, The LAM Foundation held a Patient Benefit Conference in Los Angeles, CA with the specific goal of identifying and supporting new products or services to benefit patients in the shorter term. Moderated Solutions Workshops were held with patients, researchers, clinicians, and thought leaders working together and utilizing design thinking concepts to innovate solutions. During the Exercise & LAM workshop, participants charted a process for developing exercise guidelines for women with LAM (Figure 1.1).[38]



Figure 1.1: 2017 Patient Benefit Conference: Considerations for Patient-Centered Exercise Guidelines in LAM. Participants in the Exercise & LAM workshop at the 2017 Patient Benefit Conference charted considerations for the development of patient-centered guidelines for unsupervised exercise training in LAM. Adapted from "Short-Term Goals, Long-Term Effects: Outcomes of the 2017 LAM Patient Benefit Conference."[38]

The LAM*Fit* digital fitness program prioritizes several considerations from this workshop, as well as other patient-centered needs identified in our preliminary needs assessment. My primary research mentor, Dr. Mary Beth Brown, PT, PhD, co-led the Exercise & LAM workshop in 2017, and subsequently received a Patient Benefit Grant from TLF to investigate the safety, feasibility, and effectiveness of a digitally-enabled exercise program among n=15 individuals with LAM, with baseline and final in-person study visits. I joined the Brown Lab in the fall of 2020. I immediately gained the opportunity to assist with these study activities, data analysis, and dissemination of results. The "Exercise & Fatigue in LAM" study was successfully completed in 2022 with no adverse study-related safety events, and results are published.[3]

In 2022, Dr. Brown received an Established Investigator award from The LAM Foundation to pilot test 'LAM*Fit*', a program to offer a similar exercise intervention to the one that was tested in the "Exercise & Fatigue in LAM" study[16] on an innovative, fully-remote, digital health technology platform. The aims of this dissertation are generously supported by this award to Dr. Brown (Principal Investigator) and I (Co-Investigator).

1.5 Theoretical Framework

The decision by individuals to become more active is made in relation to specific contexts and environments. Our research approach is supported in part by *Social Cognitive Theory (SCT)*, a causal model in which self-efficacy influences human behavior directly and indirectly via other mediating processes, including reciprocal interactions between the person, the social environment, and the behavior (Figure 1.2).[39–42] The LAM*Fit* program leverages social and environmental interactions to promote physical activity and exercise routine behavioral changes among individuals with LAM.

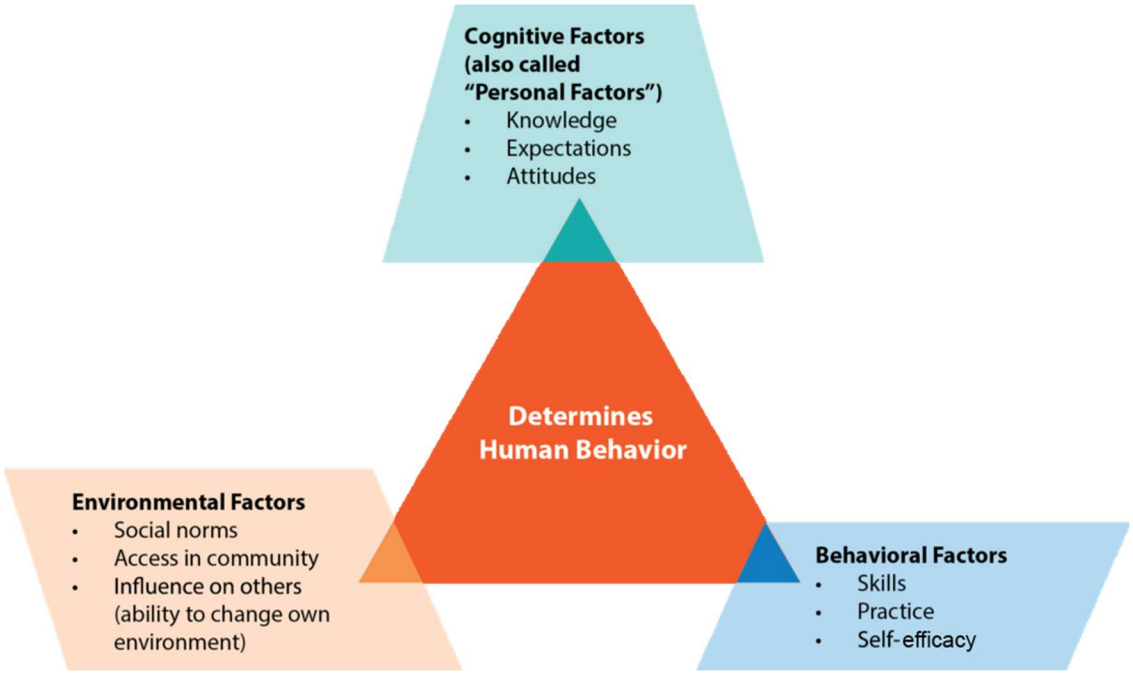


Figure 1.2: An Overview of Social Cognitive Theory. Framed by the Social Cognitive Theory, the LAM*Fit* program seeks to educate to enhance knowledge, expectations, and attitudes about the benefits of exercise in LAM, and leverage social and environmental interactions to promote physical activity behavioral changes among individuals living with LAM. From the Health Communication Capacity Collaborative (HC3) Cooperative, Emergency Preparedness Implementation Kit, USAID Bureau for Global Health.[42]

Our approach also incorporates tools of human-centered design (HCD) to optimize person-centered care delivery. HCD is an iterative design process in which the primary focus is on the current and anticipated user needs in each phase of the design process.[43] To structure our study methods, we used the University of Washington (UW) Institute of Translational Health Science (ITHS)-supported Dissemination and Implementation (D&I) Toolkit (shared by Allison Cole, MD, MPH via email communication, June 2022), among other resources. The ITHS D&I Toolkit is based on the Expert Recommendations for Implementing Change (ERIC) guidelines,[44] a proven set of strategies for implementing evidence-based interventions and measuring outcomes. The toolkit recommends three specific steps for disseminating a research product among individuals, within a specific organization, or in a community-based setting (Figure 1.3).

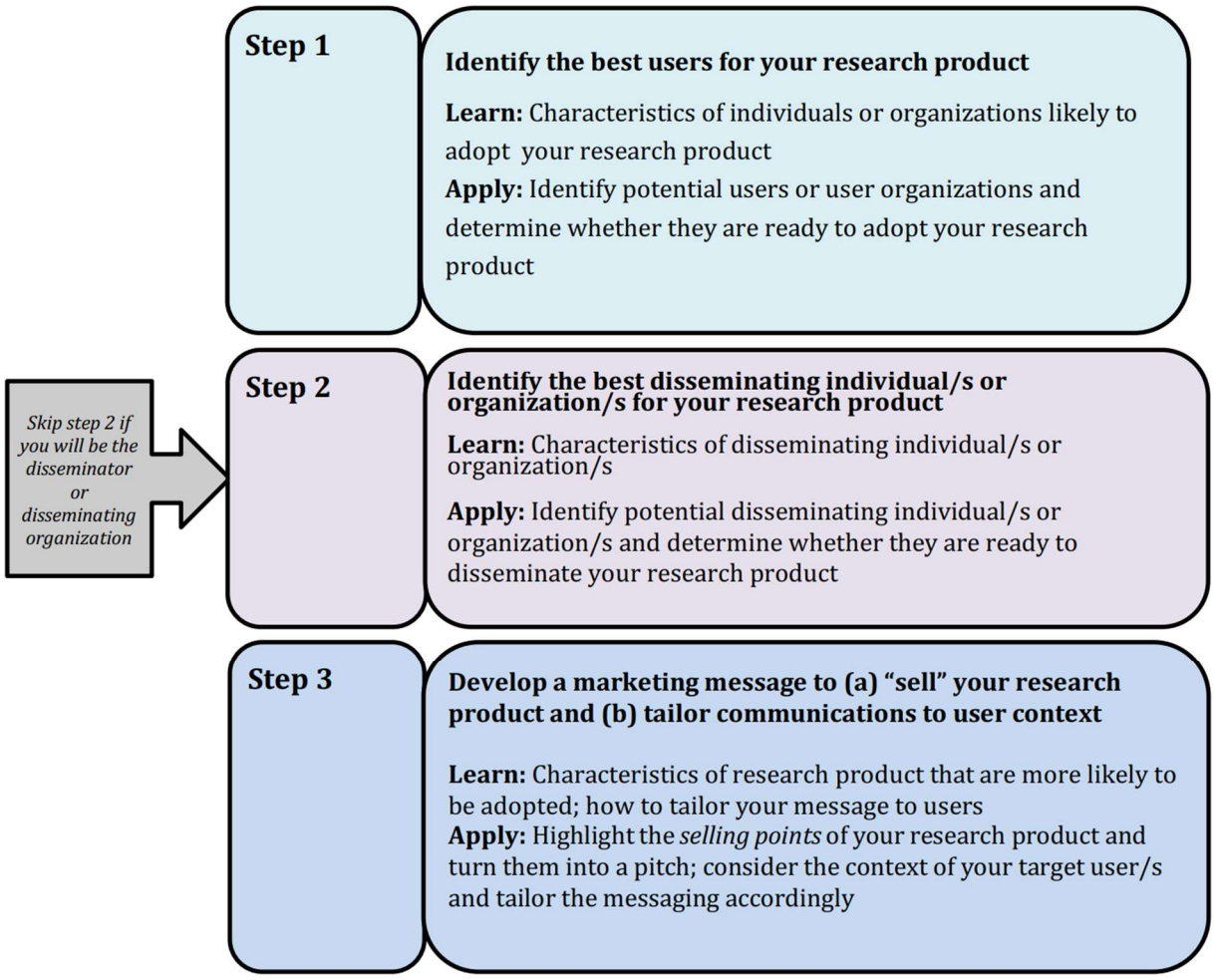


Figure 1.3: Promoting the Use of Research in the Real World: A Step-by-Step Guide to Disseminating Research Findings. From the University of Washington Institute of Translational Health Sciences (ITHS) Dissemination & Implementation (D&I) Toolkit (shared by Allison Cole, MD, MPH via email communication, June 2022), which is based on the Expert Recommendations for Implementing Change (ERIC) guidelines,[44] a proven set of strategies for implementing evidence-based interventions and measuring outcomes.

To learn the preliminary needs and characteristics of the individuals that would be most likely to adopt our research product, we conducted 17 semi-structured interviews with women with LAM between Nov 2021 and July 2022. We used reflexive thematic analysis[45,46] of interview transcripts to identify emergent themes[46] and inform the preliminary design of the LAM*Fit* program (Figure 1.4). We continued to partner closely with patient representatives living with LAM during each of the design and delivery phases to maximize the patient-centeredness of the LAM*Fit* program.

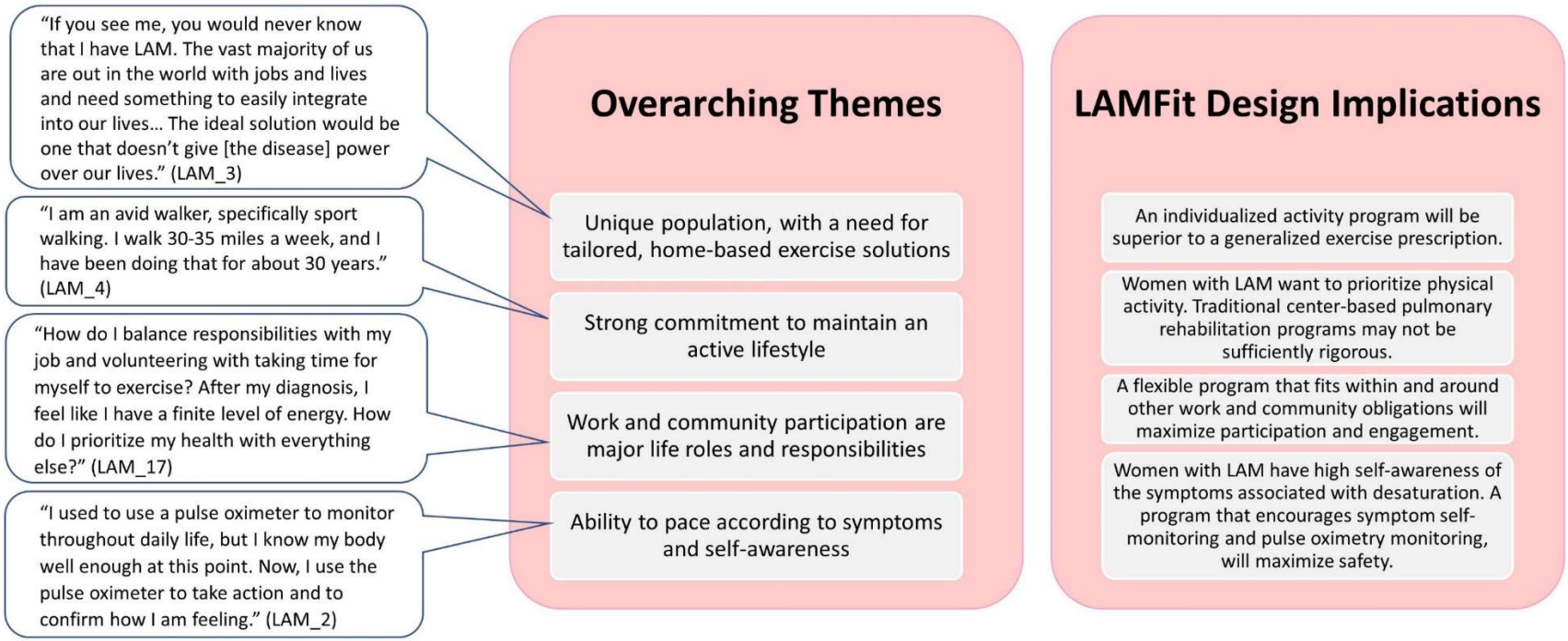


Figure 1.4. Overarching Themes and Patient-centered Design Implications for the LAM*Fit* Program were derived from an end user-centered needs assessment of patients with LAM. Specific efforts were made to tailor the design of LAM*Fit* to meet the needs and preferences of patients with LAM.

1.6 Aims and Objectives

Restoring and scaling access to evidence-based exercise interventions for people living with interstitial lung diseases (ILD), including rare diseases like LAM, is critical. This dissertation addresses the unmet need of providing guidance to patients, clinicians, researchers, and other stakeholders on how to best tailor home-based exercise interventions to individuals with LAM and other ILDs that have unique physiological risks for adverse event(s) during non-medically supervised exercise. We also investigated the feasibility and safety of using a fully-remote, digital technology-enabled approach to deliver an exercise intervention to individuals with LAM living in the United States during a 6-month pilot study of LAM*Fit*.

We report the outcomes of the following research aims:

Aim 1: Develop a consensus risk stratification tool for 'LAM*Fit*' participant enrollment by conducting a modified Delphi study with a panel of key stakeholders. In this aim, we sought to answer the research question of which screening steps are essential to determine whether a patient with LAM is medically appropriate to participate in LAM*Fit,* a remote, unsupervised exercise program. To synthesize expert opinions related to medical appropriateness for unsupervised exercise in LAM, we conducted a two-round modified Delphi study consisting of a first-round online survey and a second round in-person meeting for consensus development. After completion of the Delphi study, an expert consensus, LAM-specific exercise preparticipation screening tool was designed and disseminated, along with instructions for use to providers located at LAM Centers of Excellence. The LAM*Fit* exercise preparticipation screening tool was posted on the LAM*Fit* study recruitment website, with resources to orient LAM medical care providers and patients with LAM to the LAM*Fit* program.

Aim 2: Validate a formula or heart rate threshold that can be used for aerobic exercise prescription in high-functioning individuals with interstitial lung disease, in the absence of a maximal cardiopulmonary exercise test. In the absence of a recent maximal cardiopulmonary exercise test (CPET), which is not always feasible to obtain, no formulas have been published for estimating an appropriate target heart rate (HR) range or threshold for exercise prescription from a six-minute walk test (6MWT) or another standardized field test in interstitial lung disease (ILD). To optimize aerobic exercise prescription during the LAM*Fit* digital fitness program, we sought to answer the question of how best to prescribe aerobic exercise intensity in higher-functioning individuals with ILD, in the absence of a CPET. We conducted a secondary analysis of the results of clinical exercise testing (6MWT and CPET) performed during two prior studies in the Brown Lab – the "Exercise & Fatigue in LAM"[3] and the "IPF mHealth Exercise" (manuscript in review) studies. From this analysis, we make recommendations for a HR-guided aerobic exercise prescription in higher functioning individuals with ILD, in the absence of recent maximal CPET.

Aim 3: Conduct a 6-month prospective pilot feasibility study of 'LAM*Fit*' to determine program feasibility and effectiveness among n=25 individuals with LAM. After design of the LAM*Fit* digital technology platform, we conducted a 6-month pilot study of a fully-remotely monitored exercise program for lymphangioleiomyomatosis (LAM). All participants were pre-screened by their own care provider using the consensus LAM*Fit* exercise preparticipation screening tool developed in the Aim 1 study. All participants completed in-clinic exercise testing to ensure adequate availability of home supplemental oxygen for aerobic exercise training. Providers electronically attested with signature whether their patients were medically appropriate to participate in the fully-remote LAMFit program prior to study enrollment. Our

primary outcome of interest was the feasibility and safety of the novel LAM*Fit* fully-remote, digital technology-enabled exercise program. Secondary endpoints included daily physical activity amounts and duration of exercise activities, total METs*mins and average METs achieved during exercise sessions, and changes in self-reported fatigue, health-related quality of life, and dyspnea.

1.7 Overview of the Dissertation

This dissertation is organized into three linked manuscripts formatted as chapters. Chapters 2, 3 and 4 report on the outcomes of the three dissertation aims. Chapter 2 describes the results of a two-round modified Delphi study among 16 experts in ILD and LAM to develop consensus, disease-specific recommendations for safety and preparticipation screening prior to unsupervised, remotely administered exercise in LAM. The primary product of this study was a clinical decision aid for providers to use when medically screening patients prior to participation in LAM*Fit*. Chapter 3 describes a secondary analysis of in-person clinical exercise testing – both 6MWT and maximal CPET – during two prior studies in the Brown Lab – the 'Exercise & Fatigue in LAM'[3] and 'IPF mHealth Exercise' (manuscript in review) studies. The primary outcome of this study is the identification of a "ceiling effect" limitation to using $HR_{peak6MWT}$ to inform aerobic exercise prescription in higher functioning individuals with ILD. Chapter 4 presents the feasibility, safety, and preliminary effectiveness results of a 6-month prospective pilot study of the LAM*Fit* digital fitness program among 25 individuals with LAM. The pilot feasibility study of LAM*Fit* was a noteworthy success, and stakeholder interest in the LAM community is very high for continuing to scale access to the LAM*Fit* program nationally and internationally. Chapter 5 concludes the dissertation and provides an overview of next steps within this dissertation's specific line of inquiry.

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Chapter 2 – Unsupervised Exercise in Interstitial Lung Disease: A Delphi Study to Develop a Consensus Preparticipation Screening Tool for Lymphangioleiomyomatosis

PREFACE

Aim 1: Develop a consensus risk stratification tool for 'LAM*Fit*' participant enrollment by conducting a modified Delphi study with a panel of key stakeholders.

In this aim, we sought to answer the research question of what exercise preparticipation screening steps are essential to determine whether a patient with LAM is medically appropriate to participate in LAM*Fit,* a remote, non-medically supervised exercise program. To synthesize expert opinions related to medical appropriateness for unsupervised exercise in LAM, we conducted a two-round modified Delphi study consisting of a first-round online survey and a second round in-person meeting for consensus development. After completion of the Delphi study, an expert consensus, LAM-specific exercise preparticipation screening tool was developed and disseminated, along with instructions for use to providers located at LAM Centers of Excellence. The LAM*Fit* exercise preparticipation screening tool was posted on the LAM*Fit* study recruitment website, along with educational resources to orient LAM medical care providers and patients with LAM to the LAM*Fit* digital fitness program.

2.1 ABSTRACT

Background: Little research is available to provide practical guidance to health care providers for exercise preparticipation screening and referral of patients with interstitial lung diseases (ILD), including lymphangioleiomyomatosis (LAM), to participate in remote, unsupervised exercise programs.

Research Question: What exercise preparticipation screening steps are essential to determine whether a patient with LAM is medically appropriate to participate in a remote, unsupervised exercise program?

Study Design and Methods: Sixteen experts in LAM and ILD participated in a two-round modified Delphi study, ranking their level of agreement for ten statements related to unsupervised exercise training in LAM, with an *a priori* definition of consensus. Additionally, 60 patients with LAM completed a survey of the perceived risks and benefits of remote exercise training in LAM.

Results: Seven of the 10 statements reached consensus among experts. Experts agreed that an in-person clinical exercise test is indicated to screen for exercise-induced hypoxemia and prescribe supplemental oxygen therapy as indicated prior to initiating a remote exercise program. Patients with recent pneumothorax should wait to start an exercise program for at least 4 weeks until after resolution of pneumothorax and clearance by a physician. Patients with high cardiovascular risk for event during exercise, severe resting pulmonary hypertension, or risk for falls may be more appropriate for referral to a rehabilitation center. A LAM-specific remote exercise preparticipation screening tool was developed from the consensus statements and agreed upon by the panelists.

Interpretation: A modified Delphi study approach was useful to develop disease-specific recommendations for safety and preparticipation screening prior to unsupervised, remotely administered exercise in LAM. The primary product of this study is a clinical decision aid for providers to use when medically screening patients prior to participation in the newly launched LAM*Fit* remote exercise program.

2.2 TAKE-HOME POINT

Study Question: How should providers prescreen patients with lymphangioleiomyomatosis (LAM) for medical appropriateness to participate in a remote, unsupervised exercise program?

Results: In this modified Delphi study, 7 of 10 statements achieved expert consensus for LAM-specific exercise preparticipation screening prior to initiating a remote, unsupervised exercise program.

Interpretation: A remote exercise preparticipation screening tool was developed to aid LAM providers in determining medical appropriateness for an unsupervised exercise program.

ABBREVIATIONS LIST

lymphangioleiomyomatosis, LAM; interstitial lung disease, ILD; pulmonary rehabilitation, PR; adverse event, AE; chronic obstructive pulmonary disorder, COPD; FEV_1, Forced expiratory volume in one second; oxygen saturation, SpO_2; oxygen, O_2; dyspnea on exertion, DOE, health-related quality of life, HRQoL; six-minute walk test, 6MWT; cardiopulmonary exercise test, CPET; percent, %; standard deviation, SD; tuberous sclerosis complex, TSC; United States of America, USA; metabolic equivalent, MET; maximal oxygen consumption, $\dot{V}O_2max$; pulmonary hypertension, PH; ATS, American Thoracic Society; AACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)

2.3 BACKGROUND

With the rapid uptake and growing availability of new models of exercise programming and telerehabilitation in chronic respiratory diseases, the exercise setting is an important new variable to consider in exercise risk stratification. In settings where exercise training occurs without direct supervision, health care providers have a reduced capacity to respond to an adverse event (AE) or medical emergency. However, a hybrid or remote exercise or pulmonary rehabilitation (PR) delivery model reduces barriers to referral, attendance, and affordability.[1–3] The 2023 American Thoracic Society (ATS) clinical practice guideline on "Pulmonary Rehabilitation for Adults with Chronic Respiratory Disease" strongly recommends offering a choice between telerehabilitation and center-based PR for stable patients with chronic respiratory disease, but acknowledges that the majority of telerehabilitation studies to date are in chronic obstructive pulmonary disorder (COPD).[4] Compared to COPD, less evidence is available to support the development of guidelines for exercise programming in interstitial lung disease (ILD).[3]

ILD comprises a heterogenous group of disorders that share some, but not all, similarities in risks for events during exercise. Individual disease pathology, sequelae, and other system comorbidities can contribute additional risks for exertional complications. Thus, a patient-centered and disease-specific approach to exercise preparticipation risk screening is preferred for risk mitigation. Patients with the rare, female-predominant ILD lymphangioleiomyomatosis (LAM) commonly experience exertional hypoxemia as the disease progresses,[5,6] similar to other ILDs.[7] Pulmonary manifestations of LAM include cystic lung destruction,[8] slow annual FEV_1 decline, and progressive gas exchange impairment.[9] Patients with LAM are generally younger than patients with other chronic respiratory diseases, with an average age of onset of symptoms

of 38.9 ± 0.73 years.[10] Many patients are still heavily involved in career and family responsibilities.[11]

Traditionally, patients with ILD, including LAM, have been referred to supervised, center-based PR programs for availability of supplemental oxygen, assistance with oxygen titration, and direct supervision during exercise. However, center-based PR programs may not be as accessible as home-based programs and may not be preferred by patients with LAM. The recent 2023 ATS Guideline authors suggest that exercise-based PR for adults with ILD should be delivered in a setting in which supplemental oxygen can be administered during training, given the primary risk for exertional desaturation.[4] If sufficient supplemental oxygen is available to support exercise training, a home-based approach removes many of the participation barriers encountered by patients with LAM and ILD.[12] Most adults with LAM are young- to middle-aged at the time of diagnosis,[11] and thus are less likely to have age-related challenges to digital health literacy and barriers to use of wearable fitness trackers,[13] both important factors to the success of a digitally-enabled care approach in chronic respiratory disease.[14,15] It has been recently demonstrated that a remote, asynchronously monitored home exercise program is safe in LAM, with no study-related AEs and high participant satisfaction, and improves symptoms of dyspnea, fatigue, and exercise intolerance.[5] In community-academic partnership[16] with The LAM Foundation, we will now implement 'LAM*Fit*', a program to expand access to the health benefits of exercise for more individuals with LAM.

Current population-based models for exercise preparticipation screening, including the 2015 American College of Sports Medicine (ACSM) Exercise Preparticipation Health Screening Tool[17] and the 2018 Physical Activity Guidelines for Americans,[18] are based on an individual's current physical activity levels, the presence of signs or symptoms and/or known cardiovascular,

metabolic, or renal disease, and planned exercise intensity, all of which are risk modulators of exercise-related cardiovascular events.[19] Notably, both of these resources do not advise on risk factors related to chronic respiratory diseases. There is a gap in the literature of available screening tools to assist providers when prescreening patients with LAM and other chronic respiratory diseases who want to initiate an unsupervised home exercise program. The purpose of this study was to develop an expert consensus exercise preparticipation screening tool specifically for patients with LAM, to be used by LAM providers when determining medical appropriateness to participate in the remote, unsupervised LAM*Fit* exercise program.

2.4 METHODS

To synthesize the opinions of health care providers, patients, and other stakeholders in the LAM community related to screening for medical appropriateness for unsupervised exercise in LAM, we conducted a two-round modified Delphi study consisting of a first-round online survey and a second round in-person meeting for panel discussion. A Delphi study methodology is an acceptable method for generating consensus when there is a paucity of available literature and an urgent need to develop guidelines.[20,21] A modified RAND/UCLA Appropriateness Method[22] (Figure 2.1) was used to structure each round, as it is a rigorous Delphi-style method with extensive use cases in health care for generating consensus about the appropriateness of procedures and the prospective development of clinical decision aids.[23–27] Refer to Table 2.1 for key components and methodological priorities of the RAND/UCLA Appropriateness Method, adapted from the published user manual.[22] Study procedures were approved by the University of Washington Institutional Review Board (STUDY017539).

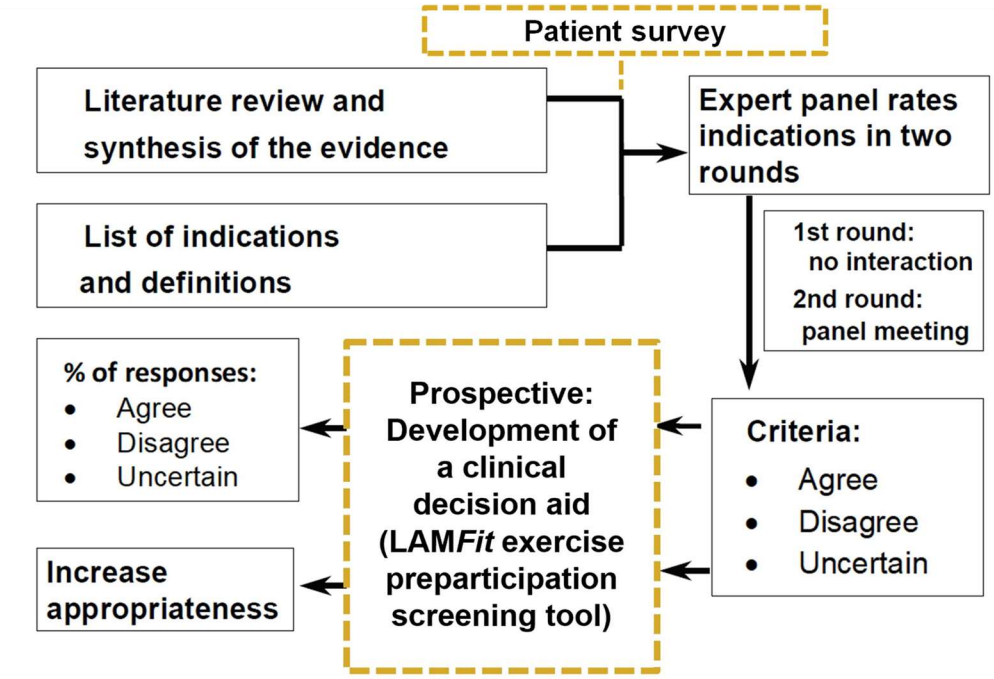


Figure 2.1: An Overview of the Delphi Study Method, adapted from the RAND/UCLA Appropriateness Method[22] for the prospective development of a clinical decision aid by the LAM*Fit* Delphi panel in this study. The RAND/UCLA Appropriateness Method user manual[22] provides guidance for structuring expert panel processes to measure and increase the appropriateness of a clinical tool or set of guidelines. Investigators in this study generally adhered to the RAND/UCLA Appropriateness Method user manual by 1) conducting a literature review and sharing with invited experts a synthesis of the evidence, 2) conducting a first-round online survey and a second-round, in-person panel meeting, 3) using specific RAND/UCLA criteria for grading of consensus agreement, disagreement, or uncertainty about statements, and 4) prospectively developing a clinical decision aid for exercise preparticipation screening prior to patient enrollment in the LAM*Fit* program.

Table 2.1. Key Components and Methodological Priorities of the RAND/UCLA Appropriateness Method

Key Component	Description
1. Identify a panel of experts	Experts are often identified using purposive sampling[28] and based on recommendations from relevant professional societies or patient advocacy groups.
2. Conduct a literature review and share with the panelists	A detailed literature review is performed to synthesize the latest available scientific evidence on the procedure or clinical decision to be rated.
3. Develop a list of statements for appropriateness related to the procedure or the clinical decision	A list of concise statements and definitions are written in accordance with the literature review and any background research, and shared with the panelists.
4. Organize a two-round modified Delphi panel process	The panel process usually consists of a first round survey with no interaction among panelists, and a second round meeting where panel members convene under the leadership of a moderator.
5. Discussion during the second-round meeting	During the meeting, expert panelists discuss the ratings and are given the opportunity to modify the wording of the original list of statements, if desired.
6. Final ratings	Panelists individually rate each finalized statement. Each statement is evaluated for levels of agreement among the panelists.
Methodological Priorities	
• Define what is considered professional expertise for invited panel members. • Encourage rigorous panel discussion, focusing on areas of disagreement, but allow experts to remain anonymous during ratings. • Follow an a priori definition of consensus. • Use standardized surveys for all participants. • Evaluate group answers statistically as representative of the whole. • Provide regular, anonymous feedback of panel results to participating experts. • No attempt is made to force the panel to achieve full consensus. • A third round of ratings may be held if medical necessity criteria for a procedure are also to be developed, but it is not required.	

Purposive sampling[28] was used to identify and invite a diverse panel of 16 providers, researchers, and other professionals in LAM and ILD. Our panel size was informed by other Delphi studies in health care,[29,30] as there is no standard size.[31] Physician directors of at least 5 geographically distinct LAM Centers of Excellence, other clinician scientists with expertise and recent publications in the pathophysiology of LAM and ILD, hypoxia, altitude, and exercise, and leadership from The LAM Foundation were invited to participate.

Review of the Literature

A MEDLINE database search was performed for relevant articles published in the English language between 1992 and 2022. MeSH headings of "exercise" and "exercise training" were combined with other relevant search terms, including *guidelines, preparticipation screening*, *risk of event, remote, physical activity, chronic respiratory disease, interstitial lung disease,* and *lymphangioleiomyomatosis.* Additional online resources were compiled and reviewed from the websites of medical professional associations, including the ATS, ERS, ACC, AHA, ISHLT, ACSM, and AACVPR. Full articles of available clinical practice guidelines and evidence-based exercise preparticipation screening tools for chronic diseases were reviewed and summarized by two investigators. Prior to Round 1, all invited expert panelists were asked to read a summary of existing literature regarding exercise preparticipation screening in chronic diseases.

Existing tools for exercise preparticipation screening have been developed and disseminated,[17,32,33] but are less specific to LAM and ILD. Population-based screening tools consider cardiovascular risks first and foremost – without intact cardiac electrophysiology and pump function, increasing the cardiovascular workload can result in an abnormal exercise response.[34] Patients with ILD can develop comorbid cardiovascular conditions, especially as they age.[35] Thus, in addition to risk for exertional desaturation,[4] current literature suggests that patients

with LAM and ILD should also be prescreened for cardiovascular risks[17] prior to initiating an unsupervised exercise program.

Round 1

A Round 1 survey for experts was developed by the research team utilizing concepts from literature on population-based exercise preparticipation screening, cardiopulmonary rehabilitation, and LAM-specific exercise physiology. Initial survey questions were reviewed by three content experts in medicine, pulmonology, and LAM, and revisions were made based on feedback. The Round 1 survey for experts consisted of short-answer, ranking, and open-ended questions about the risks and benefits of unsupervised exercise in LAM (Supplemental Material). The Round 1 survey was administered to expert panelists via REDCap (Research Electronic Data Capture), a secure, web-based platform designed to support research data capture,[36] and remained open for 3 weeks. To maximize response rates, the tailored design method devised by Dillman et al[37] was used with reminder emails 3 additional times, 4 days apart until completion.

Patient Survey

Recognizing that patients are key stakeholders in a community-engaged approach to the development of a health promotion program,[16] patients with LAM were also invited to complete a separate online survey (different than the Round 1 survey for experts) about their own lived experience and their perceptions of exercise in LAM (Supplemental Material). Since there is little available literature about the patient experience of exercising with LAM, the research team felt that the patient voice was important for experts to consider during panel activities, in addition to their own professional experience in LAM. A convenience sample of patients with LAM were recruited via email, social media, and word of mouth, in collaboration with designated patient liaisons for The LAM Foundation. The survey was administered anonymously via REDCap and

remained open for 3 weeks. Importantly, patient survey results were not used in the drafting of statements, and patients did not comment on the statements or the preparticipation screening tool that are the primary outcomes of this study. The patient survey results were summarized as major themes with example raw quotes and provided to experts as background material prior to the in-person panel meeting.

Round 2

Round 1 expert survey results were shared electronically with panelists 4 weeks before the Round 2 panel meeting. For this, two investigators drafted initial statements based on review of published exercise preparticipation screening guidelines in the literature[17,32,38,39] and final themes from the primary risks and concerns expressed by LAM experts. Two other content experts in medicine, pulmonology and LAM reviewed and provided feedback on the initial statements for clinical and methodological appropriateness. Four experts in total participated in an iterative process of review, revision, and interpretation to arrive at the final statements that were reviewed by the expert panel. Round 2 occurred as an in-person meeting at the May 2023 ATS International Conference in Washington, D.C., USA. Panelists received complimentary breakfast and no monetary compensation. The moderator presented each statement individually for panel discussion. Final level of agreement assessment occurred via anonymous paper survey at the end of the Round 2 meeting, with options to select "Agree," "Disagree," or "Uncertain" for 9 of the 10 statements. One statement provided numerical options for acceptable desaturation threshold for exertional oxygen use in LAM. Consensus was defined *a priori* as ≥ 78% of panelists selecting the same option (e.g., "Agree") for a statement, similar to the RAND/UCLA Appropriateness mean threshold of ≥ 7 out of 9 on a 9-point Likert scale.[22]

The moderator also presented for panel discussion a draft of the LAM*Fit* preparticipation screening tool based on the primary risks perceived by experts in Round 1. During the Round 2 meeting, each component and decision point of the screening tool was openly discussed and evaluated by panel members. After the Round 2 meeting, a revised LAM*Fit* preparticipation screening tool was designed and shared with experts electronically for another round of feedback and consensus approval. Statements that did not reach consensus in Round 2 were not included in the final design of the LAM*Fit* preparticipation screening tool.

Post-Delphi Panel Assessment Survey

Panelists were also asked to complete an anonymous post-Delphi assessment survey about their experience, with questions adapted from an example survey in the RAND/UCLA Appropriateness Method user manual[22] (Supplemental Material). The post-Delphi assessment survey remained open for 3 weeks.

Data Analysis

Qualitative data from the Round 1 expert survey, patient survey, and expert post-Delphi panel assessment survey were analyzed using content analysis[40] and inductive thematic analysis,[41,42] employing constant comparative coding methods[43] in Dedoose *version 9.0.107* (SocioCultural Research Consultants, Los Angeles, CA). Determination of the major themes occurred in a three-step process. Open-ended survey responses were closely read by two investigators to create code categories, and continuously revise and refine them. In the second step, open coding terms were triangulated and grouped into salient themes via axial coding. Finally, a third reviewer and content expert in pulmonology confirmed the selection of a final list of themes and assessed whether they reflected the main constructs of expert-perceived risks of remote,

unsupervised exercise in LAM. Final themes from the expert survey data structured the drafting of guideline statements.

In addition to qualitative data analysis as described above, descriptive statistics were used to characterize study participants and survey responses. Quantitative group results were analyzed using counts and frequency analysis in GraphPad Prism *version 10.1.0* (Boston, MA) to identify statements meeting the definitions of consensus. Group survey ratings and other quantitative data are presented as mean with standard deviation (SD).

2.5 RESULTS

One hundred percent of invited experts in LAM (n=16) completed the Round 1 online survey. One hundred percent of Round 1 survey questions were answered by experts, and most respondents utilized free text response boxes for optional elaboration. Of the 16 experts that completed Round 1, 14 (87.5%) attended the Round 2 panel meeting and completed the Round 2 survey. Wide geographic representation was achieved in both Rounds, with 5 regions of the United States represented and 2 international experts from Europe and Australia (Table 2.2). Sixty patients with LAM completed the anonymous patient survey.

Table 2.2: Delphi Panel Characteristics

Patients with LAM	**Round 1 (Online Survey)**
Response rate, n	60
Female gender, n (%)	60 (100%)
LAM Subtype, n (%)	
Sporadic LAM	55 (91.7%)
TSC-associated LAM	5 (8.3%)
Responded "I don't know"	1 (1.7%)
Age (years), mean ± SD	52.2 ± 11.4
Time since diagnosis (years), mean ± SD	8.1 ± 7.3
Home supplemental oxygen available	20 (33.3%)
Uses supplemental oxygen at rest, n (%)	4 (6%)
Uses supplemental oxygen during exertion, n (%)	20 (33.3%)
Uses supplemental oxygen during sleep, n (%)	19 (31.7%)
Receives care from a pulmonologist at a designated LAM Center of Excellence, n (%)	33 (55%)
Has participated in a supervised pulmonary rehabilitation program, n (%)	17 (28.3%)
Currently participates in regular exercise or physical activity program, n (%)	37 (61.7%)

LAM Care Providers	**Round 1 (Online Survey)**	**Round 2 (In-person Survey)**
Response / participation rate, n/total (%)	16/16 (100%)	14/16 (87.5%)
Years working with patients with LAM and other chronic respiratory diseases, mean ± SD	13.5 ± 7.1	12.2 ± 6.5
Female gender, n (%)	7/16 (44%)	7/14 (50%)
Geographical location, n (%)		
Northeast United States	1 (6%)	1 (7%)
Southeast United States	2 (13%)	2 (14%)
Mid-Atlantic United States	2 (13%)	2 (14%)
Central United States	4 (25%)	4 (56%)
Northwest United States	5 (31%)	3 (21%)
Europe	1 (6%)	1 (7%)
Australia	1 (6%)	1 (7%)
Occupation, n (%)		
Physician	12 (75%)	10 (71%)
Physical Therapist	3 (19%)	3 (21%)
Nurse	1 (6%)	1 (7%)
Actively conducts research in LAM	14/16 (87.5%)	12/14 (85.7%)
Physician Director of a designated LAM Center of Excellence	6 (37.5%)	6 (42.9%)

Round 1 Expert and Patient Surveys

Round 1 expert and patient survey results revealed that the top 5 perceived fears and concerns related to unsupervised exercise in LAM differed somewhat between patients and experts (Table 2.3). Major themes and example raw quotes from patients can be found in e-Table 2.1, Supplemental Material; these data in the patients' own voice add rich insights into the patient experience associated with exercising with LAM. Despite these perceived risks during exercise, most patients (83.3%) and experts (81.3%) were comfortable participating in or prescribing remote exercise training, without direct supervision of a physician or exercise professional. Remote exercise monitoring variables of oxygen saturation (SpO_2), dyspnea on exertion (DOE), and health-related quality of life (HRQoL) were rated as highly valuable data by experts (mean >7 on a 9-point Likert scale), while respiratory rate and sleep quality data were rated lower (Figure 2.2). Crosscutting themes related to safety included the importance of 1) an in-person medical screening prior to starting an exercise program, 2) a clinical exercise test to ensure adequate home supplemental oxygen availability during exercise, and 3) a patient-centered approach to screening, including asking the patient about exertional dyspnea and exercise tolerance to guide prescription of supplemental oxygen. See e-Table 2.2, Supplemental Material, for an overview of the results for expert-perceived risks of unsupervised exercise in LAM and statements created for the Delphi panel.

Table 2.3. Specific Risks, Fears and Concerns About Unsupervised Exercise in LAM

Patients with LAM (n=60)		**LAM Expert Panelists (n=16)**	
Fear or Concern	**Present (% of respondents)**	**Primary Potential Risk**	**Present (% of respondents)**
Oxygen desaturation during exercise	Yes (39.9%)	Exercise-induced desaturation	Yes (87.5%)
Pulse oximetry not detecting desaturation	Yes (27.5%)	Syncope/Other Cardiovascular Events	Yes (50%)
Other health complications during exercise	Yes (24.1%)	Pneumothorax during exercise	Yes (50%)
Pneumothorax during exercise	Yes (22.4%)	Pulmonary hypertension	Yes (35.7%)
Wearing oxygen during exercise	Yes (8.6%)	Falls	Yes (31.3%)

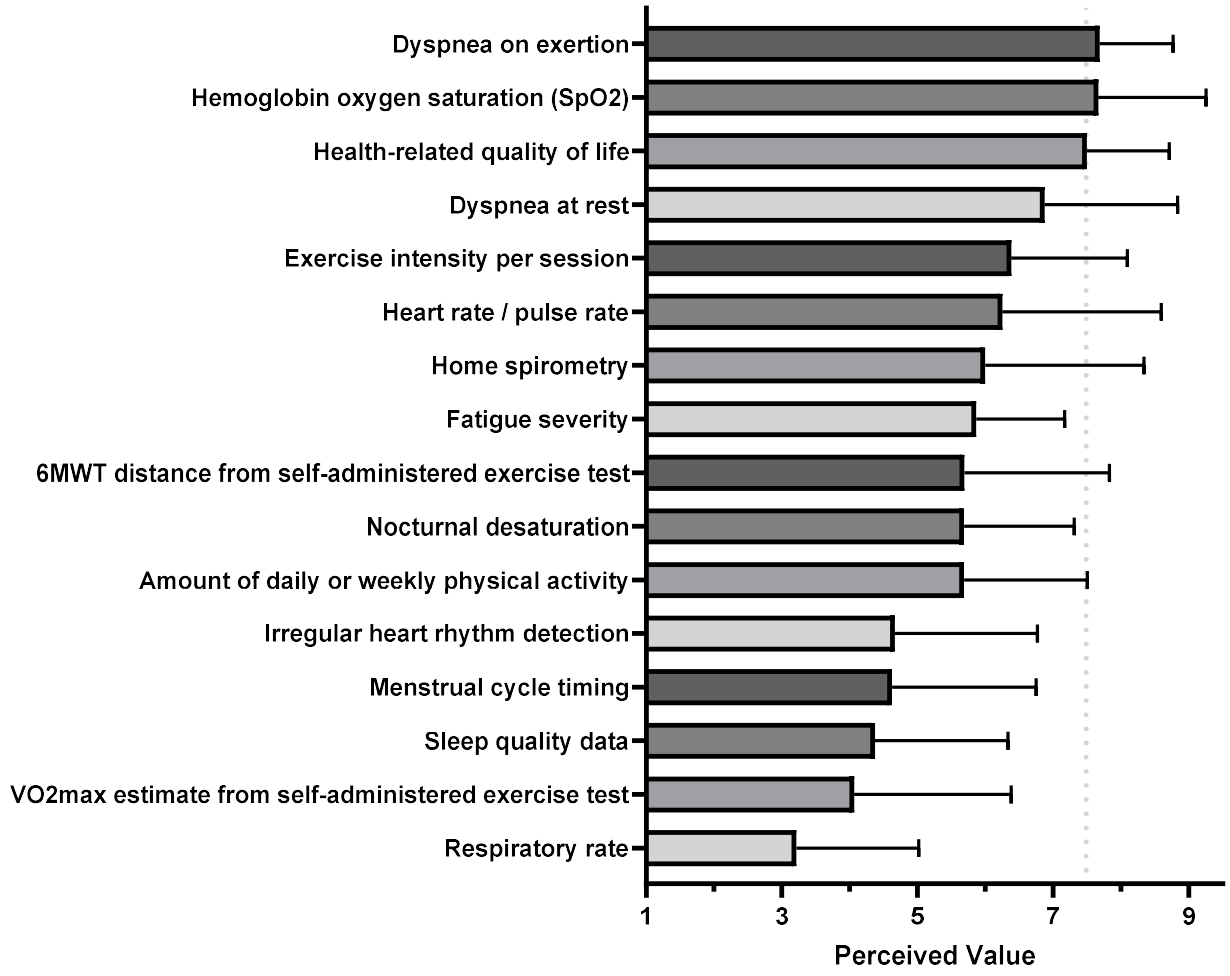


Figure 2.2: Perceived Value of Remote Exercise Monitoring Variables in LAM, as rated by LAM experts (n=16) on a 9-point Likert scale. Variables of hemoglobin oxygen saturation (SpO_2), dyspnea on exertion, and health-related quality of life ranked highly at >7 out of 9. Respiratory rate, estimate of $\dot{V}O_2max$ from a self-administered exercise test, irregular rhythm detection, menstrual cycle timing, and sleep quality data scored lower than 5 out of 9.

Round 2 Panel Consensus

Of the 10 statements presented to the expert panel in the Round 2 survey, 7 met consensus for agreement (Table 2.4). All experts agreed that patients with LAM and recent pneumothorax should not immediately start a remote exercise program, but instead should wait until after resolution of the pneumothorax and clearance by their physician. There was strong agreement that patients with LAM with severe resting pulmonary hypertension and/or risk for falls may be better served by a center-based PR program until they are medically optimized, consistent with current clinical practice guidelines.[44,45]

Round 2 Panel Non-Consensus and Uncertainty

Some disagreement arose regarding whether patients with LAM needed to complete an in-person clinical exercise test, such as 6MWT, to screen for exercise-induced desaturation prior to starting a remote exercise program. Two panelists felt that the 6MWT protocol is not vigorous enough to detect exertional desaturation for some patients with LAM who are more fit or have less severe disease. After discussion, the language in the first statement was changed from recommending completion of an "in-person 6MWT" to "in-person, standardized exercise test [e.g., six-minute walk test (6MWT)]" to screen for exercise-induced desaturation prior to initiating a remote exercise program. Consensus was reached for this revised statement, with the caveat that some individuals with LAM and mild to moderate disease severity may require maximal CPET to screen adequately for exertional desaturation.

Three statements did not reach the consensus threshold for expert agreement (Table 2.4). All experts were uncertain whether isolated exertional hypoxemia during exercise training leads to the development of pulmonary hypertension in patients with LAM. Consensus was not met concerning a desaturation threshold for recommending exertional oxygen use in patients with

LAM. Experts felt that a cardiac workup is priority only for patients with LAM exhibiting cardiac symptoms and/or with known history of cardiovascular disease.

Table 2.4: Delphi Panel Statements and Levels of Agreement for Exercise Preparticipation Screening in LAM

Statements That Achieved Consensus	Agree (n)	Disagree (n)	Uncertain (n)
Exercise-induced desaturation			
Patients with LAM should complete an in-person, standardized exercise test [e.g., six-minute walk test (6MWT)] to screen for exercise-induced desaturation prior to initiating a remote exercise program.	11	2	1
Pneumothorax			
In the absence of symptoms suggestive of pneumothorax, patients with LAM do not need to be prescreened by chest radiograph prior to initiating a remote exercise program.	12	2	0
Patients with LAM that have recently experienced pneumothorax should not start a remote exercise program until at least 4 weeks after the pneumothorax has resolved and they have been cleared by their physician.	14	0	0
Syncope and Other Cardiovascular Events			
Patients with LAM with known cardiovascular disease should be prescreened for risk of cardiovascular events, as defined by the 2012 AACVPR risk stratification tool, prior to initiating a remote exercise program.	13	1	0
Patients with LAM that are at high risk for cardiovascular exercise event(s), as defined by the 2012 AACVPR risk stratification tool, should exercise only under the direct supervision of a health care provider.	13	1	0
Pulmonary Hypertension			
Patients with LAM and severe resting pulmonary hypertension should exercise only under the direct supervision of a health care provider.	12	0	2
Isolated exertional hypoxemia does not lead to the development of pulmonary hypertension in patients with LAM.	0	0	14
Falls			
Patients with LAM with a recent history of fall(s) should be prescreened for fall risk by their health care provider prior to initiating a remote exercise program.	11	0	3

Statements That Did Not Achieve Consensus	Agree (n)	Disagree (n)	Uncertain (n)
Exercise-induced desaturation What should be the recommended threshold for supplemental oxygen use during exertion in patients with LAM? A. <80% B. <85% C. <89% D. <90% E. None of the above	A. 1 B. 10 C. 0 D. 1 E. 0		2
Syncope and Other Cardiovascular Events			
Patients with LAM should complete an in-person standardized exercise test [e.g., six-minute walk test (6MWT)] to screen for inappropriate cardiovascular response to exercise prior to initiating a remote exercise program.	9	4	1

2.6 LAM*Fit* Exercise Preparticipation Screening Tool

During the Round 2 meeting, each component and decision node of an initial draft of the LAM*Fit* exercise preparticipation screening tool was openly discussed and evaluated by the panel. Panelists agreed with the visual layout, major categories, and clinical decisions prompted by the screening tool. The initial draft suggested use of the AACVPR Stratification Algorithm for Risk of Cardiovascular Event[46] for all patients with LAM, but the panel recommended addition of a decision node at the beginning of the tool for "known cardiovascular disease – yes/no." Requiring a cardiac workup for all patients with LAM prior to starting an exercise program was felt by the panel to be excessively cautious, not cost effective, and inconsistent with other clinical practice guidelines in chronic respiratory diseases. Clarification was added to the tool that only those exhibiting cardiac symptoms and/or with known history of cardiovascular disease need a cardiac workup as part of LAM*Fit* prescreening. After the Round 2 meeting, the final LAM*Fit* Exercise Preparticipation Screening Tool (Figure 2.3) was designed to integrate consensus statements from the Delphi panel, panel feedback about the tool, and planned LAM*Fit* study eligibility criteria. In accordance with panel discussion, an adapted version of the 2012 AACVPR Stratification Algorithm for Risk of Cardiovascular Event[46] was incorporated into the decision support tool (Figure 2.4) for use with patients with LAM *and* known history of cardiovascular disease.

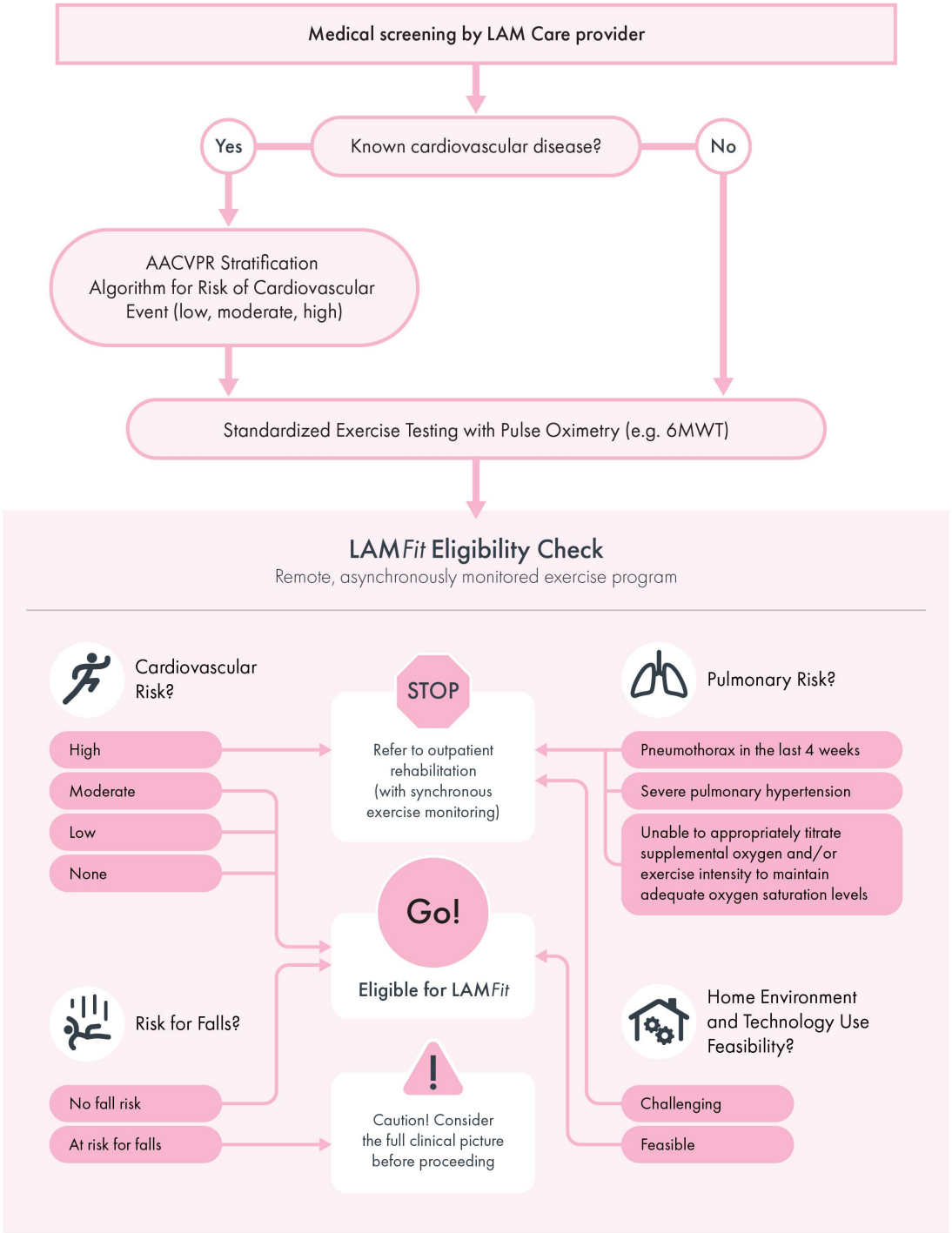


Figure 2.3: The LAM*Fit* Exercise Preparticipation Screening Tool incorporates the consensus statements from the Delphi panel and the AACVPR Stratification Algorithm for Risk of Cardiovascular Event[46] (Figure 2.4) into a decision support algorithm. The LAM*Fit* screening tool is intended to help providers decide whether a patient with LAM is medically appropriate to participate in LAM*Fit*, a home exercise program delivered on a digital health platform with remote monitoring.

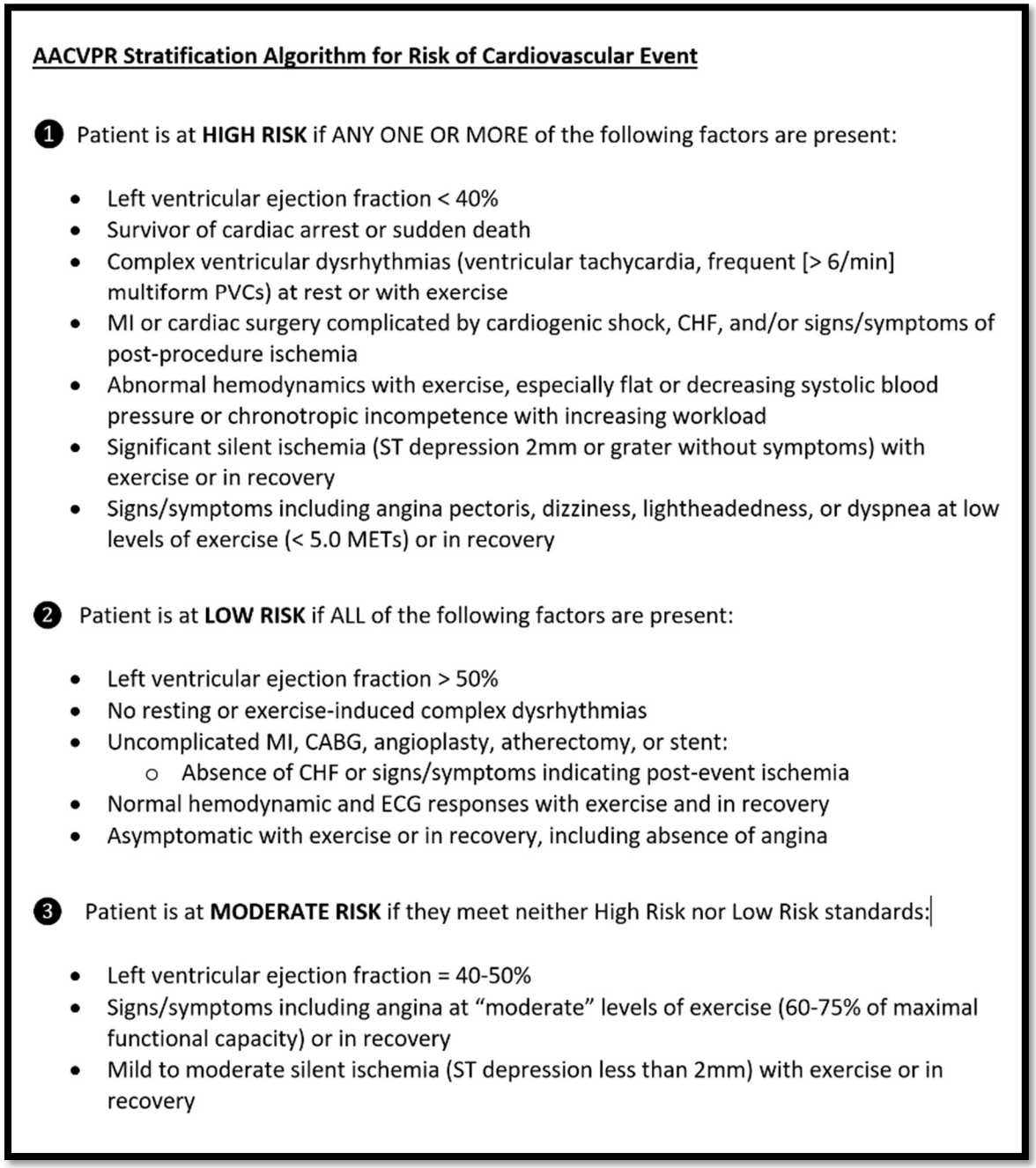


Figure 2.4: The 2012 AACVPR Stratification Algorithm for Risk of Cardiovascular Event[46] was perceived by panel members to be useful when screening patients with LAM with a known history of cardiovascular disease. During preparticipation screening for LAM*Fit,* providers can use this stratification algorithm to classify a patient as high, low, or moderate risk for cardiovascular event during exercise, and choose whether to refer them to participate in LAM*Fit* (no, low, or moderate risk) or to a center-based rehabilitation program instead (high risk). Providers can refer to the AACVPR Registry Resources website[47] for more information about the algorithm. Premature ventricular contractions, PVCs; myocardial infarction, MI; congestive heart failure, CHF; millimeter, mm; metabolic equivalent, MET; coronary artery bypass graft, CABG; electrocardiogram, ECG

Evaluation of the Delphi Process

According to the post-Delphi assessment survey results, panelists (n=15) generally felt that the instructions were clear, the moderators functioned well as group leaders, the panel's ratings reflected expert consensus in LAM well, and participation in the expert panel was highly satisfying. See Supplemental Materials for other assessment survey results (e-Figure 2.1). One hundred percent of experts agreed that the final version of the LAM*Fit* Exercise Preparticipation Screening Tool (Figure 2.3) is appropriate for screening use by LAM care providers prior to patient enrollment in LAM*Fit*.

2.7 DISCUSSION

In this study, we demonstrate the utility and outcomes of a modified Delphi study to develop consensus recommendations for ILDs like LAM that have limited research available to guide provider referral to new models of exercise programming delivered outside of center-based rehabilitation settings. The primary product of this Delphi study is a patient-centered, disease-specific exercise preparticipation screening tool for patients with LAM who want to become more active and participate in LAM*Fit*. Experts in LAM achieved consensus that individuals with LAM that have no, low, or moderate cardiovascular risk of event during exercise, no recent pneumothorax within the last 4 weeks, and no risk for falls can safely participate in remote exercise during the LAM*Fit* program. In the post-Delphi assessment survey, Delphi panelists agreed that the panel's ratings reflected expert consensus in LAM well and gave unanimous approval for the final version of the tool, showing support of future plans to implement the consensus exercise preparticipation screening tool into LAM provider clinical practices during the upcoming LAM*Fit* program.

Other population-based exercise preparticipation screening tools consider cardiovascular risks first and foremost,[17,32,33] recommend center-based risk stratification processes only,[48] and do not account for ILD-specific exercise risks such as exertional desaturation or pulmonary hypertension. Extant literature shows that even in patients with known cardiovascular disease, there are only few patients for whom unsupervised exercise at home should be avoided or requires significant caution.[7,49–51] Higher risk patients with heart failure receiving continuous inotropic support, mechanical circulatory support, or who are symptomatic at very low workloads [≤2 metabolic equivalents (MET)] may be at an increased risk of complication.[52,53] Otherwise, when considering cardiovascular risks during exercise, most patients with chronic, stable cardiopulmonary disease(s) should be able to exercise on their own at a lower risk of complication.

The LAM*Fit* exercise preparticipation screening tool incorporates cardiovascular screening for patients with LAM that also have a known history of cardiovascular disease using the 2012 AACVPR Stratification Algorithm for Risk of Exercise Event,[46] a validated resource that is widely used in cardiopulmonary rehabilitation centers. The tool also recommends completion of an in-person clinical exercise test prior to LAM*Fit* enrollment to screen for exercise-induced desaturation. Completion of a submaximal or maximal exercise test is standard practice for assessing whether patients with ILD are at risk for exercise-induced hypoxemia and would benefit from short-term supplemental oxygen therapy.[54,55] This screening step is anticipated to increase the safety and outcomes of the LAM*Fit* program, without adding additional costs and burden to the current standard of care for ILD in the United States. Additional steps should be taken by the screening provider to ensure that the participant has adequate home supplemental oxygen available for use during exercise, including determining

whether O_2 supply is currently present in the home, whether a necessary type of O_2 source can be available at the specific location of exercise, and whether the O_2 delivery system and accessories constitute any significant safety hazards during exercise.

The six-minute walk test (6MWT) is a low-resource test[56] that is routinely used as an outcome measure in rehabilitation settings, especially among patients without evidence of ischemic heart disease, and when providers don't need the additional data provided by a maximal cardiopulmonary exercise test (CPET).[57] However, 6MWT performance may represent a lower percent of $\dot{V}O_2$max in some individuals with LAM and may not identify exercise-induced desaturation in LAM as well as in other ILDs.[58] Other standardized exercise testing protocols, including maximal CPET, may be preferred on a case-by-case basis when screening for exercise-induced desaturation.

All panelists expressed uncertainty whether isolated exertional hypoxemia leads to the development of pulmonary hypertension in patients with LAM. In a recent Delphi study by Lim et al on oxygen use in fibrotic ILD, 74% of experts agreed that resting hypoxemia leads to the development of pulmonary hypertension in patients with fibrotic ILD, but consensus was not achieved for whether isolated exertional hypoxemia leads to the development of pulmonary hypertension.[59] Similar to our study, Lim et al reported no consensus for a recommended SpO_2 threshold for supplemental oxygen use during exertion in patients with fibrotic ILD.[59] Forty five percent of experts in that study recommended oxygen use below an SpO_2 threshold of <89%, 21% at a threshold <90%, and 21% at a threshold <85%.[59] Experts on our panel tended to be more accepting of lower exertional SpO_2 thresholds, with 10/14 (71%) recommending oxygen use at a threshold <85%, and emphasized the importance of considering patient symptoms and exercise tolerance when recommending exertional oxygen use. The LAM*Fit* screening tool asks

providers to judge whether patients are able to titrate supplemental oxygen and/or exercise intensity to maintain adequate oxygen saturation levels, but providers are challenged by a lack of expert consensus on SpO_2 threshold for supplemental oxygen use during exertion. More research is needed to elucidate safety concerns and risk mitigation strategies related to exertional desaturation in patients with ILD.

Other published recommendations for virtual or remote exercise programming in pulmonary and cardiac rehabilitation include screening for risk for falling and ability to exercise independently.[4,50,52,60] Consistent with panel recommendations, the LAM*Fit* tool recommends screening for risk for falls and assessing home environment and technology use feasibility to further ensure safety. Digital literacy and technology readiness may be barriers to uptake of new models of telerehabilitation,[14,60,61] but to our knowledge, there are no universally accepted methods of measuring these patient factors in telerehabilitation. Thus, LAM*Fit* prescreening providers will rely on their own knowledge of the patient in judging home exercise environment and technology use feasibility.

Evidence and momentum are growing for new models of exercise programming and telerehabilitation for people living with chronic, stable diseases like LAM. The important benefits of structured exercise training in chronic respiratory diseases are recognized perhaps now more than ever, as reflected in the higher level of recommendation for PR in ILD in recent clinical practice guidelines.[4] New strategies are being sought to help bridge gaps in delivery of PR around the world, since only a very small percentage of eligible patients are currently participating.[62] Exercise preparticipation screening by the patient's own provider and, as appropriate, referral to participate in a remote, self-monitored exercise program like LAM*Fit,* is

another strategy to increase uptake of structured exercise training as an essential component of disease management.

Next Steps

Subsequent to the development of the exercise preparticipation screening tool, a launch of 'LAM*Fit',* a home-based, self-monitored exercise program is planned that incorporates target heart rate-guided aerobic exercise, resistance training, daily activity goal setting, reminder messaging, and LAM-specific social connection. In collaboration with The LAM Foundation, a 6-month prospective pilot test of LAM*Fit* will be conducted (Figure 2.5; www.lamfit.org). Pilot study results will inform any necessary changes to the program before invitations to enroll in LAM*Fit* are extended to all individuals with LAM that are medically safe to participate.

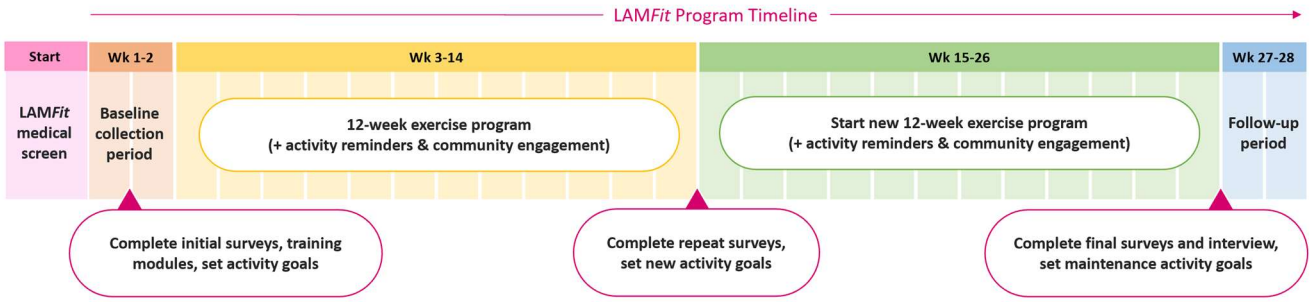


Figure 2.5: The LAM*Fit* 6-month Pilot Study Protocol. After preparticipation screening, eligible patients with LAM will be invited to enroll in a 6-month pilot study of LAM*Fit,* a home-based, self-monitored exercise program that incorporates two subsequent 12-week exercise programs, daily activity goal setting, reminder messaging, and LAM-specific social connection.

Key to the LAM*Fit* program is upfront involvement of the patient's own provider to determine medical appropriateness for unsupervised exercise, using the LAM*Fit* Exercise Preparticipation Screening Tool developed here (Figure 2.3). The screening provider's knowledge of the patient's risk for exertional desaturation and other systems risks will help the study team to maximize safety and outcomes of remote exercise programming. The screening tool developed in this study is intended for clinical use by LAM care providers; any future modifications for patient-facing use should be mindful of patients with LAM that are not yet established with a specialized LAM pulmonologist, as one expert emphasized in the post-Delphi assessment survey (Supplemental Material), and optimize readability for diverse patient literacy levels. Offering LAM*Fit* as a digital program designed for adults with LAM with sufficient technology literacy may have some implications for equity of accessibility,[13] but efforts will be made to minimize inequities wherever possible, including providing smartphones with active cellular plans and additional training in technology use as necessary. Since LAM is a rare lung disease, and patients may be located far from specialists, it is possible that the use of digital technology will actually increase access to exercise programming for this community, similar to other innovative, evidence-based rural health approaches that integrate technology to increase access.[63,64]

Limitations

Our study has some limitations. Expert consensus obtained during a Delphi study is considered a lower level of evidence than other study designs,[65] but was useful in our circumstances given the urgent need to develop practical guidance for LAM*Fit* exercise program prescreening, and given the smaller literature base available for the rare interstitial lung disease LAM. Our methods differed from published guidelines for the RAND/UCLA Appropriateness

Method in a few ways. Many Delphi studies do not include the patient voice in any rounds as a key stakeholder.[66] We chose not to include patients as named panelists in Rounds 1 or 2 to facilitate candid discussion among experts; other studies have shown that panelists tend to be less open about their medical opinions when patient stakeholders are present.[22] However, we did choose to conduct an anonymous patient survey alongside the expert surveys to add more patient perspective. Our choice for convenience patient sampling limited representation of patient voice to those with internet access and existing connections to The LAM Foundation patient advocacy group, and not the broader population of patients living with LAM. While we did collect several demographics from respondents, we did not collect data about patient race/ethnic identity, sexuality, or socio-economic status, and thus cannot describe these demographic trends in patient experience. In addition to the patient themes obtained during this study (e-Table 2.1, Supplemental Material), continued solicitation and incorporation of patient feedback and experience during the LAM*Fit* pilot study will help optimize the patient-centeredness[67,68] of the program.

Instead of engaging the full expert panel to develop statements for consensus rating, a smaller team of only 4 experts drafted initial statements from the literature and expert surveys. Furthermore, given time limitations, additional Delphi rounds were not held to refine and increase the appropriateness of statements that did not reach consensus. These modifications to the traditional RAND/UCLA Appropriateness Method helped expedite the panel process to create a useful consensus screening tool, but may have added some bias to statements and group ratings. The expert panel was relatively small in size (n=16); while the size was in line with other published Delphi studies,[29,30] a larger panel size may have yielded more diverse representation of expert opinion. The panel primarily included LAM providers and researchers from the United States, with limited international representation. Future development of guidelines should seek to recruit

experts from around the world. Given these limitations, the screening tool is not intended to change the current standard of care or policy for all patients with LAM, and will be tested and revised as necessary during the LAM*Fit* pilot study. If shown to be useful during the LAM*Fit* study, screening tool appropriateness should subsequently be studied for expanded clinical use in other chronic respiratory diseases.

2.8 INTERPRETATION

Experts in LAM and ILD achieved consensus on 7 of 10 items to guide exercise preparticipation screening by a LAM provider and determine medical appropriateness prior to enrollment in an unsupervised exercise program. The resulting preparticipation screening tool will be used to inform provider screening and referral processes for the upcoming LAM*Fit* digital fitness exercise program.

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2.10 Supplemental Material

Round 1 Survey of Experts in Lymphangioleiomyomatosis (LAM)

Demographics:

Personal information
- Name(s) and credentials
- Job Title(s)
- Approximate years of experience working with patients with LAM and ILD
- Actively conducting research in LAM
- Primary place of employment
- Other affiliation(s)
- City and State of primary place of employment
- Email address

What are the primary potential health risks for patients with LAM during exercise without direct medical supervision (remote, asynchronous exercise)?

Exercise preparticipation screening:
- Do you currently use any exercise preparticipation screening tools to screen patients with LAM for appropriateness to participate in exercise? If yes, please list and describe.

What do you believe to be the best practices for medically screening patients with LAM that may be at risk for:
- Exercise-induced desaturation
- Pneumothorax during exercise
- Adverse cardiac event(s) during exercise
- Fall(s) during exercise
- Other adverse events during exercise

Do you have any other concerns related to patients with LAM exercising remotely at home, in the community, or at a gym without the direct supervision of a physician or another exercise professional? (Yes/No)
- If yes, please describe.

During LAMFit, we will remotely monitor multiple physiological variables during routine physical activity and intentional exercise training. We also plan to collect patient-reported outcome measures.

Rate each remote exercise monitoring physiological variable by the contribution of value to the medical management of LAM: (on a scale of 1-9)
- Heart rate/pulse rate
- Blood oxygen saturation (SpO_2)
- Respiratory rate
- Irregular heart rhythm detection

- Distance walked during six-minute walk test (6MWT) self-administered by patient
- Estimate of maximum oxygen consumption (VO_{2max}) using submaximal exercise test self-administered by the patient
- Metrics for intensity of exercise achieved per session (average or peak HR or METs)
- Metrics for amount of physical activity achieved per day or week (e.g., steps or minutes of moderate-to-vigorous physical activity)

What are the primary potential risks associated with patients self-monitoring during exercise using remote physiological monitoring technology like those named above?

Rate these other remote monitoring variables and patient-reported outcome measures by the contribution of value to the medical management of LAM: (on a scale of 1-9)

- Sleep quality data
- Nocturnal desaturation
- Dyspnea at rest
- Dyspnea on exertion
- Home spirometry
- Menstrual cycle timing
- Fatigue severity
- Health-related quality of life

Is there is any other input that you would like to share to help optimize the design of a LAM-specific exercise preparticipation screening tool?

Survey of Patients with LAM

Demographics

- Age (years)
- Gender
- Sporadic LAM / TSC-associated LAM / I don't know (choose one)
- Approximate month and year of diagnosis with LAM
- Use supplemental oxygen at rest? Yes/no During exercise? Yes/no
    - If yes, how many liters of supplemental oxygen at rest?
    - During exercise?
- Do you have a primary care physician? Yes/no
- Are you regularly followed (at least once/year) by a pulmonologist? Yes/no

- Have you ever completed a six-minute walk test or a cardiopulmonary exercise test as part of your medical care? Yes/no
    - If you use supplemental oxygen, did you complete a clinical exercise test for prescription of oxygen? Yes/no
- Have you ever participated in a supervised pulmonary rehabilitation program? Yes/no
    - If yes, when did you participate in pulmonary rehabilitation?

    - If yes, what aspects of pulmonary rehabilitation did you like? What aspects of pulmonary rehabilitation did you not like (if any)?
- Do you currently participate in a regular exercise or physical activity program? Yes/no
    - If yes, approximately how many minutes of intentional exercise or physical activity do you perform per week?
    - If yes, how do you choose an intensity for your exercise program?
    - If no, are you interested in starting a regular exercise or physical activity program in the next year?
    - If no, or if you are not participating in an exercise program to the extent that you want to, what are reasons or barriers that are preventing you from exercising?
- Have you ever experienced health complications during exercise or physical activity that have made you stop exercising? If yes, please describe.
    - Do you have concerns regarding oxygen desaturation occurring during exercise? If yes, please describe.
    - Do you have concerns about wearing oxygen during exercise? If yes, please describe.
    - Do you have concerns about your pulse oximeter not detecting desaturation during exercise? If yes, please describe.
    - Do you have concerns regarding pneumothorax occurring during exercise? If yes, please describe.
    - Do you have any fears or concerns about any other health complications occurring during exercise? If yes, please describe.
- Do you have any fears and concerns related to exercising remotely in your home, in the community, or at a gym without the direct supervision of a physician or another exercise professional?
    - If yes, please describe.

Post-Delphi Panel Assessment Survey of Experts in LAM

As a final favor, we would appreciate you completing this brief questionnaire about your experience as a Delphi study participant. For each item, please circle the appropriate number or fill in the blank.

REVIEW OF THE SCIENTIFIC LITERATURE

How much did a review of the literature influence your first-round ratings?

How much did your own professional experience/expertise influence your first-round ratings?

FIRST-ROUND RATINGS (online survey done before the panel meeting)

How easy did you find the task?

How clear were the instructions?

PANEL MEETING (in-person at 2023 American Thoracic Society International Conference)

How well did the moderators function as group leaders?

How much did the feedback from the first-round ratings influence your second-round ratings?

How much did the panel discussion influence your second-round ratings?

OVERALL IMPRESSIONS OF YOUR EXPERIENCE

How well do you believe the panel's ratings will reflect expert consensus in LAM?

How satisfying did you find your participation on this panel?

Do you approve of the final version of the LAM*Fit* Exercise Preparticipation Screening Tool, and that it is appropriate for screening use by LAM care providers prior to patient enrollment in LAMFit? (link to tool)

Yes/no

Additional comments:

*Note: Questions are adapted from an example survey in the RAND/UCLA Appropriateness Method user manual.[22]

e-Table 2.1. Patient-Reported Fears and Concerns About Unsupervised Exercise

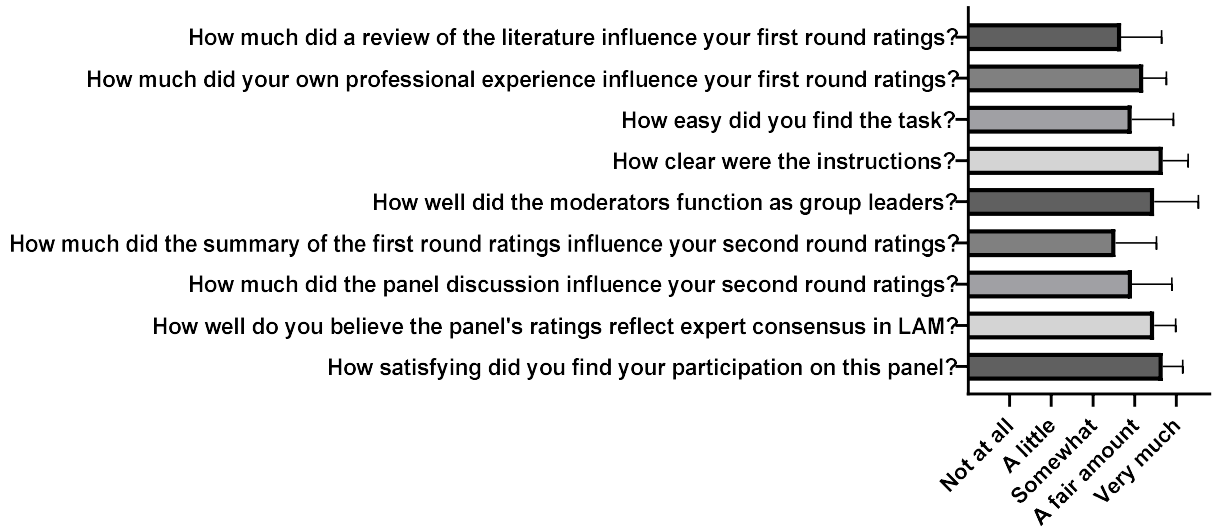
Fear or Concern (Codes)	Frequency Reported (% of respondents)	Code Count Frequency (% of all coding)	Example Quotes
Oxygen desaturation during exercise	39.9%	36.1%	"I wonder if when I am really exerting myself if I might have oxygen desaturation. Especially when hiking uphill, I sometimes just have to stop because… I feel like I need to catch my breath....more so than others I am hiking with who don't have LAM, but are not in as good of shape as me." Patient_17 "[I think I] definitely desaturate quickly…. I will often not be overtly breathless, but more start to feel unwell, slightly nauseated, etc., then if [I[stop, breathlessness may catch up!" Patient_59
Pulse oximetry not detecting desaturation	27.5%	16.4%	"Yes. Difficult reading while exercising. It takes too long for the number to register. By that time, you are no longer desaturating." Patient_45 "Sometimes it won't read [on] my finger if I'm swollen or sweaty, which usually happens with rigorous exercise." Patient_5
Pneumothorax during exercise	22.4%	14.1%	"I have had recurrent pneumothoraces so I have a bigger concern of making sure it's fully healed before starting back up with exercise." Patient_58 "In theory, I've had pleurodesis in both lungs so I SHOULD be protected, but I still have LAM, so the possibility [of pneumothorax] is there." Patient_1
Wearing oxygen during exercise	8.6%	13.1%	"It is heavy." Patient_21 "Social stigma." Patient_53
Other body system complications during exercise	24.1%	11.0%	"Osteoporosis and age-related aches and pains cause me concern." Patient_29 "Low blood sugars." Patient_42

e-Table 2.2: Expert-Perceived Risks During Unsupervised Exercise in LAM and Panel Statements Created

Open Codes	Axial Codes (Major Themes)	Frequency Reported (% of respondents)	Code Count Frequency (% of all coding)	Statement(s) / Question(s) Created
Perceived Risks				
Oxygen desaturation during exertion	Exercise-induced desaturation	87.5%	30.7%	Patients with LAM should complete an in-person, standardized exercise test [e.g., six-minute walk test (6MWT)] to screen for exercise-induced desaturation prior to initiating a remote exercise program. What should be the recommended threshold for supplemental oxygen use during exertion in patients with LAM?
Hypoxemia				
Tissue hypoxia				
Insufficient availability of supplemental oxygen during exertion				
Pneumothorax	Pneumothorax during exercise	50%	24.1%	In the absence of symptoms suggestive of pneumothorax, patients with LAM do not need to be prescreened by chest radiograph prior to initiating a remote exercise program. Patients with LAM that have recently experienced pneumothorax should not start a remote exercise program until at least 4 weeks after the pneumothorax has resolved and they have been cleared by their physician.
Undiagnosed pneumothorax				
Recurrent pneumothorax				
Syncope/Fainting	Syncope and Other Cardiovascular Events	50%	17.5%	Patients with LAM with known cardiovascular disease should be prescreened for risk of cardiovascular events, as defined by the 2012 AACVPR risk stratification tool, prior to initiating a remote exercise program. Patients with LAM that are at high risk for cardiovascular exercise event(s), as defined by the 2012 AACVPR risk
Cardiac arrhythmias / dysrhythmias				

Cardiac ischemia / infarction Exercise intolerance				stratification tool, should exercise only under the direct supervision of a health care provider. Patients with LAM should complete an in-person standardized exercise test [e.g., six-minute walk test (6MWT)] to screen for inappropriate cardiovascular response to exercise prior to initiating a remote exercise program.
Pulmonary hypertension Right-sided heart failure Acute right heart strain Undiagnosed pulmonary hypertension Development of exertional pulmonary hypertension Severe pulmonary hypertension Pulmonary hypertension not medically optimized	Pulmonary Hypertension	35.7%	20.4%	Patients with LAM and severe resting pulmonary hypertension should exercise only under the direct supervision of a health care provider. Isolated exertional hypoxemia does not lead to the development of pulmonary hypertension in patients with LAM.
History of fall(s) Balance impairment Frailty Fatigue, exhaustion	Falls	31.3%	6.3%	Patients with LAM with a recent history of fall(s) should be prescreened for fall risk by their health care provider prior to initiating a remote exercise program.

Ability to safely get on and off home exercise equipment				
Long oxygen tubing				
Musculoskeletal injury or muscle soreness	Other Risks	1%	1%	No statements created, as these are other common risks of exercise training that will be incorporated into the participant consent document.
Thermal injury/stress				
Additional Thematic Codes				
Importance of an in-person medical visit prior to starting an exercise program	Prescreening			Incorporated into screening algorithm
Baseline clinical exercise test				
Patient symptoms as guide				
Ability to appropriately titrate supplemental oxygen and/or exercise intensity				
Falls risk screening				
Home environment safety / exercise setup				
Medical grade pulse oximetry	Technology use feasibility			Incorporated into screening algorithm
Technology literacy				
Internet access				



e-Figure 2.1: Post-Delphi Assessment Survey Results. Fifteen of 16 expert panelists (93.8%) completed a post-Delphi assessment survey, with questions adapted from the RAND/UCLA Appropriateness Method user manual.[22] The majority of panelists felt that the Delphi instructions were clear, the moderators functioned well as group leaders, the panel's ratings reflected expert consensus in LAM well, and panel participation was highly satisfying.

Other Panelist Qualitative Feedback from the Post-Delphi Assessment Survey:

One panelist shared: "Congratulations on developing this very useful tool. It has a well-balanced approach to risk assessment and facilitating participation." Another emphasized the importance of explaining all potential risks in patient-friendly language on the consent document. One care provider shared ideas for how to supplement the tool if it is changed to be patient-facing in the future:

> "The screening tool algorithm with risk stratification and whether to use LAM*Fit* or outpatient pul[monary] rehab seems appropriate. The risk stratification appears primarily based on cardiac risk and this is very important, but appears to be geared towards providers. [I]f the survey is going to be administered to patients [in the future] prior to providing access to LAM*Fit*, then having [t]hem ensure oxygen sats are ok with exercise and no significant pulmonary hypertension or checking if they have had a [cardiac] echo[cardiogram] in the past year would be questions I would include. This may be especially important for LAM women who may not be seen in a LAM Center regularly."

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The co-authors affirm that the first author Dr. Child conceived and designed the study under the supervision of senior author Dr. Brown, and took the lead role in acquisition, analysis, and interpretation of study data. Dr. Child alone drafted the manuscript and received only minor

suggestions for edits from co-authors for important intellectual content. During revisions, the Editor-in-chief at CHEST Journal recommended an upgrade of the manuscript from "Original Research" to a "Clinical Practice Guideline." All co-authors agreed with the final version of the manuscript.

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The Authors declare that there is no conflict of interest.

Chapter 3 – Identification of a 'Ceiling Effect' Limitation to Use of 6MWT for Aerobic Exercise Prescription in Higher Functioning Persons with Interstitial Lung Disease

PREFACE

Aim 2: Validate a formula or heart rate threshold that can be used for aerobic exercise prescription in high-functioning individuals with interstitial lung disease, in the absence of a maximal cardiopulmonary exercise test.

In the absence of a recent maximal cardiopulmonary exercise test (CPET), which is not always feasible to obtain, no formulas have been published for estimating an appropriate target heart rate (HR) range or threshold for exercise prescription from a six-minute walk test (6MWT) or another standardized field test in interstitial lung disease (ILD). To optimize aerobic exercise prescription during LAM*Fit*, we sought to answer the research question of how best to prescribe aerobic exercise intensity in higher-functioning individuals with ILD in the absence of a recent maximal CPET. We conducted a secondary analysis of the results of clinical exercise testing (6MWT and CPET) performed during two prior studies in the Brown Lab – the "Exercise & Fatigue in LAM" and the "IPF mHealth Exercise" studies. From this analysis, we make recommendations for HR-guided aerobic exercise prescription in higher functioning individuals with ILD when a recent maximal CPET has not been completed.

3.1 ABSTRACT

Objective: To determine whether the peak HR reached on six-minute walk test can be used to estimate the HR at the first ventilatory threshold (VT1) on incremental cardiopulmonary exercise test (CPET) for aerobic exercise prescription in patients with ILD.

Study Design: A secondary cohort analysis of submaximal and maximal clinical exercise testing in ILD

Setting: Ambulatory and community care settings

Participants: Adults with lymphangioleiomyomatosis (LAM; n=15) and idiopathic pulmonary fibrosis (IPF; n=14) enrolled in two prior prospective interventional studies

Interventions: Not applicable

Main Outcome Measures: Peak HR on 6MWT ($HR_{peak6MWT}$) and HR at VT1 on CPET ($HR_{VT1onCPET}$), the criterion standard for aerobic exercise prescription

Results: In the combined sample of LAM+IPF, a moderate correlation existed between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ (r=0.442, p=0.016), with unbiased (-0.72bpm), but very wide limits of agreement (±31.6bpm). For participants that walked 6MWT distance <85% predicted, a very strong correlation (r=0.871, p=0.011) existed, with small negative bias (-2.71bpm), more narrow limits of agreement (±19.4bpm), and small mean absolute difference (7.0±6.8 bpm) compared to other subgroups. For participants that walked a 6MWT distance ≥85% predicted, no correlation existed between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ (r=0.220, p=0.325), and the limits of agreement were very wide (±35.0 bpm), indicating the use of $HR_{peak6MWT}$ to estimate aerobic exercise intensity is not appropriate.

Conclusion: We identified a ceiling effect at or above a cut-off of 85% predicted 6MWT distance, which impacts the predictive utility of $HR_{peak6MWT}$ for aerobic exercise prescription among patients with ILD. In the absence of incremental CPET, patients with ILD and lower cardiorespiratory fitness that walk 6MWT distance <85% predicted may use $HR_{peak6MWT}$ to estimate the true HR threshold for aerobic exercise intensity. For those that walk ≥85% predicted 6MWT distance, the use of $HR_{peak6MWT}$ to estimate aerobic exercise intensity is not appropriate.

Key Words: interstitial lung disease, lymphangioleiomyomatosis, idiopathic pulmonary fibrosis, exercise testing, rehabilitation

3.2 INTRODUCTION

Dyspnea on exertion and exercise-induced hypoxemia are hallmark in interstitial lung disease (ILD), leading to reduced quality of life.[1] Patients with ILD that want to use exercise to improve control of dyspnea and quality of life[2] are challenged to determine a target heart rate (HR) to guide aerobic exercise training in the absence of maximal HR on incremental cardiopulmonary exercise test (CPET). Incremental CPET is not currently recommended as routine monitoring in ILD,[3] requires trained personnel and expensive equipment,[4] and may not be available in all centers. The 6MWT is a low-resource, easy to administer, and well-tolerated submaximal exercise test[5] with prognostic value for morbidity and mortality in ILD,[6,7] including idiopathic pulmonary fibrosis (IPF).[8] In addition to frequent use as a primary outcome of exercise training in pulmonary rehabilitation,[9] 6MWT is routinely performed in pulmonary care settings to stage disease[6] and assess patient need for short-term (exertional) supplemental oxygen.[10,11]

Guidelines exist for exercise specialists in pulmonary rehabilitation to calculate a percent (%) of VO_2max obtained on CPET[4,12] or 6MWT[13] to prescribe treadmill-based walking speed, duration of exercise sessions, and exercise progression for patients with chronic lung diseases. Prediction formulas have also been developed for end-stage lung disease[14] and other cardiopulmonary diseases[15,16] to estimate VO_2max using distance walked on 6MWT and other demographic and clinical variables. However, a meta-analysis by Ross et al of multiple published VO_2max prediction formulas in diverse cardiopulmonary populations[16] showed that although a generalized equation may be helpful in characterizing groups of patients, a major source of error is the inherent variability in physiological responses to CPET and 6MWT, which limits the clinical utility of VO_2max estimation formulas for prognostication and exercise

prescription in individual patients. Constant walking or cycling speed at a %VO_2max is not easily adaptable to real-world, free-living environments where individuals often exercise with different modalities than in center-based pulmonary rehabilitation and may not have the exercise equipment necessary to be able to adhere to a prescribed treadmill walking or cycling speed.

The use of a target HR threshold or HR zone for exercise prescription is attractive as it is more intuitive for patients to use for exercise pacing than %VO_2max and translates easily to other exercise modalities like brisk overground walking and outdoor hiking. Expanded consumer access to wearable HR/physical activity monitors,[17] digital health applications, and continuous, medical-grade pulse oximetry increases patient access to real-time HR and SpO_2 monitoring, including during unsupervised exercise. Despite extensive consumer fitness market implementation,[18] a population-based, age-predicted maximal HR formula (APMHR), such as APMHR = (220 – age) commonly attributed to Fox et al[19], may be less appropriate in ILD due to risk for respiratory exercise limitation before reaching APMHR.

Identification of an individual's heart rate at first ventilatory threshold (VT1) on CPET ($HR_{VT1onCPET}$) is the standard criterion for delineating between slight and moderate exercise intensities,[4] and exercising above this threshold stimulates aerobic metabolism.[20,21] A target HR threshold that is at or near VT1 promotes aerobic exercise training at a moderate intensity or greater. Studies support the use of peak (or highest) HR on 6MWT ($HR_{peak6MWT}$) to estimate VT1 on CPET and guide aerobic exercise prescription in medically stable patients with COPD,[22] cystic fibrosis,[23] CAD,[24] heart failure,[25] and post coronary artery bypass graft (CABG) surgery.[26] To our knowledge, no prior studies have compared $HR_{peak6MWT}$ to $HR_{VT1onCPET}$ to determine the utility of 6MWT to guide aerobic exercise prescription in ILD.

The aims of this study were (1) to investigate relationships between HR responses on 6MWT and CPET in a secondary analysis of patients with ILD; and (2) to elucidate the presence or absence of a ceiling effect for using $HR_{peak6MWT}$ to guide aerobic exercise prescription in ILD when recent incremental CPET is not available.

3.3 METHODS

Our research team recently completed two unique studies of a 12-week, home-based exercise program in two cohorts of patients with lymphangioleiomyomatosis (LAM; n=15)[27] and idiopathic pulmonary fibrosis (IPF; n=29, clinicaltrials.gov NCT04838275, manuscript in review), and demonstrated the feasibility of using a digital health platform with remote HR and medical-grade SpO_2 monitoring to enable safe, structured exercise training in ILD outside of a pulmonary rehabilitation center. Both studies were approved by the University of Washington Institutional Review Board [STUDY00007271 (LAM); STUDY00012537 (IPF)]. All patients were screened for study eligibility by a pulmonary physician and a physical therapist on the investigator team. Eligibility criteria for each study are detailed in Table 3.1.

Table 3.1: Eligibility Criteria

LAM Exercise & Fatigue Study

Inclusion Criteria	Exclusion Criteria
1) Diagnosis of LAM via biopsy or high-resolution CT scan of the chest	1) Unstable condition
2) Age 18-60 years	2) Functional class IV on the Specific Activity Scale[24]
3) Functional class I-III on the Specific Activity Scale[24]	3) Musculoskeletal or other conditions which would limit exercise participation
4) In stable condition	4) Non-compliance with medical therapies
5) No changes in medical treatment for past 3 months	5) Prior lung transplantation
6) Stable six-minute walk test (6MWT) for past 3 months (± 20 m)	6) Currently pregnant

IPF mHealth Exercise Study

Inclusion Criteria	Exclusion Criteria
1) Diagnosis of idiopathic pulmonary fibrosis (IPF), consistent with the ATS 2018 Guidelines	1) Forced expiratory volume in one second (FEV1)/FVC ratio <0.7 after administration of bronchodilator at screening
2) Age 40-80 yrs at randomization	2) Require >5LPM supplemental O2 at rest
3) Maintained on stable doses antifibrotic therapy (pirfenidone or nintedanib) during the preceding minimum 3 months	3) Expected to receive a lung transplant within 1 year from randomization or, for patients at sites in the United States, on a lung transplant waiting list at randomization
4) No changes in any other medical treatment for at least 4 weeks before enrollment	4) Active infection
5) Percent Forced Vital Capacity (%FVC) ≥50% at screening	5) History of asthma or chronic obstructive pulmonary disease
6) Percent predicted diffusion capacity of lung for Carbon Monoxide, corrected to hemoglobin (%DLCO) ≥30% at screening	6) Ongoing concurrent treatments for IPF including investigational therapy, immunosuppressants (other than prednisone 20 mg daily or less), and cytokine modulating agents
7) Willing and able to participate in an exercise regimen	7) Participation in a supervised exercise program including pulmonary rehab within the previous 12 months
8) Ambulatory without the use of assistive device	8) History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months
9) Have another person available (e.g., partner, caregiver) for support during an exercise regimen if needed	9) Major orthopedic, psychiatric, neurological, or other conditions that would impair performance of the study exercise outcomes
10) Preexisting prescription if indicated for use of supplemental O2 during exercise/exertional activities as needed at home.	10) Currently pregnant
11) Able to understand the consent in English	11) Any other condition at the discretion of the enrolling physicians

Outcome Measures

In this cross-sectional secondary analysis, we included only baseline measures collected during in-person study visits for patients with LAM or IPF. Study visits were conducted within a 12-hour time period at the same exercise research facility located in Seattle, WA (Fred Hutchinson Cancer Research Center – Prevention Center Shared Resource), by the same testers, under the same standardized testing conditions, on the same equipment, and using the same standardized testing protocols. Baseline study visit measurements included: 1) 6MWT to assess distance, continuous HR and SpO_2 responses, distance desaturation ratio (DDR),[26] and cardiac effort,[28] 2) maximal treadmill cardiopulmonary exercise test (CPET) (Balke protocol or modified Balke protocol[27,28]); 3) anthropometrics; and 4) pulmonary function testing (PFTs)[29].

Six-Minute Walk Test (6MWT)

The 6MWT was performed under standardized conditions adapted from the American Thoracic Society protocol[5] using an indoor corridor 20 meters in length. Standard encouragement using even, neutral tones was used for each subject. HR via continuous measurement with 12-lead electrocardiogram (Mortara Wireless Acquisition Module, Milwalkee, WI), pulse rate (PR) and SpO_2 via continuous medical grade fingertip oximeter (Nonin Medical, Plymouth, MN) were recorded pre-test, each second during 6MWT, and during 5 minutes of quiet sitting after the test. $HR_{peak6MWT}$ was identified and recorded by the tester. Other 6MWT parameters included total distance, percent predicted distance using normative data from age- and sex-matched healthy adults[30], cardiac effort, distance desaturation ratio (DDR), and change in heart rate, SpO_2, dyspnea, and rating of perceived exertion (RPE) during the test. DDR was calculated as previously described[27,31] as the ratio of oxygen desaturation area (area under the curve, DAO_2) to the distance walked in meters (DAO_2/distance walked). Cardiac effort (CE) was calculated using

record of continuous electrocardiogram monitoring during 6MWT as previously described, (heart beats during 6MWT)/6MWD).[28,32]

Cardiopulmonary Exercise Test (CPET)

CPETs were performed using a continuous, speed- and incline- incremented maximal treadmill ramp walking protocol (Balke protocol or modified Balke protocol[4]) with 1 to 3-min stages until volitional fatigue or other symptomatic limitation. Ventilation (V_E), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were measured continuously by open-circuit spirometry using a Cardiopulmonary Exercise System (MGC Diagnostics Ultima CardiO_2, Saint Paul, MN) with an integrated 12-lead electrocardiogram (Mortara Wireless Acquisition Module, Milwalkee, WI). The first and second ventilatory thresholds were detected using the simplified V-slope method.[33,34] Resting energy consumption and HR was measured during 5 min of standing on the treadmill before exercise testing. HR and RPE (using a modified Borg 0-10 point scale) were recorded in the middle and last 30 seconds of each stage. Rating of perceived dyspnea (RPD) (using a modified Borg 0-10 point scale) was recorded at rest and end exercise. Pulse rate and SpO_2 were also monitored by a fingertip [NoninConnect 3230 or Nonin WristOx$_2$ Model 3150 with Bluetooth Low Energy (BLE) with finger probe, Nonin Medical, Inc., Plymouth, MN] or forehead (Nonin WristOx$_2$ Model 3150 with BLE with 8000R forehead reflectance probe) pulse oximeter. HR and SpO_2 were recorded every minute during 5 min of sitting immediately after CPET completion.

Pulmonary Function

Lung function measurements were performed using a whole-body plethysmograph and open-circuit spirometry (MGC Diagnostics Platinum Elite^{TM} DX Plethysmograph and Ultima^{TM} CardiO_2, Saint Paul, MN). FEV_1, FVC, and DLCO were measured using recommended

maneuvers, and DLCO was corrected for hemoglobin using published guidelines.[29] Predicted normal values[35] were used to calculate percent predicted values.

Statistical Analysis

Multiple methods were used to compare HR data between cohorts and determine the validity of $HR_{peak6MWT}$ in estimating true aerobic exercise intensity, or the $HR_{VT1onCPET}$. These methods included Pearson correlations, Bland Altman limits of agreement methods[36], and mean absolute difference. On Bland Altman method comparisons, the limits of agreement were set at ±2 SD. If $HR_{peak6MWT}$ provided an unbiased estimate of $HR_{VT1onCPET}$, then the mean of differences would not be significantly different from 0. This null hypothesis was tested using a paired t test. The mean absolute difference of $HR_{peak6MWT}$ (or the amount of error introduced by using $HR_{peak6MWT}$ as an estimate of aerobic exercise intensity) was calculated as the absolute value of the mean group difference between $HR_{peak6MWT}$ and the criterion standard of $HR_{VT1onCPET}$, expressed in beats per minute (bpm). To determine a cutoff score based on % predicted 6MWT distance, we used an receiver operating characteristics (ROC) curve[37] and tested the agreement between the true $HR_{VT1onCPET}$ and $HR_{peak6MWT}$ at levels of 100% predicted 6MWT, 95% predicted 6MWT, 90% predicted 6MWT distance, 85% predicted 6MWT distance, 80% predicted 6MWT distance, on so on for the sample, seeking to minimize the mean absolute difference between $HR_{peak6MWT}$ and the criterion standard $HR_{VT1onCPET}$. Data are presented for individual subjects, and as group means with standard deviation (SD). Statistical analysis utilized GraphPad Prism version 9.3.1, and differences at α level of 0.05 were considered statistically significant.

3.4 RESULTS

Twenty-nine of thirty participants with LAM (n=15) and IPF (n=14) that completed baseline in-person exercise testing and were assigned to participate in the 12-week exercise program were included in this secondary analysis. One participant with IPF was excluded due to stable, persistent atrial fibrillation impacting the accuracy of HR self-pacing via consumer-grade, commercially available heart rate monitor.[38] Baseline demographic characteristics of the combined sample and ILD subtypes are presented in Table 3.2.

Table 3.2: Baseline Demographics

	Combined Sample (LAM + IPF) (n = 29)	**LAM (n = 15)**	**IPF (n = 14)**
	n (%)	n (%)	n (%)
Female/Male	19/10	15/0	4/10
Race/Ethnicity			
White	28 (97)	15 (100)	13 (93)
Non-White	1 (4)	0	1 (7)
Etiology			
Sporadic LAM	NA	13 (87)	NA
TSC-associated LAM		2 (13)	
Medications			
Sirolimus	NA	8 (53)	0
Pirfenidone		0	5 (36)
Nintedanib		0	9 (64)
Beta blocker	4 (14)	0	4 (29)
Inhaled treprostinil	1 (4)	0	1 (7)
Short term O_2 therapy (with exertion)	10 (34)	2 (13)	8 (57)
Long term O_2 therapy	3 (10)	0	3 (21)
Other Medical History / Comorbidities			
COPD or asthma	3 (10)	2 (13)	1 (7)
OSA	3 (10)	0	3 (21)
COVID-19 pneumonia	1 (3)	0	1 (7)
Lung cancer post resection	1 (3)	0	1 (7)
PH-ILD	2 (7)	0	2 (14)
GERD	11 ()	2 (13)	9 (64)
Prior pneumothorax	9 (31)	9 (60)	0
Epilepsy	2 (7)	2 (13)	0
HTN	6 (21)	1 (7)	5 (36)
HLD	8 (28)	0	8 (57)
CAD	4 (14)	0	4 (29)

Prior paroxysmal atrial fibrillation	1 (4)		0		1 (7)	
Osteoarthritis	9 (31)		5 (33)		4 (29)	
Osteopenia or osteoporosis	4 (14)		2 (13)		2 (14)	
Depression or anxiety	7 (24)		5 (33)		2 (14)	
	Mean	±SD	Mean	±SD	Mean	±SD
Age (yrs)	57.9	12.3	40.9	7.8	68.7	7.1
Clinical						
Time since diagnosis (yrs)	6.0	5.7	8.7	6.9	3.1	1.8
Time since initiation on sirolimus (mos)	NA		45.6	30	NA	
Time since initiation on antifibrotic (mos)			NA		27.8	20.3
Anthropometrics						
Body mass index (kg/m^2)	26.1	4.7	25.1	4.5	27.1	4.6
Weight (kg)	75.8	14.9	69.0	11.0	83.3	15.0
Height (cm)	170.6	9.7	166.0	7.0	176.4	10.1
Resting pulse standing (bpm)	81	13	74	13	82	13
Resting SpO_2 standing (%)	97	1.7	97	1.5	97	1.8
Resting SBP supine (mmHg)	131	21	126	24	135	16
Resting DBP supine (mmHg)	78	12	80	14	75	8
Pulmonary Function						
FEV_1 (liter)	2.2	0.7	2.0	0.7	2.4	0.6
FEV_1 (% predicted)	73.1	19.9	66.8	20.1	80.0	16.8
FVC (liter)	3.0	0.7	3.1	0.8	3.0	0.7
FVC (% predicted)	76.1	17.8	81.6	18.5	74.8	17.9
FEV_1/FVC (ratio; %)	73.3	13.4	65.4	14.1	80.3	7.1
DLCO (corrected for hemoglobin; ml/min/mmHg)	NA		NA		14.0	3.5
DLCO (% predicted)					48.4	11.9
Exercise Capacity						
VO_2max on CPET (ml/kg/min)	25.2	6.4	26.0	6.5	24.3	6.4
VO_2max (% predicted)	88	28	95	28	81	27
HR at VT1 on CPET (bpm)	118	15	123	14	111	13
HR at VT2 on CPET (bpm)	139	13	142	14	135	13
6MWT distance (meters)	503	80	537	62	466	84
6MWT distance (% predicted)	91	14	93	9	91	18
6MWT Peak HR (bpm)	116	15	115	14	118	15
6MWT Peak RPE (Borg 0-10)	4.1	2.0	3.9	1.4	4.3	2.5
6MWT Peak Dyspnea (Borg 0-10)	2.7	1.8	2.7	1.8	2.9	2.0

Combined Sample (LAM+IPF) and ILD Subtypes

Relationships and agreement were visualized between the $HR_{peak6MWT}$ value and the HR value at the determined VT1 on CPET for the combined sample of participants with LAM and IPF (Figure 3.1a), and for ILD subtypes of IPF (Figure 3.1b), and LAM (Figure 3.1c). $HR_{peak6MWT}$ moderately correlated with $HR_{VT1onCPET}$ in the combined sample (r=0.442, p=0.016),

and strongly correlated with $HR_{VT1onCPET}$ when examined just in patients with IPF (r=0.743, p=0.0036). There was no correlation between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ when examined just in patients with LAM (r=0.290, p=0.294). The average of $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ was plotted against the difference between the 2 values for the combined sample and for each ILD subtype using Bland Altman methods. For the combined sample, the mean bias was –0.72bpm, a value not significantly different from 0, and the limits of agreement (±2 SD) were ±31.6bpm. Large limits of agreement indicated wide variability in agreement with the true $HR_{VT1onCPET}$ in our combined sample. When examined just for patients with IPF, the mean bias was 6.15bpm, a value significantly different from 0, and the limits of agreement were ±24.2bpm. Use of $HR_{peak6MWT}$ may overestimate the true HR at VT1 in individuals with IPF. When examined just for patients with LAM, the mean bias was -8.13bpm, a value significantly different from 0, and the limits of agreement were ±33.0bpm. Use of $HR_{peak6MWT}$ may underestimate the true HR at VT1 in individuals with LAM.

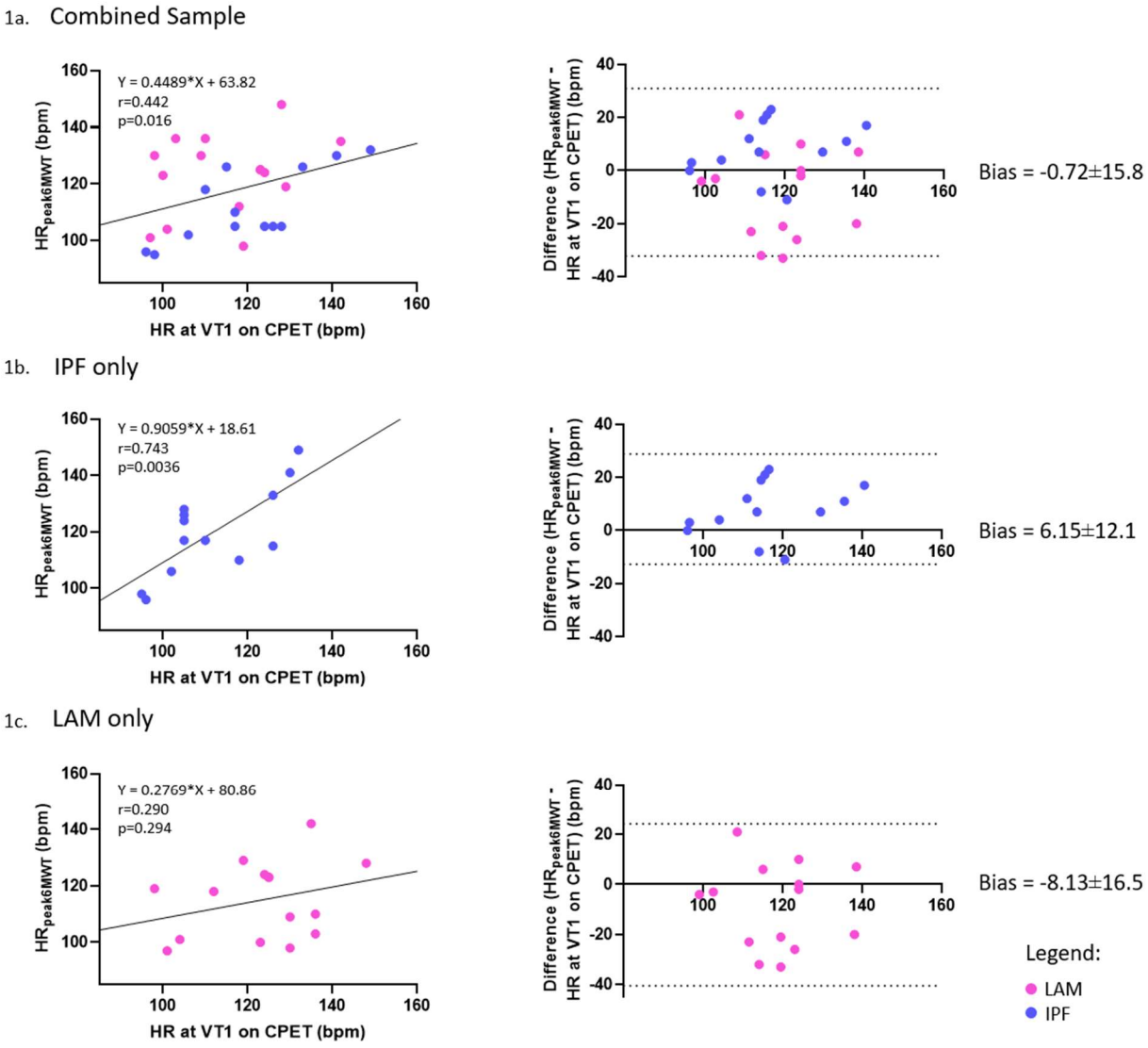


Figure 3.1. Assessment of the agreement between peak HR on 6MWT ($HR_{peak6MWT}$) and HR at VT1 on CPET ($HR_{VT1onCPET}$) for the combined sample of patients with ILD (IPF+LAM) (1a), and ILD subtypes of IPF (1b) and LAM (1c).

Agreement Using a Threshold of 85% Predicted 6MWT Distance

For participants that walked a 6MWT distance <85% predicted (Figure 3.2a), a very strong correlation (r=0.871, p=0.011) was observed between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$. For participants that walked a 6MWT distance ≥85% predicted (Figure 3.2b), $HR_{peak6MWT}$ did not correlate significantly with $HR_{VT1onCPET}$ (r=0.220, p=0.325). Using Bland Altman methods, the average of $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ was plotted against the difference between the 2 values for (a) participants with 6MWT distance <85% predicted (Figure 3.2a) and (b) participants with 6MWT distance ≥85% predicted (Figure 3.2b). For 6MWT distance <85% predicted, the mean bias was –2.71 bpm, a value minimally different from 0, and the limits of agreement were relatively narrow at ±19.4bpm. In individuals that walk a 6MWT distance <85% predicted, $HR_{peak6MWT}$ is a close estimate of the true HR at VT1, and narrow limits of agreement in this subgroup indicate low variability in agreement with the true HR at VT1 among individuals. For 6MWT distance ≥85% predicted, the mean bias was -0.09 bpm, a value not significantly different from 0, but the limits of agreement were very wide at ±35.0 bpm. Large limits of agreement in this subgroup indicate significant variability in agreement with the true HR at VT1 among individuals that walk a 6MWT distance ≥85% predicted.

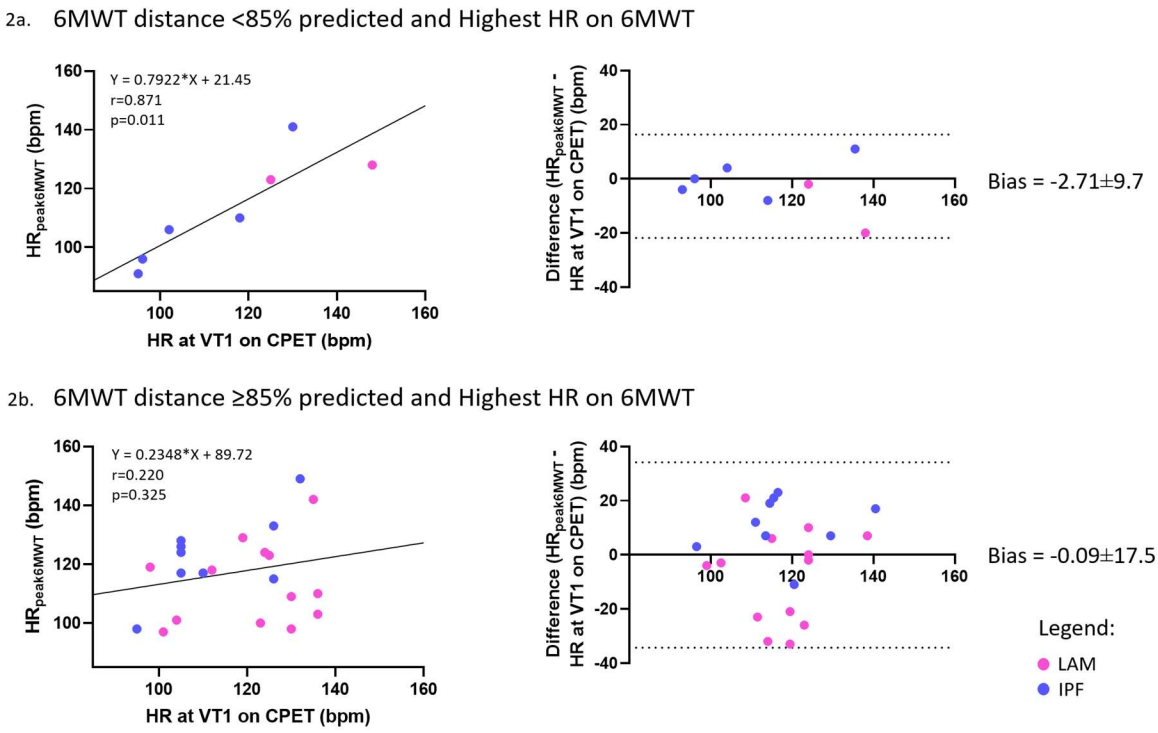


Figure 3.2. Assessment of the agreement between peak HR on 6MWT ($HR_{peak6MWT}$) and HR at first ventilatory threshold (VT1) on CPET ($HR_{VT1onCPET}$) for subgroups defined by a threshold of 85% predicted 6MWT distance: 6MWT distance <85% predicted (2a) and 6MWT distance ≥85% predicted (2b).

Agreement Using an Age-Predicted Maximal HR (APMHR)

Use of an age-predicted maximal HR (APMHR) of [220-age] (commonly attributed to Fox et al[19]) and calculation of 65% heart rate reserve (HRR) using the formula of Karvonen[39] also yielded a very strong correlation (r=0.870, p=0.012) with the criterion standard of $HR_{VT1onCPET}$ for participants that walked a 6MWT distance <85% predicted (Figure 3.3a). For participants with ≥85% predicted 6MWT distance, use of an APMHR and 65% HRR (APMHR+HRR) correlated moderately with $HR_{VT1onCPET}$ (r=0.647, p=0.0011). The average of APMHR+HRR and $HR_{VT1onCPET}$ was plotted against the difference between the 2 values for (a) participants with 6MWT distance <85% predicted (Figure 3.3a) and (b) participants with 6MWT distance ≥85% predicted (Figure 3.3b) using Bland Altman methods. For 6MWT distance <85%

predicted, the mean bias was 15.10 bpm, a value significantly different from 0, and the limits of agreement were ±22.2bpm. Bias and limits of agreement for the APMHR+HRR were much larger than the those for $HR_{peak6MWT}$ (bias = -2.71, limits of agreement = ±19.4), indicating the method of using $HR_{peak6MWT}$ had tighter agreement with the true HR at VT1 than the APMHR+HRR method in this subgroup of patients with 6MWT distance <85% predicted. For 6MWT distance ≥85% predicted, the mean bias was 17.36 bpm, a value significantly different from 0, and the limits of agreement were ±20.6 bpm. As shown in Figure 3.3b, the APMHR+HRR method did moderately correlate with the true HR at VT1 for individuals with 6MWT distance ≥85% predicted, but the very large positive bias indicates a high risk for overestimating the true HR at VT1 using this method in this subgroup of patients with ILD.

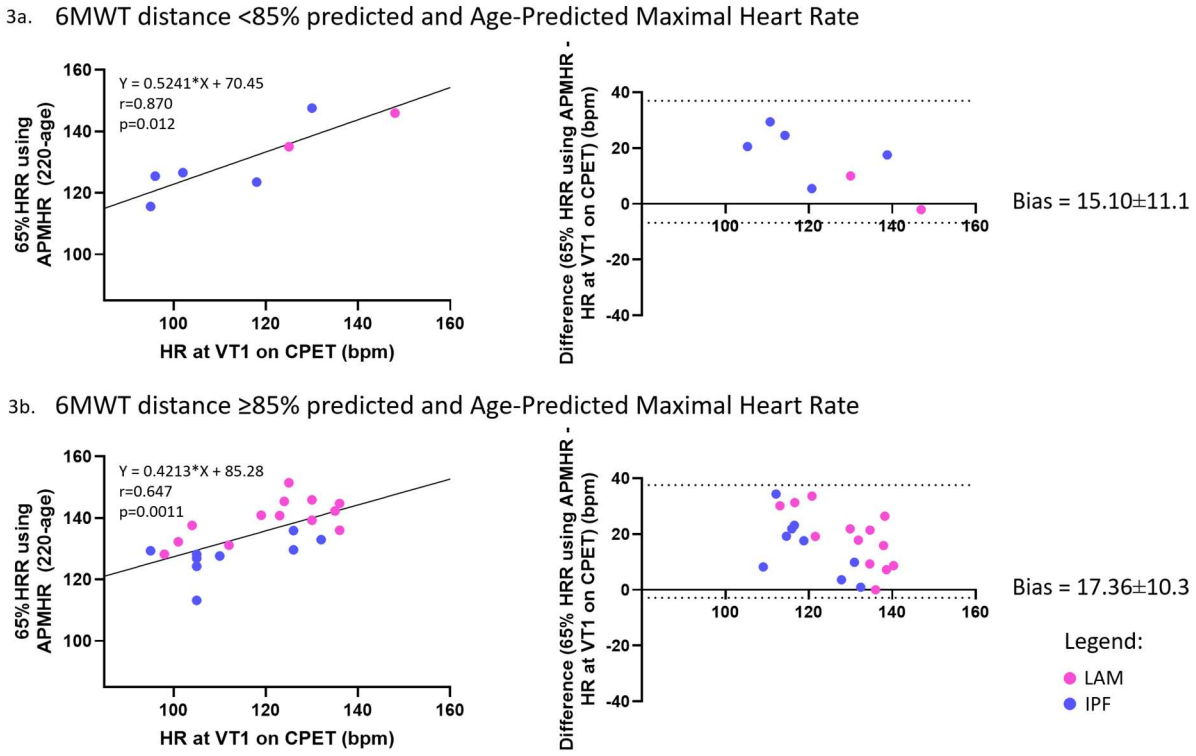


Figure 3.3. Assessment of the agreement between 65% heart rate reserve (HRR) using an age-predicted max HR (APMHR) and HR at VT1 on CPET ($HR_{VT1onCPET}$), for subgroups defined by a threshold of 85% predicted 6MWT distance: 6MWT distance <85% predicted (3a) and 6MWT distance ≥85% predicted (3b).

Mean Absolute Difference to Measure Validity of Peak HR on 6MWT

For participants that walked a 6MWT distance <85% predicted, the mean absolute difference of $HR_{peak6MWT}$, or the absolute value of the mean group difference between the $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ (criterion standard), was relatively small at 7.0±6.8 bpm, indicating a low amount of error introduced by using $HR_{peak6MWT}$ to estimate of aerobic exercise intensity. This mean value was significantly lower than $HR_{peak6MWT}$ mean absolute difference for the combined sample (12.3±9.7 bpm) and other subgroups, including ILD subtypes and nadir SpO_2 <90% on CPET. See Table 3.3 for subgroup measurements of $HR_{peak6MWT}$ mean absolute difference as a measure of validity, as well as correlations with clinical variables. Although there were no correlations between $HR_{peak6MWT}$ mean absolute difference and measures of pulmonary function in any of the subgroup analyses, $HR_{peak6MWT}$ mean absolute difference did negatively correlate with peak dyspnea on 6MWT in the combined sample (r=-0.453, p=0.014), the LAM subgroup (r=-0.684, p=0.005), and in patients with <90% nadir SpO_2 on CPET (r=-0.579, p=0.049). In other words, as peak dyspnea on 6MWT increased in patients with LAM and in patients that desaturated to nadir SpO_2 <90%, $HR_{peak6MWT}$ mean absolute difference tended to increase, with the $HR_{peak6MWT}$ trending closer to and increasing in validity to the criterion standard of HR at VT1 on CPET.

Table 3.3: Subgroup Analyses: Mean Absolute Difference of Peak HR on 6MWT and Correlations with Clinical Variables

		Combined IPF & LAM (n=29)		LAM (n=15)		IPF (n=14)		<90% Nadir SpO_2 on CPET (n=12)		≥90% Nadir SpO_2 on CPET (n=17)		<85% Pred. 6MWT distance (n=7)		≥85% Pred. 6MWT distance (n=22)	
Mean Absolute Difference ($HR_{peak6MWT} - HR_{VT1onCPET}$) (bpm)		12.3±9.7		14.0±11.6		14.5±12.6		12.3±8.3		16.0±9.9		7.0±6.8		14.0±9.9	
Correlations with Clinical Variables		r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
6MWT	Distance (meters)	0.287	0.131	0.249	0.371	0.253	0.383	0.478	0.116	0.367	0.147	0.498	0.255	0.080	0.724
	Distance (% predicted)	**0.482**	**0.008**	0.480	0.070	**0.636**	**0.014**	0.454	0.139	**0.546**	**0.023**	-0.016	0.972	**0.446**	**0.037**
	Peak HR (bpm)	0.020	0.918	-0.418	0.121	**0.681**	**0.007**	0.206	0.522	0.044	0.866	0.627	0.132	-0.171	0.448
	Cardiac Effort (bts/meters)	-0.093	0.673	-0.407	0.243	0.362	0.224	0.108	0.781	-0.310	0.303	0.226	0.667	0.005	0.984
	DDR (DA_{O2} /meters)	-0.239	0.284	-0.452	0.190	-0.010	0.975	-0.096	0.793	-0.261	0.413	-0.064	0.892	-0.152	0.588
	End SpO_2 on 6MWT (%)	0.079	0.684	0.039	0.889	0.133	0.649	0.305	0.336	-0.070	0.789	-0.204	0.661	-0.034	0.881
	Peak RPE (Borg 0-10)	-0.145	0.452	**-0.564**	**0.028**	0.269	0.352	-0.390	0.210	-0.017	0.948	0.410	0.361	-0.281	0.205
	Peak Dyspnea (Borg 0-10)	**-0.453**	**0.014**	**-0.684**	**0.005**	-0.136	0.643	**-0.579**	**0.049**	-0.277	0.283	0.152	0.745	**-0.573**	**0.005**
CPET	VO_{2max} (ml/kg/min)	0.185	0.336	0.300	0.277	-0.060	0.839	0.305	0.334	0.173	0.506	0.408	0.363	0.071	0.753
	VO_{2max} (ml/min)	-0.204	0.288	0.496	0.060	-0.196	0.502	-0.340	0.279	-0.330	0.195	-0.449	0.312	-0.106	0.638
	VO_{2max} (% predicted)	**0.410**	**0.026**	0.468	0.079	0.249	0.391	0.477	0.116	0.428	0.087	0.296	0.519	0.359	0.101
	HR_{max} (bpm)	0.171	0.374	0.329	0.231	-0.184	0.529	0.390	0.210	0.171	0.510	0.604	0.151	0.086	0.703
	End SpO_2 on CPET (%)	0.258	0.177	0.100	0.724	0.491	0.075	0.553	0.062	0.256	0.320	-0.161	0.730	0.135	0.550
	Peak RPE (Borg 0-10)	0.180	0.350	0.414	0.125	0.008	0.977	0.127	0.694	0.261	0.311	0.174	0.710	0.022	0.922
	Peak Dyspnea (Borg 0-10)	0.207	0.282	0.382	0.160	0.109	0.712	-0.225	0.483	0.251	0.331	0.203	0.662	0.345	0.116
PFTs	FEV1 (% predicted)	0.194	0.333	0.341	0.300	0.300	0.297	0.159	0.622	0.131	0.627	0.065	0.890	0.096	0.688
	FVC (% predicted)	0.053	0.798	-0.195	0.545	0.258	0.374	-0.444	0.171	0.315	0.235	0.051	0.913	-0.233	0.338
	FEV1/FVC (% predicted)	0.022	0.915	0.451	0.122	0.055	0.853	0.133	0.680	-0.371	0.157	0.005	0.991	0.036	0.566
	DLCO (corr. for hemoglobin; % predicted)					0.297	0.324								

3.5 DISCUSSION

The most important finding from this secondary analysis is the presence of a 'ceiling effect' *at or above a cut-off of 85% predicted 6MWT distance*, which impacts the utility of $HR_{peak6MWT}$ for aerobic exercise prescription among patients with ILD. This is the first report to quantify a ceiling effect in the use of HR data from 6MWT to prescribe aerobic exercise in ILD. Subgroup analyses using a threshold of 85% predicted 6MWT distance yielded the strongest correlations between $HR_{peak6MWT}$ and the criterion standard of $HR_{VT1onCPET}$, compared to any other variables, including ILD subtype and end SpO_2 on exercise testing.

The calculation of % predicted 6MWT distance is based on published reference equations that incorporate age, sex, height, and weight-matched normative data.[30] As the broader ILD population comprises >200 different disease subtypes with unique pathophysiologies,[2] the use of % predicted 6MWT distance is clinically useful as it may account for more individual-level differences than disease diagnosis alone when making decisions about aerobic exercise prescription. In our sample, patients that walked <85% predicted 6MWT distance demonstrated a very strong correlation (Figure 3.2a) between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$. Additionally, a very strong correlation was observed in patients that walked <85% predicted 6MWT distance between 65% HRR using APMHR and $HR_{VT1onCPET}$. For patients with ILD that walk a distance <85% predicted on 6MWT, our study suggests that clinicians should estimate a target HR of aerobic exercise intensity using the $HR_{peak6MWT}$. This is preferred over using an APMHR (such as 220-age) and the formula of Karvonen[39] to calculate a % of heart rate reserve (HRR), as the APMHR+HRR method will likely result in overestimating the aerobic training threshold in patients that walk a 6MWT distance <85% predicted. An exercise prescription derived from an overestimated aerobic training threshold runs the risk of being too difficult for these patients.

However, for patients who achieve at or above 85% predicted 6MWT distance, the use of APMHR and the Karvonen method to calculate a % of HRR may be preferred for aerobic exercise prescription over $HR_{peak6MWT}$, in the absence of a CPET, due to risk of underestimating the aerobic training threshold and undertraining these individuals if using the $HR_{peak6MWT}$.

In the combined sample of patients with ILD, $HR_{peak6MWT}$ demonstrated moderate correlation and no significant mean difference (bpm) compared to the criterion standard of $HR_{VT1onCPET}$, showing some potential for clinical utility of the $HR_{peak6MWT}$ for aerobic exercise prescription in the broader ILD population. This finding is similar to other published evidence supporting the use of $HR_{peak6MWT}$ for aerobic exercise prescription in CF[23] and COPD.[22] Additional subgroup analyses revealed a stronger correlation between the $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ in patients with IPF (Figure 3.1b) than in the combined sample of all patients with ILD. No significant correlation was observed between $HR_{peak6MWT}$ and $HR_{VT1onCPET}$ in patients with LAM (Figure 3.1c), as nearly all of our sample of patients with LAM were more highly functioning, with a 6MWT distance at or above 85% predicted.

Patients with ILD who are more physically active may experience some cardiac or peripheral remodeling commonly seen in more aerobically trained individuals,[40] even in the presence of reduced pulmonary function and/or gas exchange impairment. In our combined sample, there were no significant correlations between disease severity, as measured by PFTs, and the validity of $HR_{peak6MWT}$ in estimating $HR_{VT1onCPET}$. However, a moderate correlation was present between % predicted 6MWT distance, % predicted VO_2max, and $HR_{peak6MWT}$ mean absolute difference. In a study by Holland et al of 47 individuals with ILD (including 27 with IPF) that compared peak oxygen consumption during 6MWT and CPET, VO_2max during 6MWT represented on average 94% (range 62-135%) of VO_2max during CPET.[41] Although there was

significant variability in individual responses, the 6MWT elicited a higher %VO2max for individuals with more severe disease.[41] Of note, the Holland et al sample had a lower average functional capacity [mean±SD; VO_2max 16±4 mL/kg/min] and distance walked on 6MWT (429±130 meters) compared to our study sample (VO_2max 25±6 mL/kg/min; 6MWT distance 503±80 meters), despite similar disease severity [FVC (combined sample), 74±18% predicted vs. 76.1±17.8% predicted; DLCO (IPF subgroup), 44±11% predicted vs. 48±12% predicted].[41] Differences in functional capacity between samples may be related to differences in provider referral patterns to supervised pulmonary rehabilitation centers (which was the setting of the Holland et al study)[41] vs. home-based exercise programming with remote monitoring, which was employed in our studies. Regardless of exercise setting, our results suggest that a patient's functional capacity (e.g., 6MWT performance) is an important variable to consider, in addition to disease severity, when deciding whether to use $HR_{peak6MWT}$ to prescribe aerobic exercise.

Population-based studies in healthy adults also show evidence of a 'ceiling effect' for 6MWT in estimating cardiorespiratory fitness (CRF) levels in individuals with a higher VO_2max on CPET.[42] Dourado et al evaluated VO_2max on CPET and 6MWT distance in 1295 asymptomatic adults aged 18-80 years old, and investigated a 6MWT distance (% predicted) cut-off with high sensitivity to different classifications of cardiorespiratory fitness based on 6MWT distance and VO_2max on CPET.[43] The authors demonstrated that in asymptomatic adults, % predicted 6MWT distance showed excellent ability to identify very low cardiorespiratory fitness (6MWT distance ≤ 96% predicted) and good ability to differentiate CRF as low (6MWT distance = 97%–103% predicted), but it was not possible to differentiate between participants with regular and good CRF (6MWT distance >103%).[43]

Similarly, our study investigated a 6MWT distance (% predicted) cut-off value or threshold for using $HR_{peak6MWT}$ to accurately prescribe aerobic exercise in ILD. In the absence of an incremental CPET, patients with ILD and low cardiorespiratory fitness below 6MWT distance <85% predicted may be able to utilize the $HR_{peak6MWT}$ as a target HR threshold to guide aerobic exercise prescription. In the absence of an incremental CPET, patients with ILD and higher levels of cardiorespiratory fitness (6MWT distance ≥85% predicted) are more likely to estimate their true aerobic exercise intensity by using an age-predicted maximal heart rate (APMHR) and ~65% heart rate reserve (HRR), compared to using $HR_{peak6MWT}$, but this method (APMHR+HRR) is highly biased. A moderate correlation between a HR-based aerobic exercise prescription using APMHR and the criterion standard of $HR_{VT1onCPET}$ may be reassuring to some patients with ILD that have higher fitness levels and want to self-pace aerobic exercise training using consumer-grade, wearable HR/physical activity monitors that incorporate an APMHR formula and HR-based training zones by default.

Limitations

Our study has some limitations. The combined sample size was relatively small and limited to two subtypes of ILD. Study visits were conducted at a single center. The results of subgroup analyses are limited in their size and generalizability to the broader ILD population. More research is needed to confirm our results in larger, more diverse samples of patients with ILD. We were unable to measure DLCO in patients with LAM, so only patients with IPF were included in those data. Analysis of expired gases was only performed in CPET and not 6MWT, however participants did wear the same 12-lead electrocardiogram during 6MWT and CPET, facilitating continuous, criterion standard measurements of HR and rhythm, and permitting valid comparisons of participants' HR responses between subsequent tests.

The use of a target HR for aerobic exercise prescription is not appropriate for all patients with ILD. Some patients with ILD have comorbid cardiovascular conditions, including cardiac arrhythmias (e.g., atrial fibrillation), heart failure, Reynaud's phenomenon, and other known causes of digital hypoperfusion, which can impact the accuracy of photoplethysmographic HR readings.[44] Some patients are prescribed beta blockade for blood pressure control, which can blunt chronotropic and inotropic changes to exercise workload.[45] Only 4 participants with IPF were prescribed beta blockade in our sample, and a subgroup analysis of participants on beta blockade showed no significance. Some studies suggest a HR prescription using a lower % of HRR may still be appropriate for patients on beta blockade,[46] while others recommend using a % of VO_2max, a % of maximal workload, or RPE as alternative methods for aerobic exercise prescription.[47]

Potential underlying mechanisms for why higher levels of dyspnea on exertion on 6MWT correlated with the validity of the $HR_{peak6MWT}$ for aerobic exercise prescription in LAM remain to be determined. Baldi et al demonstrated that dyspnea on exertion, oxygen desaturation, and exercise limitation in LAM are related to frequent dynamic hyperinflation (DH) during exercise, even in patients with mild spirometric abnormalities.[48] During 6MWT, dyspnea and oxygen desaturation levels are greater in patients with LAM and DH than those without DH.[48] DH was not measured in this study, so its impact on $HR_{peak6MWT}$ validity in estimating aerobic exercise intensity in our sample is unknown. Since it is uncommon for patients with LAM to perform maneuvers to measure exertional DH during routine clinic visits,[48] but the 6MWT is frequently performed, LAM care providers may want to consider desaturation and peak dyspnea on 6MWT when deciding whether to use HR data from 6MWT to prescribe aerobic exercise, especially in patients for whom exertional DH measures have not been performed.

Similar to other studies comparing maximum oxygen consumption during 6MWT and CPET in cardiopulmonary populations,[16,24,41] variability in physiological responses was somewhat high amongst our sample. Our results support the use of $HR_{peak6MWT}$ for aerobic exercise prescription in some patients with ILD, but not all. Some patients with ILD will need incremental CPET to determine an accurate, personalized exercise prescription; extant literature[49] supports completion of an incremental CPET for the highest quality individual measures of VO_2max, maximal HR, and ventilatory thresholds for use during prognostication and aerobic exercise prescription.

3.7 CONCLUSION

In the absence of an incremental CPET, patients with ILD and very low cardiorespiratory fitness that walk a 6MWT distance <85% predicted may benefit from use of $HR_{peak6MWT}$ to estimate a target HR threshold for aerobic exercise prescription. For patients with ILD that walk ≥85% predicted 6MWT distance, the use of $HR_{peak6MWT}$ to estimate target HR threshold is not suitable, and an age-predicted maximal HR and the formula of Karvonen to calculate a percent of heart rate reserve, or completion of incremental CPET, may be preferred.

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Chapter 4 – Feasibility and Safety of LAM*Fit,* a Fully-Remote Digital Fitness Program for Lymphangioleiomyomatosis

PREFACE

Aim 3: Conduct a 6-month prospective pilot feasibility study of 'LAM*Fit*' to determine program feasibility and effectiveness among n=25 individuals with LAM.

After design of the LAM*Fit* digital technology platform, we conducted a 6-month pilot study of a fully-remote exercise program for lymphangioleiomyomatosis (LAM). All participants were pre-screened by their own care provider using the consensus LAM*Fit* exercise preparticipation screening tool developed in the Aim 1 study. All participants completed in-clinic exercise testing prior to enrollment to ensure adequate availability of home supplemental oxygen for aerobic exercise training. Providers electronically attested with signature whether their patients were medically appropriate to participate in the LAM*Fit* program prior to study enrollment. Our primary outcomes of interest were the feasibility and safety of the novel LAM*Fit* fully-remote, digital technology-enabled exercise program. Secondary endpoints included change in distance walked in six minutes, daily activity amounts and duration of exercise activities, intensity of exercise, as measured by total METs*mins, average HR, and average METs achieved during exercise sessions, and changes in self-reported fatigue, health-related quality of life, and dyspnea.

4.1 ABSTRACT

Background: Individuals with lymphangioleiomyomatosis (LAM) have poor access to evidence-based exercise programs that increase physical activity, quality of life, and help control dyspnea and fatigue. An evidence-based exercise intervention delivered on a digital health technology platform may help expand access.

Research Question: Is a fully-remote exercise program delivered on a digital health technology platform safe and feasible for individuals with LAM?

Study Design and Methods: We conducted a 6-month, single-arm prospective interventional pilot study of the LAM*Fit* digital fitness program with a pre-post (before-after) study design. All participants were pre-screened by their own care provider using the consensus LAM*Fit* exercise preparticipation screening tool and in-clinic exercise testing. Two subsequent 12-week exercise programs were administered consisting of personalized goal setting for daily combined minutes of moderate-to-vigorous physical activity (MVPA) and an independent exercise protocol, with 4 times/week continuous aerobic efforts 30 to 45 minutes, and 2 times/week resistance training. Baseline, midpoint, and final remote testing measured exercise capacity via novel six-minute walk test (6MWT) with remote monitoring, home spirometry, fatigue, health-related quality of life (HRQol), and dyspnea. An optional online LAM*Fit* community forum served as a place where study participants could share insights into overcoming barriers related to exercise and LAM and celebrate activity goal achievements.

Results: All 25 participants with LAM (100%) (mean ages 53±13 years) completed the first 12-week exercise program, including baseline, and midpoint study visits. Twenty-two participants (88%) completed the second 12-week program and final study visit, with 3 discontinuations for reasons unrelated to the study intervention. No serious or non-serious study-related adverse events occurred. High adherence to aerobic exercise during the two 12-week intervention periods was achieved (first 12 weeks: 81±18%; second 12 weeks: 79±18%). In the first 12 weeks, the mean daily minutes of moderate-to-vigorous physical activity (MVPA) increased by an average of 51% (25.6 ± 32.6 min to 52.5 ± 59.2 min; p=0.0318) compared to the run-in period. Distance achieved in 6MWT increased by an average of 7.1% (36.2 ± 9.1m, p=0.0021) from baseline to midpoint, and continued benefit was seen after completion of the second exercise intervention, with an average increase of 8.5% distance walked on 6MWT (43.4 ± 10.9, p=0.0021) at final study visit compared to baseline. Significant improvements in fatigue, HRQoL, and dyspnea were observed after participation in the first 12 weeks. Participants expressed a high level of satisfaction and acceptability of the LAM*Fit* digital fitness program.

Interpretation: A fully-remote approach to delivering a home-based exercise program in LAM is demonstrated to be feasible, safe, and acceptable. Results will be used to adapt and continue to scale access to the LAM*Fit* program for individuals with LAM that are medically appropriate to participate.

4.2 BACKGROUND

Individuals with the rare disease lymphangioleiomyomatosis (LAM) have poor access to evidence-based pulmonary rehabilitation (PR) and exercise programs that increase quality of life and help control dyspnea and fatigue. Traditionally, patients with interstitial lung diseases (ILD), including LAM[1,2], have been referred to supervised, center-based PR programs after initial diagnosis, after acute exacerbation(s), after changes in functional status, or prior to listing for lung transplantation.[3,4] Of those that are eligible for PR, less than 5% participate worldwide.[5] A 2018 representative geographic survey of PR centers in the US showed that only 61.5% of Medicare beneficiaries with COPD live within 10 miles of a PR center, and for individuals living in rural areas, only 11% live within 10 miles of a center.[6] During the COVID-19 pandemic, many PR centers in the United States (US) closed or reduced their in-person capacity; some have not reopened, and others have long waitlists, creating an access problem of unprecedented scale.[7] The number of adults with LAM in the US who are disadvantaged by distance to PR centers has not been quantified in the literature, but is likely similar to COPD, and has undoubtedly become more severe than the 2018 geographic survey suggests[6] due to pandemic effects.

The 2023 American Thoracic Society (ATS) clinical practice guideline on "Pulmonary Rehabilitation for Adults with Chronic Respiratory Disease" suggests that exercise-based PR for adults with ILD should be delivered in a setting in which supplemental oxygen can be administered during training, given the primary risk for exertional desaturation.[8] The ATS practice guideline also strongly recommends offering a choice between telerehabilitation and center-based PR for stable patients with chronic respiratory disease, acknowledging that new models of synchronous hybrid and asynchronous, remotely monitored telerehabilitation are emerging as feasible and safe,[8] but with the majority of published studies in COPD.[9] A handful

of small studies have shown that telerehabilitation and home-based exercise training are feasible and safe in ILD,[10–14] with other studies ongoing.[15,16] If sufficient home supplemental oxygen is available to support exercise training, a home-based exercise approach removes many of the participation barriers encountered by patients with LAM,[17] and may be preferred.[18,19]

Our research team recently demonstrated in the 'Exercise & Fatigue in LAM' study that a remote, asynchronously monitored home exercise program is safe in LAM, with no study-related adverse events, high participant satisfaction, and improvements in symptoms of dyspnea, fatigue, and exercise intolerance.[10] In community-academic partnership with The LAM Foundation,[20] we subsequently conducted a two-round modified Delphi study with sixteen experts in LAM and ILD to develop consensus regarding disease-specific recommendations for safety during unsupervised exercise, and to synthesize essential provider considerations into an algorithm for exercise preparticipation screening.[18] The primary product of this Delphi study was a clinical decision aid for LAM care providers to use when medically screening patients with LAM who want to participate in an unsupervised exercise program. We hypothesized that by partnering with patients' own LAM care providers to prescreen for medical appropriateness, using the LAM*Fit* exercise preparticipation screening tool,[18] subsequent exercise training within the fully-remote LAM*Fit* program would be safe and feasible. After dissemination of the screening tool to providers and patients online (www.lamfit.org), via manuscript,[18] webinars, and newsletter, we embarked on designing and testing 'LAM*Fit*,' a novel digital fitness program for LAM.

In this paper, we describe the development and pilot testing of the LAM*Fit* digital technology platform and exercise program. We aimed to 1) design a custom, patient-centered digital technology platform with integrated smartphone apps, wearable fitness trackers and

medical grade pulse oximetry, and behavioral change strategies, and 2) determine the feasibility and safety of a fully-remote LAM*Fit* program over a 6-month pilot study period.

4.3 METHODS

The LAMFit Digital Health Platform

A custom LAM*Fit* remote monitoring technology platform was created and user-tested to capture all digital endpoints. Participants were shipped a remote monitoring kit including a wristworn fitness tracker (Garmin vivosmart 5; Garmin, Ltd., Switzerland), medical grade pulse oximeter (Nonin BLE 3230; Nonin Medical, Inc, Plymouth, MN), home spirometer (MIR Spirobank Smart, Roma, Italy), instructional handouts, and materials for a remote 6MWT course. The study team updated Garmin device firmware, charged devices, and pre-installed batteries prior to shipping. Participants were instructed to use their own smartphones to download health monitoring apps. If participants did not own an internet-enabled smartphone or tablet, a smartphone with cellular and internet service was provided for use during the study.

To maximize the patient-centeredness of the program[21,22], the study team involved potential end users in each program design and implementation phase. Researchers co-designed the LAM*Fit* program logo, recruitment website, and community engagement forum in collaboration with patient representatives with LAM and an educational graphic designer (Figure 4.1). In addition to logo co-design with 2 patient representatives, broader user testing was employed for choice of the final LAM*Fit* program logo, with n=14 people with LAM ranking 4 options and giving open ended feedback via anonymous survey that was broadcast via social media and word of mouth. Eleven individuals with LAM signed media release forms and provided personal photos of them being physically active for use on the LAM*Fit* recruitment website and online participant portal. Two patient representatives, in collaboration with the study

team, drafted discussion prompts and regularly posted them to the community forum to promote participant engagement.

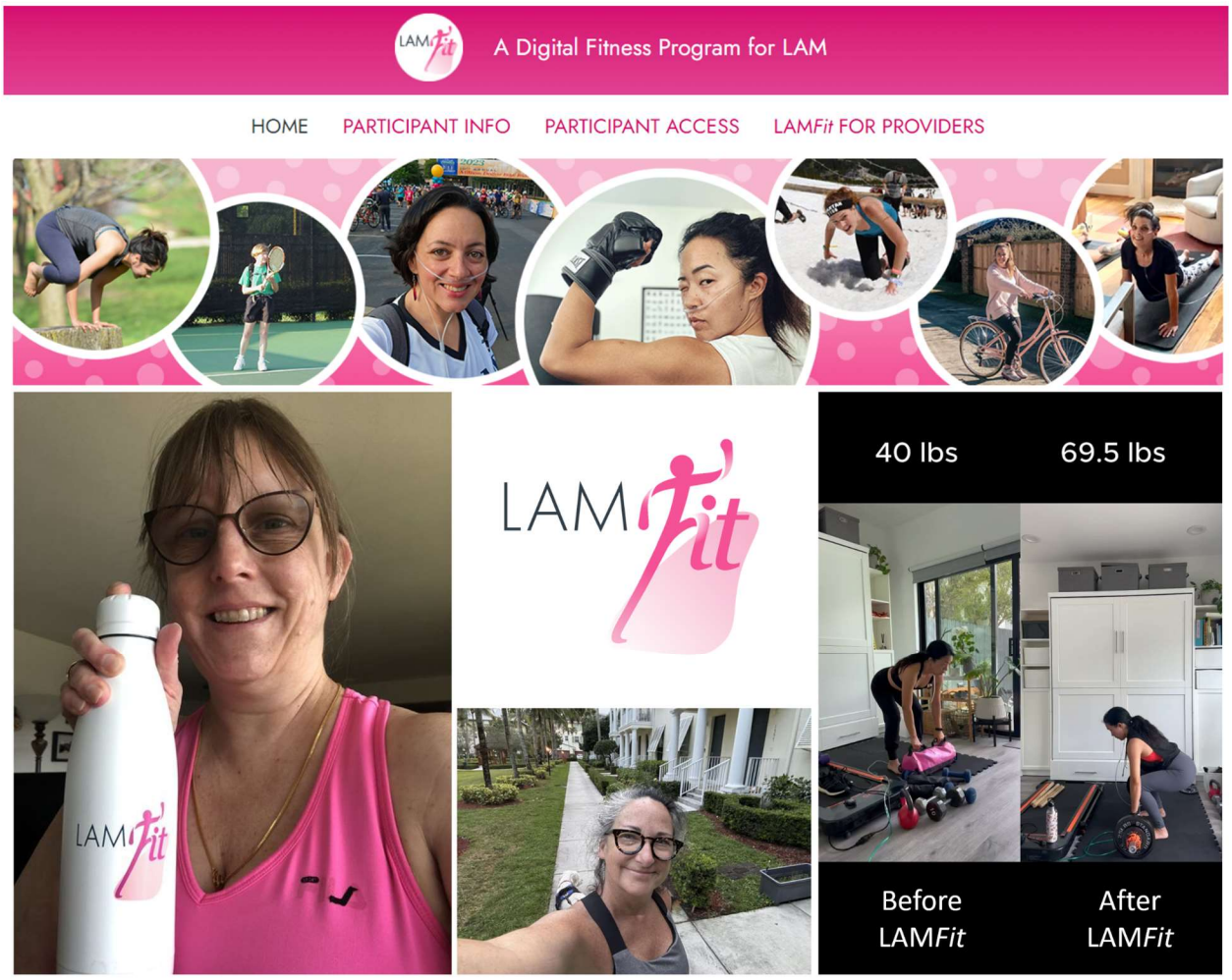


Figure 4.1: Co-Design of the LAM*Fit* program logo, recruitment website, and community engagement forum. Prospective end users of LAM*Fit* helped design the LAM*Fit* logo, contributed photos for use on the website, and drafted discussion prompts for the community engagement forum to promote the sharing of experiences related to becoming more physically active with LAM.

Participants received a 30-min training video and instructional handouts about how to use a personalized target HR, perceived levels of exertion, dyspnea, and oxygen saturation (SpO_2) to self-monitor and adjust exercise intensities as appropriate. Written instructions for how to

perform the remote six-minute walk test (6MWT) and exercise pulse oximetry monitoring within the digital health platform were developed and internally tested. All handouts and a monthly calendar were user-tested for clarity, printed, shipped to participants in remote monitoring kits, as well as posted for viewing and download on a secure, online participant portal (Figure 4.2). See Supplemental Materials for full-sized copies of instructional handouts.

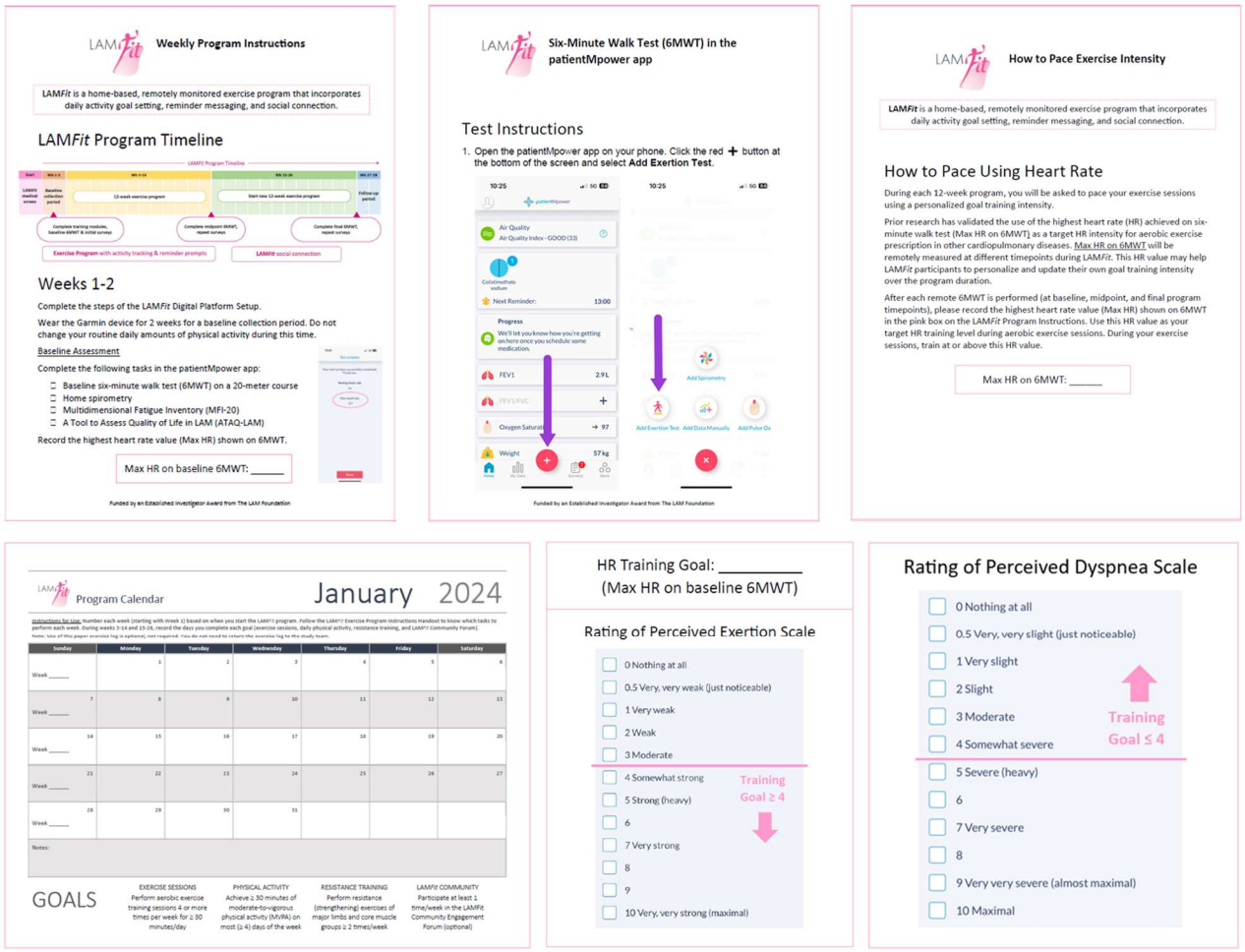


Figure 4.2: Examples of Instructional Handouts and a Monthly Calendar, which were developed, printed and shipped to participants as part of the remote monitoring kits, as well as posted for viewing and download on a secure, online participant portal. See Supplemental Materials for full-sized examples of instructional handouts.

Design of Remote Six-Minute Walk Test

A remote six-minute walk test (6MWT) with custom, in-app text and audio instructions was collaboratively developed and end user-tested with a third-party remote monitoring app (patientMpower, Dublin, Ireland) for this study (Figure 4.3). Standard encouragement using even, neutral, in-app audio recordings were provided. In-app written instructions, paper instructions, a 20-meter tape measure, cones, and a lap counter were mailed to participants to facilitate standardized conditions of the ATS protocol.[23] Similar to our use of a tape measure, Du et al demonstrated that a rope method for self-administered 6MWT (using a pre-measured piece of rope mailed to the participant) correlates very strongly to in-person 6MWT.[24] The addition of small cones and a lap counter helped standardize the walking course between participants. Participants recorded in the app the number of laps walked and distance on tape measure from the nearest cone for calculation of total distance walked. Percent predicted distance was calculated using normative data from age- and sex-matched healthy adults.[25]

In-person, internal pre-testing of the remote 6MWT in a laboratory setting demonstrated 100% agreement between self-report of 6MWT distance and distance observed by the study team. During internal pre-testing, distance walked during 6MWT was also measured by a GPS-connected Garmin fitness tracker, which tended to underestimate distance walked on the 6MWT course by about 4% compared to self-reported distance and researcher-observed distance. Thus, participant self-report of distance walked via lap counter and tape measure was chosen as the preferred measurement method during remote 6MWT. Pulse rate (PR) and SpO_2 via continuous, medical grade fingertip oximeter were recorded in a sitting position pre-test, each second during 6MWT, and during 3 minutes of quiet sitting after the test. Peak HR on 6MWT ($HR_{peak6MWT}$)

was identified automatically by the app, shown to the user at the end of the test, and recorded in the written logbook by the participant.

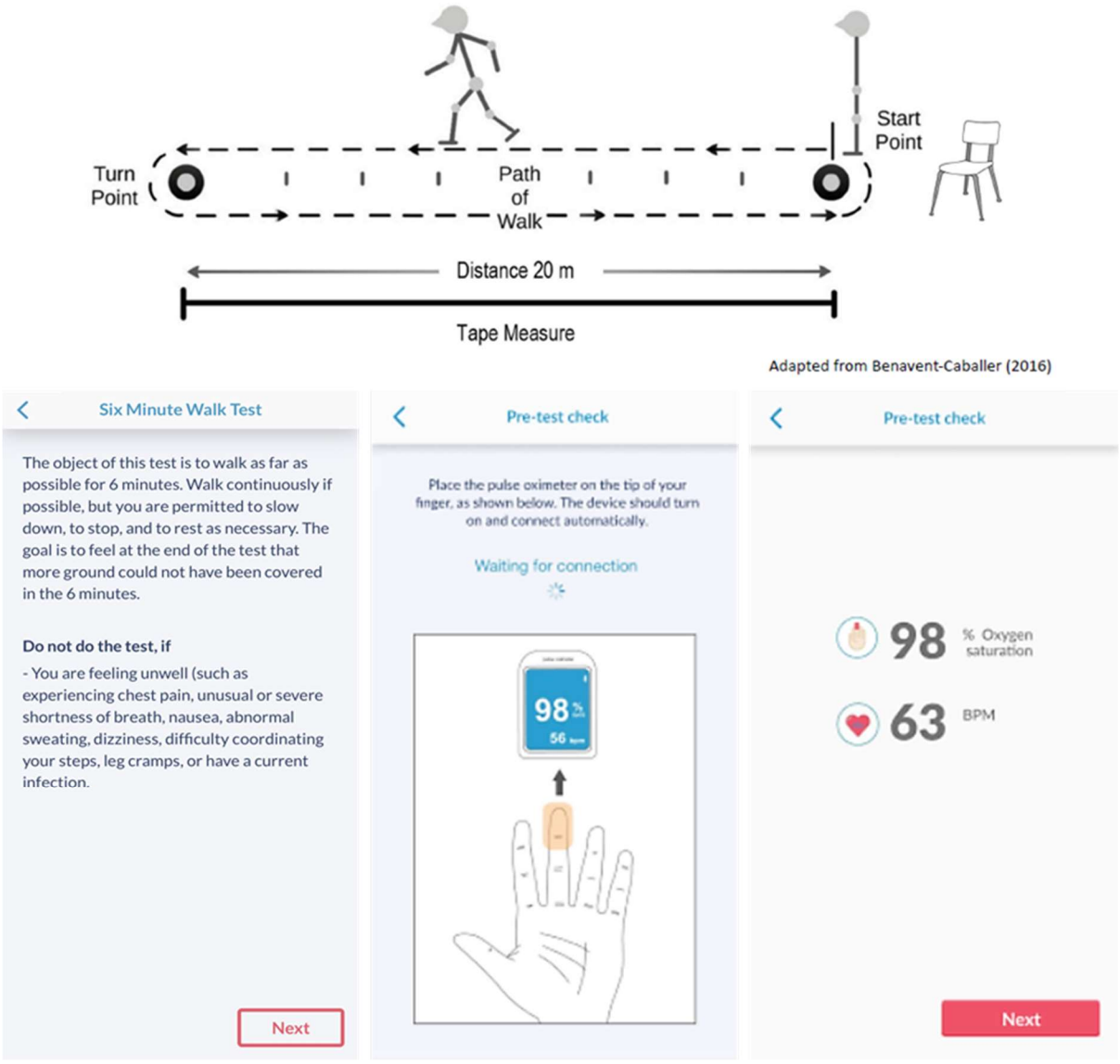


Figure 4.3: Development of the Remote Six-Minute Walk Test (6MWT). A schematic for the remote 6MWT walking course was adapted from Benavent-Caballer (2016)[26] and provided to participants in an instructional handout. A 6MWT with custom in-app text and audio instructions and remote pulse oximetry monitoring was collaboratively developed and end user-tested with a third-party smartphone app (patientMpower, Dublin, Ireland).

Co-Design of Activity Goal Setting and Accountability Features

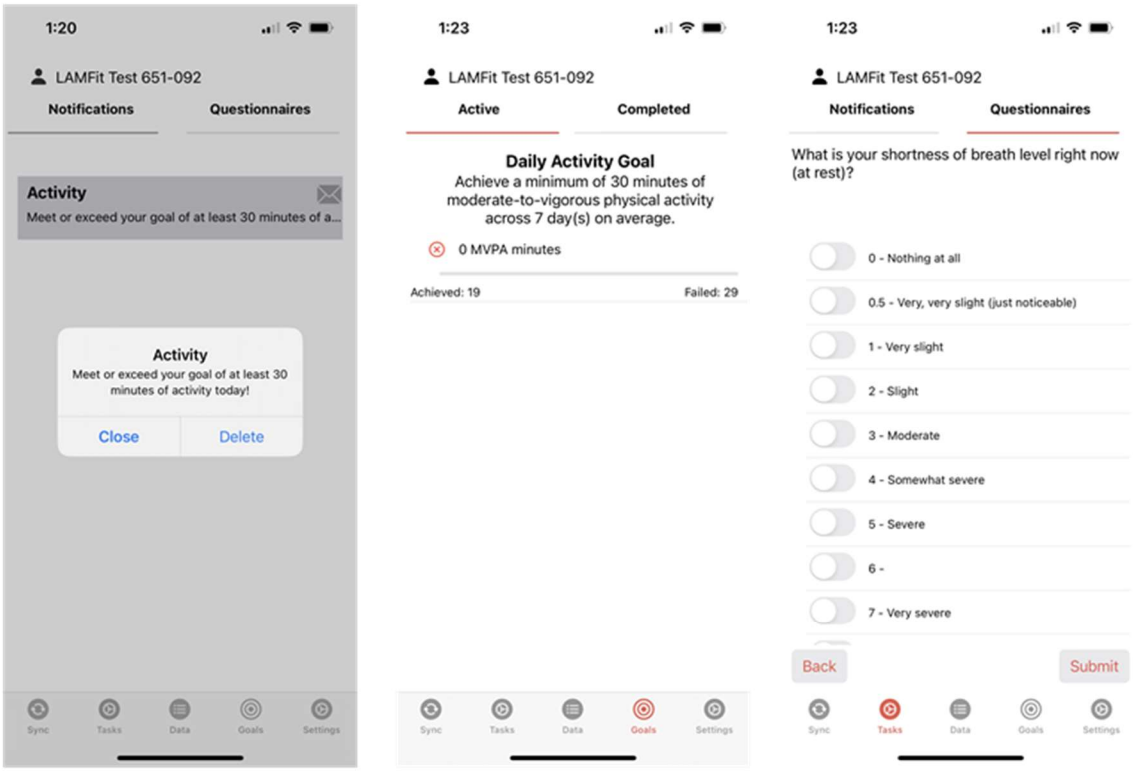
Physical activity metrics and intentional exercise sessions were recorded via fitness tracker (Garmin vivosmart 5) that was Bluetooth-connected to the Fitrockr Hub app during the first 12 weeks (Fitrockr, Berlin, Germany) and the GarminConnect app (Garmin, Ltd., Switzerland) during the second 12 weeks. Participants also set weekly goals for daily minutes of combined moderate-to-vigorous physical activity (MVPA), and progress towards goals was tracked automatically and visualized on a smartphone app (Figure 4.4a). Personalized goal reminder notifications were sent at least once weekly to participants' smartphones, and 2-3x/week if they did not achieve their weekly goals. Differing from the previous Exercise & Fatigue in LAM study[10], and consistent with a more hands-off, remote exercise approach, participants were not contacted weekly by the study team, but instead were asked to reach out to the study team or their own provider if they had questions about the exercise program or signs or symptoms of exercise intolerance.

Co-Design of the LAMFit Community Forum

An optional, online LAM*Fit* community forum (Facebook, Meta, San Francisco, CA) was developed for the purpose of facilitating group engagement, sharing of deidentified group goal achievement visualizations, and fostering organic patient-driven discussions related to physical activity and LAM. Examples of discussion posts included: 1) Consider sharing your *why* for choosing to enroll in the LAMFit program, and what you hope to get out of it; 2) Have you started to notice changes as a result of regularly exercising? Can you share what they are?; and 3) How do you manage fatigue? Group goal achievement visualizations (Figure 4.4b) were manually created every 1-2 weeks by the study team using Fitrockr physical activity data exports, deidentified, and shared on the LAM*Fit* community forum to enhance group

accountability. If group goal achievement was <80%, supportive ideas were shared on the forum for how to increase daily minutes of MVPA.

4a.



4b.



Figure 4.4: Group & Personalized Goals with Reminder Messaging were implemented within the smartphone app (Figure 4.4a; Fitrockr HUB, Fitrockr, Berlin, Germany) and LAM*Fit* community forum (Figure 4.4b; Facebook, Meta, San Francisco, CA) as innovative change strategies to promote increased physical activity behaviors among study participants.

The LAM*Fit* Remotely Monitored Exercise Program

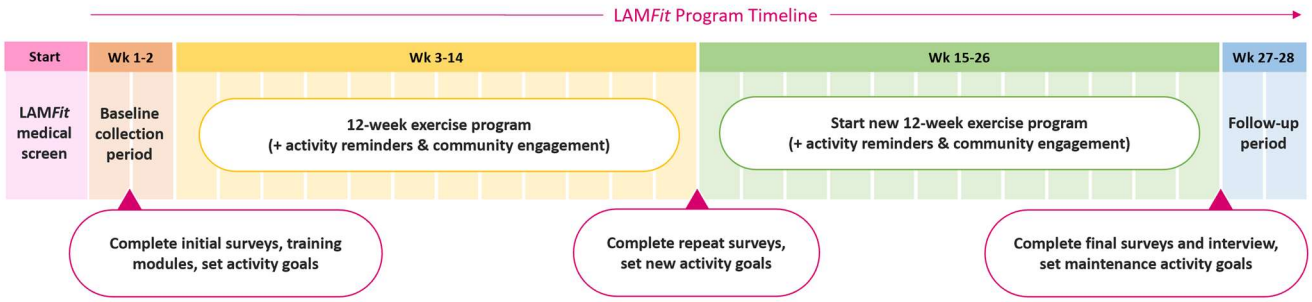


Figure 4.5: The LAM*Fit* Pilot Study Protocol. After preparticipation screening, eligible patients with LAM enrolled in a 6-month pilot study of LAM*Fit,* a home-based, self-monitored exercise program that incorporated two subsequent 12-week exercise programs, daily activity goal setting, reminder messaging, and LAM-specific social connection.

Using the digital health platform, we conducted a 28-week, single-arm prospective interventional pilot study of the LAM*Fit* program (Figure 4.5) with a pre-post (before-after) study design. The pilot study was conducted from January to October 2024. Study methods were approved by the University of Washington Institutional Review Board (STUDY00007271). Participants were recruited from the greater LAM community of the US via online webinar, word-of-mouth, study website, and participant interest and provider referral surveys hosted on the study website (**www.lamfit.org**). An interest pool of >70 individuals with LAM was developed and maintained. To achieve broad representation of people living with LAM in the US, we randomly sampled from the interest pool using blocked randomization and assist from a consulting biostatistician based on 3 self-reported variables, including 1) time since diagnosis, 2) geographical region of the US, and 3) baseline physical activity status. An enrollment goal of n=25 was based primarily on the previous Exercise & Fatigue in LAM study results[10] where a 12-week exercise intervention in a cohort of n=15 patients with LAM yielded a 9.8% increase in average daily steps, as well as significant changes in daily MVPA and distance walked on

6MWT. A sample size of n=25 was based on an *a priori* two-tailed power analysis using a power of 90% and endpoint of daily steps, expecting a 9.8% increase over 12 weeks.

Table 4.1: Eligibility Criteria

Inclusion Criteria	**Exclusion Criteria**
1) Diagnosis of LAM by a pulmonary physician	1) Unstable medical condition
2) Age ≥18 yrs at enrollment	2) Musculoskeletal or other conditions which would limit exercise participation
3) In stable medical condition	3) Non-compliance with medical therapies
4) No changes in medical treatment for past 3 months	4) Severe pulmonary hypertension
5) Able to titrate supplemental oxygen and/or exertional intensity to maintain appropriate oxygen saturation levels	5) Pneumothorax in the last 4 weeks
6) Preexisting prescription if indicated for use of supplemental O2 during exercise/exertional activities as needed at home.	6) Prior lung transplantation
7) Have another person available (e.g., partner, caregiver) for support during an exercise regimen if needed	7) Known current pregnancy
8) Able to understand the consent in English	8) Any other condition at the discretion of the pre-screening care providers

Eligibility criteria are detailed in Table 4.1. Prior to enrollment, invited participants were screened for eligibility by a licensed pulmonary physician, primary care provider, or nurse practitioner using the LAM*Fit* Exercise Preparticipation Screening Tool[18] and a physical therapist on the study team. A provider attestation form was completed and electronically signed by a patient's own medical provider and securely shared with the study team prior to enrollment (See Supplemental Materials). On this form, providers were asked to confirm study eligibility, attest that the patient had completed an in-person clinical exercise test (e.g., 6MWT or maximal

CPET) within the last 3 months, had adequate knowledge of and availability of the level of supplemental oxygen they should use during exercise (if any), and could read a pulse oximeter and make appropriate decisions for exercise pacing and self-monitoring.

Digital Platform Setup and Remote Monitoring

Upon enrollment, participants were shipped the remote monitoring kit and a phone call or secure virtual appointment was scheduled for digital platform setup. Participants donned the wristworn fitness tracker (Garmin vivosmart 5) for a 2-week run-in period to estimate baseline physical activity levels and to account for the Hawthorne effect.[27] Participants were instructed to wear their fitness tracker 24 hours/day, 7 days/week, and doff only to charge during bathing. For intentional exercise sessions, participants were instructed to record sessions as activities on their Garmin fitness tracker, monitor continuously via medical grade pulse oximetry (Nonin BLE 3230), maintain SpO_2 ≥85%, monitor for symptoms of exercise intolerance (See Supplemental Materials), and to adjust exercise intensity and supplemental oxygen levels accordingly. They were also instructed to record pulse oximetry during exercise training at least once/week. The study team received and reviewed pulse oximetry data files from exercise sessions at least once weekly. Baseline, midpoint, and final remote study visits were conducted via the digital technology platform at week 3, week 14, and week 26 of the protocol.

Exercise Prescription

Between the baseline, midpoint, and final study visits, participants completed two 12-week, 4 times/week independent home exercise protocol, with a 30 to 45-minute continuous effort at an intensity of ~65% of heart rate reserve (HRR), as calculated using the formula of Karvonen[28] during the LAM*Fit* introductory training module. In the absence of a recent maximal cardiopulmonary exercise test (CPET) for calculation of HRR, participants were instructed to use

$HR_{peak6MWT}$ as a personalized estimate of moderate intensity or greater, a HR threshold that has been validated to be at or near the first ventilatory threshold on CPET, the criterion standard for the onset of aerobic metabolism, in cystic fibrosis and COPD.[29,30] After the first 12-week exercise intervention, a repeat measure of $HR_{peak6MWT}$ during the midpoint study visit provided participants with an updated target HR for aerobic training at or above moderate intensity. Participants also completed resistance training 2 times/week, addressing all major peripheral muscle groups. Participants were asked to record all aerobic exercise sessions as activities on the Garmin fitness tracker, but it was optional to record resistance training as an activity.

Endpoints

Primary feasibility endpoints of our fully-remote approach included 1) aerobic exercise program adherence, as defined by percent of prescribed aerobic exercise sessions completed, 2) physical activity goal achievement, as defined by percent of weeks that patients accomplished or exceeded their weekly goal for daily combined minutes of MVPA, 3) completion of exercise program, as defined by completion of at least one exercise session during week 12, recorded individually for each 12-week exercise program, 4) completion of digital endpoints, including remote 6MWT, home spirometry, and remote pulse oximetry monitoring of exercise sessions, 5) occurrence of serious or nonserious study-related adverse events[31], 6) patient acceptability and satisfaction, as measured by exit survey, and 7) smartphone application usability, as measured by the system usability scale (SUS)[32]. Key process metrics were also tracked, including average number of emails/calls made for provider attestation of medical appropriateness and average time to platform setup after shipping the remote monitoring kit.

Participants also provided self-report of baseline anthropometrics, current medications, home supplemental oxygen used at rest and during exertion, and clinical measures of pulmonary

function using a validated testing protocol[33] conducted within the last 3 months (% predicted). Baseline (Initial), midpoint, and final remote study visit measures included: 1) remote 6MWT to assess distance, continuous HR and SpO_2 responses, resting and exertional ratings of perceived exertion and dyspnea, 2) health-related quality of life (HRQoL) via A Tool to Assess Quality of Life in Lymphangioleiomyomatosis (ATAQ-LAM)[34], 3) fatigue severity via the Multidimensional Fatigue Inventory (MFI-20)[35], 4) dyspnea in daily life, as measured by the modified Medical Research Council (mMRC) Dyspnea scale[36], and 5) home spirometry (MIR Spirobank Smart within patientMpower smartphone application, Dublin, IR), graded according to 2019 ATS/ERS criteria.[37] The mMRC Dyspnea scale is a self-rating tool frequently used in studies of PR to measure the degree of disability that breathlessness poses on activities on a scale from 0 to 4: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; 4, too breathless to leave the house, or breathless when dressing or undressing.[36] Physical activity metrics, including weekly combined minutes of moderate-to-vigorous physical activity (MVPA), exercise intensity (average METs / min), and volume (METs*mins) of exercise sessions were recorded and categorized via Garmin fitness tracker (Garmin vivosmart 5). For the purposes of this dissertation, a surface-level evaluation was completed of the community engagement forum using % group participation and other Facebook engagement metrics, including number of posts and active daily users.

Data Analysis

Multiple methods were used to measure feasibility outcomes and changes between pretest and posttest after the first (baseline to midpoint) and second (midpoint to final) intervention periods. Paired t-testing measured changes between the pretest and posttest in all outcome variables. Repeated measures analysis of variance (RM-ANOVA) or mixed effects analysis (if any missing data) were used to detect differences over time and percent of change for variables measured over 6 months, such distance walked on 6MWT, physical activity metrics, and self-reported quality of life, fatigue, and dyspnea ratings. Pearson correlations analyzed relationships between variables. Physical activity and exercise data during any weeks of medical instability were not included in the post-intervention analysis. For subjects that were medically inappropriate for midpoint or final remote exercise testing, efforts were still made to collect study visit surveys as able. Data are presented for individual subjects, and as group means with standard deviation (SD) in text and tables, and means with standard error (SEM) in figures. Statistical analysis utilized GraphPad Prism version 9.3.1, and differences at α level of 0.05 were considered significant.

4.5 RESULTS

Of the 31 individuals with LAM screened (Figure 4.2), 25 women with sporadic (n=23) and tuberous sclerosis complex (TSC)-associated (n=2) LAM were enrolled in the pilot study (age 53±13 years, 9±9 years after diagnosis). After prescreening, two people became not interested in participation due to upcoming travel plans (n=1) and anxiety about pulse oximetry use (n=1). One person was screened by their provider as medically inappropriate to start LAM*Fit* due to cardiac instability in the setting of arrhythmia (Wolff-Parkinson White syndrome). Three

other people did not meet eligibility criteria. Six additional individuals were randomly sampled from the interest pool, screened as medically appropriate by their provider, and enrolled in the study. Baseline sample demographic characteristics are presented in Table 4.2.

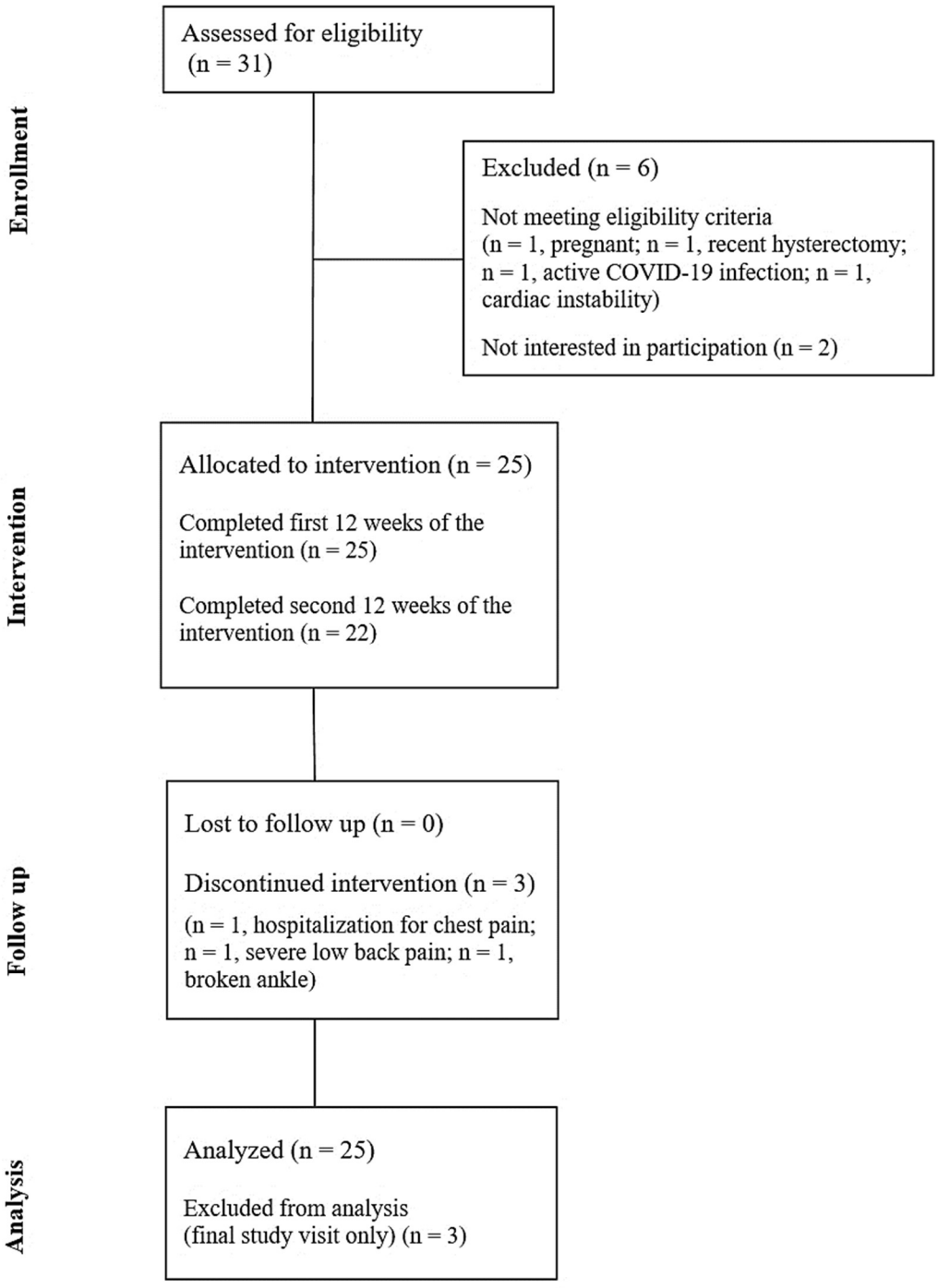


Figure 4.6: Flow of Participants through the LAM*Fit* Pilot Study

Table 4.2: Baseline Demographics

	Adults with LAM (n = 25)	
	Number (n)	%
Female	25	100
Race/Ethnicity		
White	21	84
Black	1	4
Asian	2	8
Hispanic/Latino	1	4
Etiology		
Sporadic LAM	23	92
TSC-associated LAM	2	8
Geographic Region of the United States		
Pacific Northwest	5	20
Southwest	6	24
Midwest	6	24
Southeast	5	20
Northeast	3	12
Medications		
Sirolimus	14	56
Everolimus	2	8
Inhaled corticosteroid	5	20
Beta blocker	0	0
ACE inhibitor	6	24
Short term O_2 therapy (during exertion)	10	40
Long term O_2 therapy	0	0
Menopause Status		
Premenopausal	15	60
Postmenopausal	10	40
Comorbidities		
Prior pneumothorax	15	60
Renal angiomyolipoma	12	48
Back pain / discitis	7	28
Hypertension	7	28
Epilepsy	2	8
Osteopenia / osteoporosis	6	24
How would you rate your overall health?		
Excellent	1	4
Very Good	18	72
Good	6	24
Fair	0	0
Poor	0	0
Relationship Status		
Married/partnered	19	76
Single [never married]	5	2

Divorced	1		4
Highest Level of Education			
College graduate	13		52
Post-college	10		40
Some college	2		8
Typical Household Income (per month)			
>$5000	18		72
$3201-5000	7		28
<$3200	0		0
How hard is it for you to pay for the very basics like food and medication(s)?			
Not hard at all	18		72
Somewhat hard	6		24
Very hard	1		4
	Mean	±SD	Range
Age (years)	52.7	13.4	33-78
Clinical			
Time since diagnosis (years)	8.9	9.0	0.4-36.0
Time since initiation on sirolimus/everolimus (years)	4.1	2.1	0.3-9.1
Number of prior pneumothoraces (n)	1.8	1.4	0-5
Time since last pneumothorax (years)	6.1	6.0	1.0-18.0
Anthropometrics			
Body mass index (kg/m^2)	25.0	5.3	18.3-44.5
Weight (kg)	67.1	14.1	45.4-103.4
Height (cm)	164.0	6.0	152.4-175.3
Pulmonary Function (self-reported, clinical measures within last 3 months)			
FEV_1 (% predicted)	78.3	22.2	30-108
FVC (% predicted)	93.5	16.6	61-128
DLCO (% predicted)	65.1	20.4	27-97

Completion, Adherence, and Safety

All 25 participants (100%) completed the first 12-week exercise program, baseline, and midpoint study visits. Twenty-two participants (88%) completed the second 12-week exercise program and final study visit, with 3 discontinuations for reasons unrelated to the study intervention. High adherence to aerobic exercise during the two 12-week intervention periods was achieved (first 12 weeks: 81±18%; second 12 weeks: 79±18%). Eleven participants achieved >90% adherence during the first 12 weeks, and 5 participants achieved >90% adherence during all 24 exercise weeks. Adherence to resistance training was not tracked.

No serious or non-serious study-related adverse events occurred. One subject experienced acute viral pneumonitis in week 5, leading to increased supplemental oxygen requirements during exertion, but was never hospitalized. After 4 weeks of treatment with inhaled corticosteroids, her condition stabilized and she was reassessed for medical appropriateness by her pulmonologist, who cleared her to resume exercise training in the LAM*Fit* program. Two participants were hospitalized for reasons unrelated to the study intervention. One was hospitalized for sepsis, medically stabilized, and discharged to home, and then was reassessed for medical appropriateness by her physician, who cleared her to resume exercise training in the LAM*Fit* program. Another participant was hospitalized during week 15 for unexplained chest pain and dizziness, ruled out for acute coronary syndrome, pulmonary hypertension, and other potential causes of syncope, medically stabilized, and discharged to home with referral to outpatient pulmonary rehabilitation instead of continuing on in the LAM*Fit* study. Two other participants were discontinued from the exercise intervention during weeks 15 and 16, respectively, for insidious onset of lower back pain requiring neurosurgical intervention, and a mechanical fall (not during an exercise session) complicated by a broken ankle.

As the LAM*Fit* program was administered completely remotely on a novel digital health platform, high participant completion of the majority of digital endpoints during the pilot study (Table 4.3) indicated high feasibility of our fully-remote approach. High Garmin sync rates and wear time were observed during the first 14 weeks. Completion of the in-app remote 6MWT was 100% during baseline and midpoint study visits. One participant reported a technical problem with the in-app remote 6MWT during their final study visit, and instead shared the number of laps and distance from nearest cone with the study team for manual calculation of distance walked and percent (%) predicted.

Most participants (88%, n=22) successfully used the patientMpower app at least once for home spirometry. In-app protocol adherence was 66%, with spirometry measured within ±14 days of scheduled assessments. Spirometry data consistently demonstrated high quality, with 97.42% of sessions yielding usable or acceptable FEV1 measurements. First attempts met acceptable criteria 79.31% of the time, 16.38% of second attempts achieved acceptable criteria, and 4.31% required further effort. Weekly exercise pulse oximetry (SpO_2) recording in the patientMpower app had the lowest completion rate with only 52% of participants regularly recording SpO_2 during an exercise session in the first 12 weeks, and only 36% of participants during the second 12 weeks. Pulse oximetry during remote 6MWT was successfully obtained during 100% of completed tests, in part due to a built-in automatic test stop if the pulse oximetry device's Bluetooth connection or readings faltered. Of 125 total remote 6MWT attempts during the study, 28% were cancelled by users prematurely, 6% were stopped mid-test for unspecified technical reasons, and 72% were successfully completed.

The largest amount of participant support time was required during program enrollment and digital platform setup, with support needs from the study team tapering off during the

exercise program (Table 4.4). Technology troubleshooting needs included: ensuring WiFi and/or cellular access were enabled for smartphone Internet connectivity in participants' homes, proper Bluetooth connection of the three remote monitoring devices to the smartphone, participant installation of the correct apps from iOS and Android app stores, helping participants set up secure log-ins and profiles for each remote monitoring app, connecting user accounts to the Fitrockr and patientMpower cloud-based research support platforms, assistance enabling app notifications for nudge messaging, facilitating app version and device firmware updates, occasional needs for hard device restarts, and working with participants to develop a manual syncing, charging, and wearing routine for the Garmin fitness tracker. In communications with the study team and in posts on the community engagement forum, participants immediately expressed frustrations with the manual device sync requirement within the Fitrockr HUB app, as well as a few other platform usability pain points. Some expressed survey fatigue with the dyspnea and exertion surveys administered weekly within the Fitrockr Hub app. Positively, many participants shared appreciation for the quality of the user experience associated with the Garmin fitness tracker and medical grade pulse oximeter devices.

Consistent with our patient-centered and iterative design approach, the study team responded to participant feedback, and at the midpoint study visit, all participants changed from using the custom study version of the Fitrockr HUB smartphone app to the over-the-counter GarminConnect app to support Garmin remote monitoring during the second 12 weeks of the study protocol. Not all data collection features were congruent across both apps, but both apps facilitated remote monitoring of Garmin device-collected physical activity metrics and weekly individual and group goal achievement via the Fitrockr cloud-based research support platform. Participants responded well to switching to the GarminConnect app, expressing that they valued

the automatic device sync functionality, automatic smartphone app version and device firmware updates, and improved personal physical activity data visualizations, ultimately rating the usability of the GarminConnect app higher [midpoint: 76.0±16.8 (“good”/acceptable); final: 77.6±25.0 (“good”/acceptable)] than the Fitrockr HUB app [baseline: 55.9±26.4 (“ok”/marginal acceptability); midpoint: 65.0±21.2 (“ok”/marginal acceptability)] after 12 weeks of use. Participants also rated the usability of the patientMpower app higher (baseline: 68.8±24 (“ok”/marginal acceptability); midpoint: 72.5±35 (“good”/acceptable) after 12 weeks of use.

Table 4.3: Completion Rates of Digital Endpoints

	Run-in Period (wk 1-2)	**Baseline Study Visit** (wk 3)	**Intervention Period 1** (wk 3-14)	**Midpoint Study Visit** (wk 14)	**Intervention Period 2** (wk 15-26)	**Final Study Visit** (wk 26)	**Follow-up Period** (wk 27-28)
Garmin sync >80% of days	100%		96%		95%		92%
Garmin average daily wear time (hrs)*	20.1		17.9		N/A		N/A
IPAQ-SF		100%				100%	
Remote 6MWT		100%		100%		95%	
Pulse oximetry during remote 6MWT		100%		100%		95%	
Borg RPE		100%	54%	100%		95%	
Borg RPD		100%	54%	100%		95%	
ATAQ-LAM		100%		88%		80%	
MFI-20		92%		88%		84%	
mMRC Dyspnea		100%		100%		100%	
SUS		72%		60%		88%	
Home Spirometry		88%		80%		82%	
Recorded exercise session(s) at least 1x/week			96%		95%		
Recorded pulse oximetry (SpO_2) during exercise at least 1x/ week			52%		36%		

*Note: Daily wear time was tracked by the Fitrockr HUB app during run-in (weeks 1-2) and intervention period 1 (weeks 3-14), but not by the GarminConnect app during intervention period 2 (weeks 15-26) and the maintenance period (weeks 27-28).

Table 4.4: Key Process Metrics and Participant Support Needs

	Mean ± SD
Program Enrollment (per patient)	
Initial enrollment and consent phone call [duration (mins)]	43:57 ± 18
Emails/calls for provider attestation (n)	1.2 ± 0.7
Time to provider attestation of medical appropriateness (days)	4.5 ± 4.8
Digital Platform Setup (per patient)	
Time to platform setup, after shipping monitoring kit (days)	12.8 ± 10.8
Emails/calls for digital platform setup (n)	1.4 ± 0.9
During the Exercise Program (per patient)	
Emails/calls for troubleshooting technology-related challenges (n)	0.6 ± 0.4
Emails/calls for exercise or health-related challenges (n)	0.5 ± 0.3

Activity Goal Achievement, Physical Activity and Exercise Capacity Measures

As data visualizations for personal and % group goal achievement of daily minutes of MVPA were custom technology features created for LAM*Fit*, we tracked individual and group goal accomplishments as a key feasibility metric. Individuals were encouraged to achieve ≥30 minutes of daily MVPA on most days of the week (at least 4 days a week), including time spent in intentional exercise sessions and other activities of daily living. Over the first few weeks of intervention period 1, participants tended to ramp up activity levels (Figure 4.7), and ultimately 74.3% of exercising participants achieved their goal. In the second intervention period, weekly goal achievement was more consistent, with 78.9% of exercising participants achieving their goal. In the first 12 weeks of the exercise program mean daily combined MVPA increased by an average of 51% (25.6 ± 32.6 min to 52.5 ± 59.2 min; p=0.0318) compared to run-in, with a 48% increase in daily moderate PA (20.6 ± 43.3 min, p=0.1087) and a 69% increase in daily vigorous PA (6.4 ± 12.3 min, p=0.0499). Daily sedentary time decreased by -16% (-136 ± 180 min,

p=0.0047), and daily steps increased by 30% (1281±1179 steps, p=0.0005) compared to run-in (3001 ± 1704 steps).

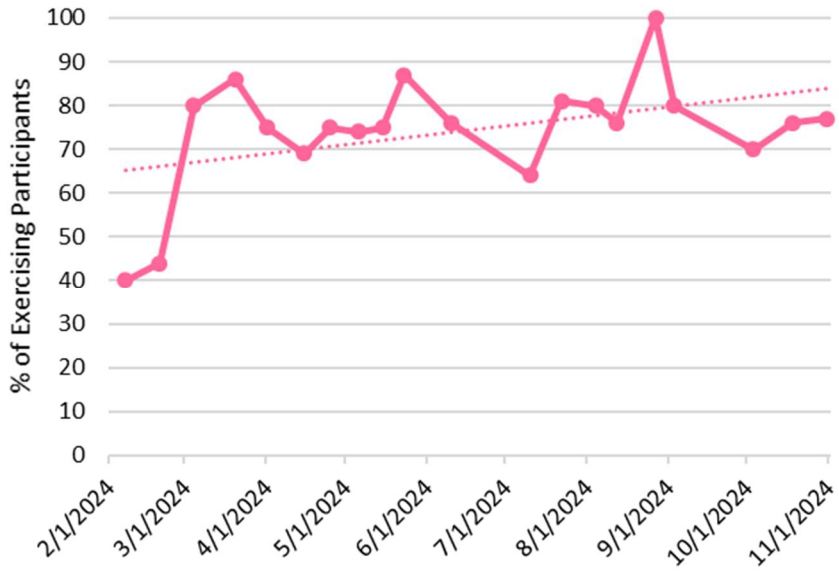


Figure 4.7: Group Goal Achievement of Daily Combined Minutes of Moderate-to-Vigorous Physical Activity (MVPA)

Distance achieved in 6MWT (Figure 4.8; Table 4.5) increased by an average of 7.1% from baseline to midpoint, and continued benefit was seen after completion of the second 12 weeks of exercise, with an average increase of 8.5% distance walked on 6MWT at final compared to baseline. Significant improvements in % predicted distance were also observed (Table 4.5).

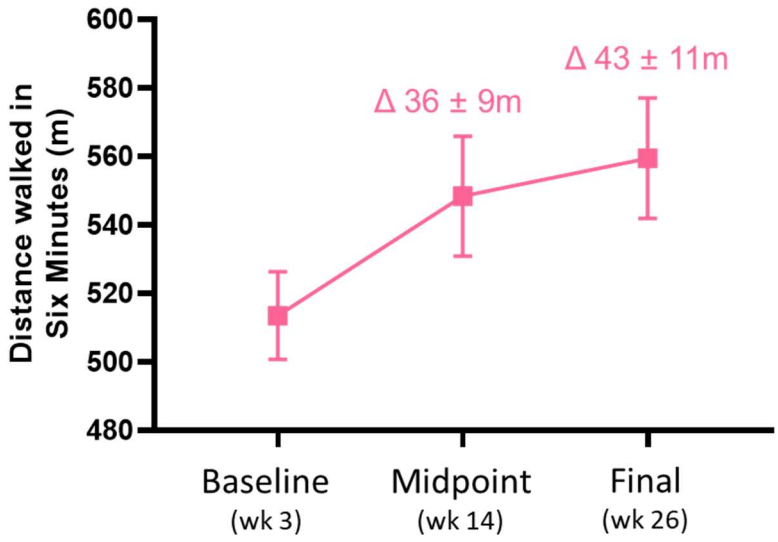


Figure 4.8: Six-Minute Walk Test Distance Measured Over 24 Weeks

Table 4.5: Changes in Six-Minute Walk Test Measures

	Baseline Study Visit (wk 3)	**Midpoint Study Visit** (wk 14)			**Final Study Visit** (wk 26)		
	Mean ± SD						
			Δ (from baseline)	**p**		**Δ** (from baseline)	**p**
6MWT distance (m)	513 ± 60	548 ± 80	36.2 ± 9.1	**0.0021**	559 ± 80	43.4 ± 10.9	**0.0021**
6MWT distance (% Predicted)	94 ± 15	101 ± 19	6.8 ± 1.8	**0.0034**	103 ± 18	8.0 ± 2.1	**0.0039**
HR_{rest} (bpm)	83 ± 10	86 ± 11	1.3 ± 2.7	0.8636	87 ± 10	5.6 ± 2.5	0.0963
SpO_{2rest} (%)	97 ± 2	97 ± 3	-0.8 ± 0.7	0.5626	97 ± 1	-0.1 ± 0.5	0.9927
RPE_{rest} (0-10)	0.4 ± 1.1	0.1 ± 0.3	0.4 ± 0.2	0.2410	0.3 ± 0.8	-0.1 ± 0.2	0.7042
RPD_{rest} (0-10)	0.3 ± 0.6	0.4 ± 0.5	-0.02 ± 0.1	0.9535	0.4 ± 0.6	-0.1 ± 0.2	0.7238
HR_{peak} (bpm)	116 ± 19	119 ± 21	4.2 ± 4.8	0.6647	119 ± 23	4.9 ± 4.8	0.5746
SpO_{2peak} (%)	93 ± 5	92 ± 5	-0.1 ± 1.2	0.9951	93 ± 4	-0.4 ± 0.9	0.8755
RPE_{peak} (0-10)	3.6 ± 2.0	4.3 ± 1.7	0.6 ± 0.4	0.2436	4.1 ± 2.3	0.7 ± 0.5	0.3353
RPD_{peak} (0-10)	2.8 ± 1.9	3.5 ± 2.2	0.6 ± 0.4	0.1958	3.0 ± 1.4	0.4 ± 0.3	0.3353

Aerobic Exercise Session Measures

At enrollment, no participants had recently completed a maximal CPET within the past 3 months; thus, all participants utilized $HR_{peak6MWT}$ on baseline and midpoint 6MWT as a personalized estimate of a target HR threshold for moderate intensity or greater during aerobic exercise sessions. During recorded exercise sessions, participants tended to stay at or near their target HR obtained from 6MWT (Figure 4.9a; Table 4.6), as measured by average HR. Figure 4.9b shows average METs/min achieved during 6MWT and average METs/min during exercise sessions, as measured by Garmin; participants consistently exercised at or above a moderate intensity (3.0 METs), averaging between 3 and 4.5 METs/min during most sessions. Similar to the trend in physical activity goal achievement, participants ramped up average exercise session duration over the first few weeks of the intervention, with a 54.6% increase in exercise session minutes from week 3 to week 14 (Table 4.6).

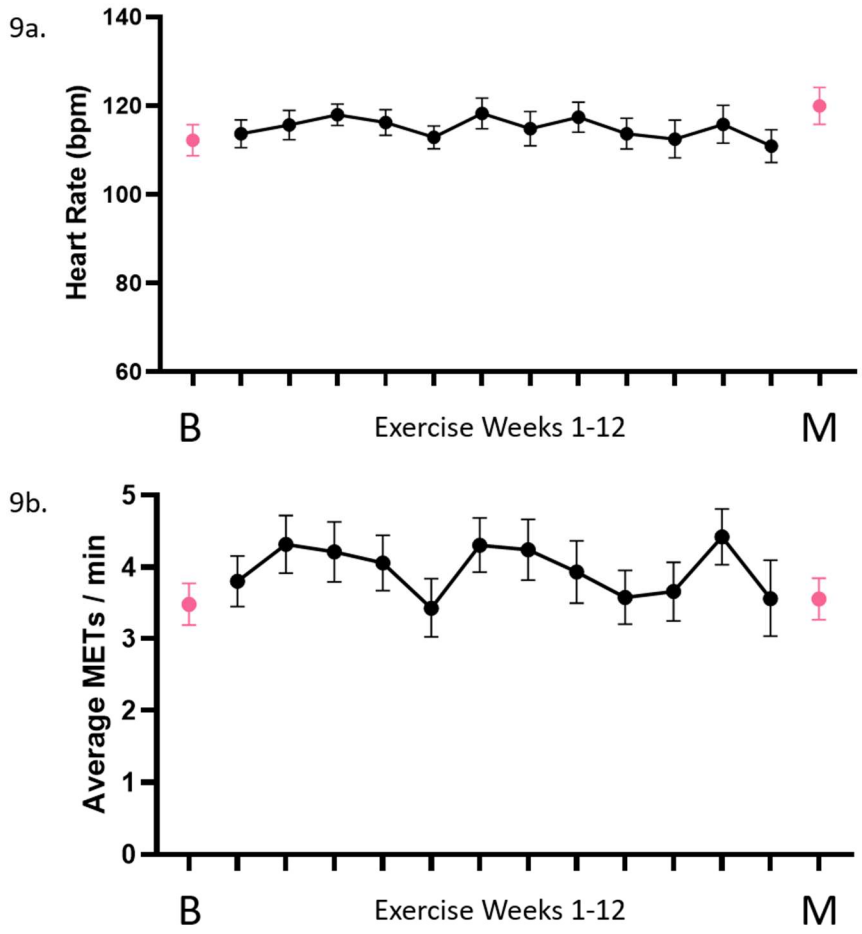


Figure 4.9: Measures of Exercise Intensity During Recorded Exercise Sessions Over the First 12 Weeks. Average heart rate (HR) (Figure 4.9a) and Average metabolic equivalents (METs) / minute (Figure 4.9b), as measured by the Garmin wearable device, are shown each week of the first 12 weeks of exercise (black color), in relationship to peak HR during baseline (B) and midpoint (M) six-minute walk tests (6MWT) (pink color).

Table 4.6: Changes in Aerobic Exercise Session Measures Over the First 12 Weeks

	Intervention Period 1 (wk 3-14)		
	Mean ± SD		
		Δ (wk 14 - wk 3)	**p**
Total Exercise Time per week (min)	262 ± 175	82.9 ± 432	0.4552
Avg (Mean) Exercise Session Duration (mins)	62.8 ± 43.8	34.3 ± 76.3	0.0929
Total METs*min / Exercise Session (avg)	252 ± 206	36.2 ± 150	0.4200
Avg (Mean) METs / Exercise Session ($ml*kg^{-1}*min^{-1}$)	3.75 ± 1.2	-0.51 ± 1.7	0.3334
Avg (Mean) HR / Exercise Session (bpm)	113 ± 11.5	-5.8 ± 9.9	**0.0348**
Max HR during Exercise Session (bpm)	136 ± 13.7	-4.7 ± 12	0.1400

Quality of Life, Fatigue, and Dyspnea

Health-related quality of life (HRQoL) indicators improved after 12 weeks of exercise training, as measured by the ATAQ-LAM Total score; training was especially impactful on exertional dyspnea (Figure 4.10, Table 4.7). Fatigue also improved with training, as assessed by the MFI-20, especially the domains related to physical fatigue and reduced activity (Figure 4.10, Table 4.7). Total HRQoL scores continued to improve during the second 12 weeks, but some of the benefits of training on fatigue seen at midpoint were reduced at final (Table 4.7). Dyspnea in daily life, as measured by the mMRC Dyspnea scale, significantly improved at midpoint, and continued to improve until the final study visit (Figure 4.10, Table 4.7). Participants with lower baseline dyspnea scores demonstrated higher adherence to the aerobic exercise program in the first 12 weeks than those who started with higher dyspnea scores (mMRC Dyspnea: $r=-0.422$, $p=0.040$), but no such correlation was observed among participants with more severe LAM disease (as measured by % predicted FEV1).

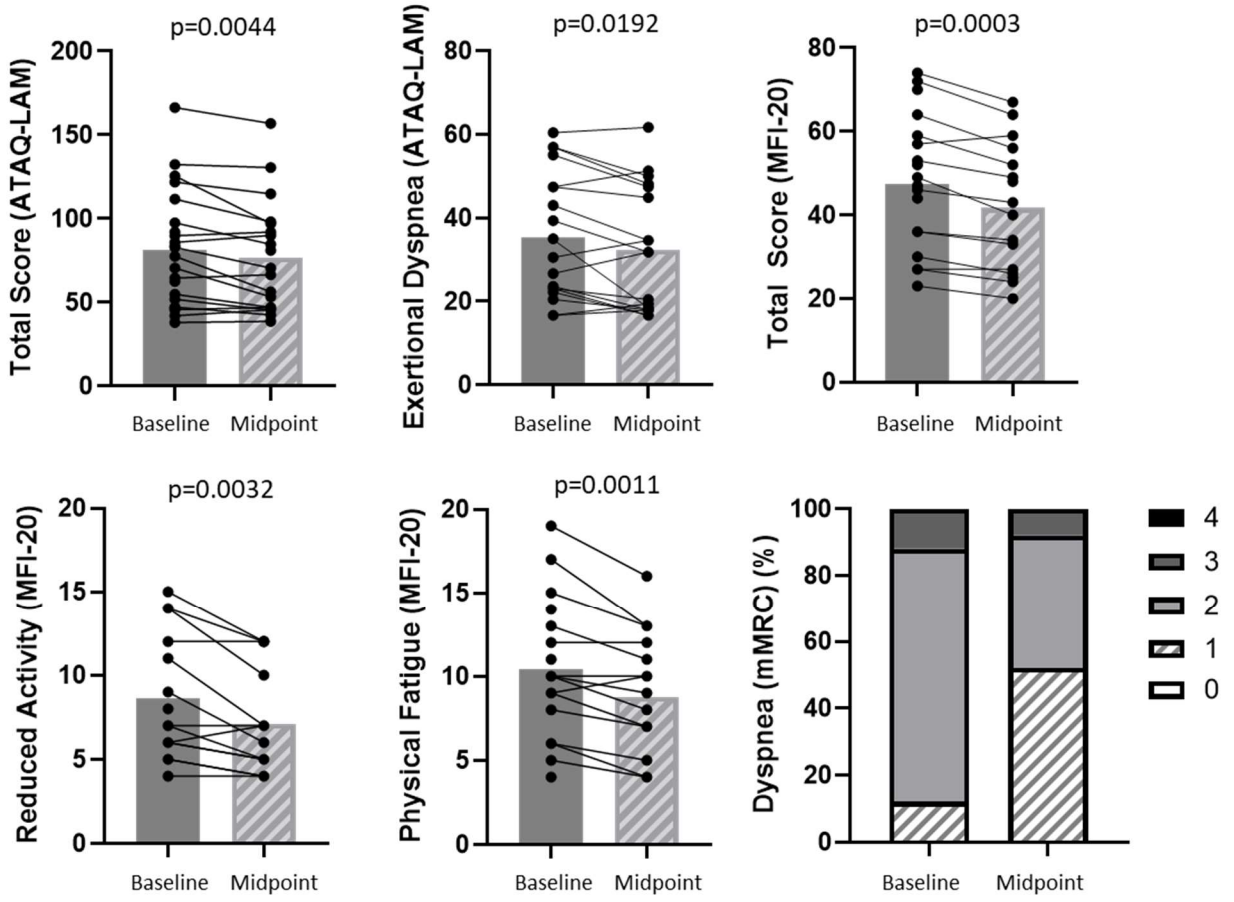


Figure 4.10: Changes in Quality of Life, Fatigue and Dyspnea Over the First 12 Weeks. ATAQ-LAM = A Tool to Assess Quality of Life in Lymphangioleiomyomatosis, MFI-20 = Multidimensional Fatigue Inventory (20-item), mMRC = modified Medical Research Council Dyspnea in daily life scale: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; 4, too breathless to leave the house, or breathless when dressing or undressing.

Table 4.7: Quality of Life, Fatigue, and Dyspnea Measured Over 24 Weeks

	Subscales	**Baseline** (wk 3)	**Midpoint** (wk 14)			**Final** (wk 26)		
				Δ (from baseline)	**p**		**Δ** (from baseline)	**p**
		Mean ± SD						
ATAQ-LAM	Total Score	81.5 ± 34.0	76.8 ± 33.0	-7.1 ± 9.2	**0.0044**	70.8 ± 28.4	-8.7 ± 17.9	**0.0100**
-Raw score ranges possible: Exertional Dyspnea: 13-78 Cough: 6-36 Energy / Fatigue: 5-30 Emotional: 5-30 Total: 32-192 -Higher = ↑ impairment	Exertional Dyspnea	35.3 ± 14.3	32.5 ± 14.5	-3.5 ± 5.7	**0.0192**	30.2 ± 13.9	-3.3 ± 9.4	0.1013
	Cough	25.5 ± 11.4	23.5 ± 12.5	-1.1 ± 5.6	0.7012	22.2 ± 13.2	-4.9 ± 7.0	0.0531
	Energy / Fatigue	41.5 ± 20.2	39.0 ± 16.1	-5.0 ± 12.7	0.1130	38.3 ± 16.1	-2.0 ± 13.0	0.0960
	Emotional Well-being	41.5 ± 22.9	41.2 ± 23.6	-3.3 ± 9.9	0.1719	35.0 ± 23.6	-7.1 ± 17.2	0.1043
MFI-20	Total Score	47.5 ± 15.8	41.7 ± 15.3	-4.2 ± 3.2	**0.0003**	49.7 ± 13.4	1.1 ± 12.7	0.9991
-Subscale ranges 4-20 -Higher = ↑ impairment	General	11.0 ± 3.8	9.9 ± 4.4	-0.5 ± 1.6	0.2509	11.3 ± 2.5	0.0 ± 2.6	0.9999
	Physical Fatigue	10.4 ± 3.9	8.8 ± 3.6	-1.4 ± 1.3	**0.0011**	10.1 ± 3.9	-0.9 ± 3.5	0.3326
	Reduced Activity	8.6 ± 3.5	7.1 ± 3.1	-1.5 ± 1.6	**0.0032**	9.4 ± 3.8	0.4 ± 3.6	0.9518
	Reduced Motivation	8.0 ± 3.6	7.3 ± 3.3	-0.3 ± 1.6	0.7832	9.0 ± 3.3	0.8 ± 3.0	0.6604
	Mental Fatigue	9.6 ± 4.1	8.6 ± 3.4	-0.5 ± 1.7	0.5299	10.0 ± 3.2	-0.1 ± 2.5	0.9999
Dyspnea (mMRC) -Ranges 0-4 -Higher = ↑ impairment		1.9 ± 0.4	1.48 ± 0.5	-0.5 ± 0.5	**<0.0001**	1.6 ± 0.8	-0.7 ± 0.8	**0.0131**

Patient Acceptability and Satisfaction

Exit surveys indicated overall high patient acceptability and perception of feasibility of the LAM*Fit* digital fitness program (Figure 4.11). Generally, participants strongly agreed that they felt more aerobically fit, stronger, and had less fatigue after the exercise program. Participants with higher adherence in the first 12 weeks tended to report feeling more aerobically fit ($r=0.566$, $p=0.004$) and stronger ($r=0.566$, $p=0.004$) after the exercise intervention than participants with lower adherence. Participants with higher adherence were also more likely to agree with the statement that "LAM*Fit* increased my active self-management of my physical fitness status" than participants with lower adherence ($r=0.433$, $p=0.030$).

On average, participants were neutral regarding whether participation in the online LAM*Fit* community forum facilitated the exercise program. Participation in the online community engagement forum was frequent for some, and limited to none for others. Twenty one participants (84%) chose to join the private Facebook group, 20 participants (80%) were active members on the group page, but only 18 participants (72%) chose to post anything in response to a discussion post. During the study, the average (mean) number of active daily users was 9. There were no age- or adherence-related differences among the cohort in perceptions of the feasibility of posting on the online LAM*Fit* community forum at least 1x/week, or whether participation in the optional LAMFit community forum facilitated the exercise program. One participant expressed on exit survey that "Sharing my experience on social media does not feel emotionally safe for me and, since I am not active on Facebook, I did not participate [in that]. It was my choice not to engage there." Another person that did participate in the LAM*Fit* community forum shared that "The online forum [was] great and I liked seeing the group data,

but more individualized information would be helpful to discuss obstacles patients are having with meeting their goals."

Overall program satisfaction was very high. 100% of participants agreed or strongly agreed that they were likely to continue exercising after the study. Most participants agreed that LAM*Fit* was a feasible alternative to center-based pulmonary rehabilitation when a PR center is not easily accessible. One participant shared on exit survey:

> "I loved being in the study! It kept me on a schedule and accountable which helped me stick to it (even on days I was tired or did not feel like exercising). My quality of life improved and my fatigue decreased. Everyone with LAM should be in this program!"

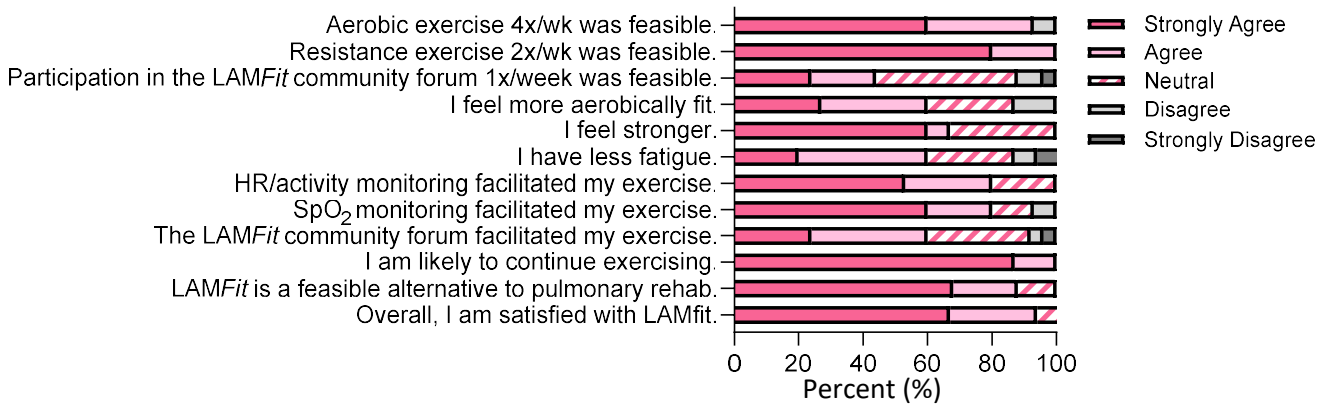


Figure 4.11: High Patient Satisfaction and Acceptability of the LAM*Fit* Program. Overall, participants agreed that it was feasible to perform the prescribed frequency of aerobic exercise and resistance training within LAM*Fit*. Most participants reported feeling more aerobically fit and stronger, although less reported feeling less fatigue after the exercise intervention. Interestingly, participation in the LAM*Fit* community forum did not appear to facilitate exercise as much as other aspects of the program. Satisfaction with the program was very high, and all participants agreed or strongly agreed that they were likely to continue exercising after the study.

4.6 DISCUSSION

The results of the LAM*Fit* pilot study indicate that a fully-remote approach to delivering LAM*Fit* is safe, feasible, and acceptable to individuals with LAM that are medically appropriate to participate. Aerobic adherence and program completion rates were high for both the first and second 12-week exercise programs, with only 3 discontinuations for health complications unrelated to the exercise intervention. Completion of digital endpoints was high, including during the run-in period, baseline, midpoint, and final remote study visits, and all 24 weeks of exercise training. Across the entire program, average weekly group goal achievement was nearly 80% for ≥30 minutes of daily combined MVPA. Participants were neutral regarding whether participation in the online LAM*Fit* community forum facilitated the exercise program, but some participants reported feeling more motivated by the addition of group accountability features and posting of deidentified data visualizations on the online LAM*Fit* community forum. At the end of the study, participants expressed a high level of satisfaction and acceptability of the LAM*Fit* digital fitness program.

Improvements after 12 weeks in exercise capacity, fatigue, HRQoL, and dyspnea were equivalent to or better than those previously reported after supervised pulmonary rehabilitation in LAM[1,2], as well as those reported in our recent 'Exercise & Fatigue in LAM' study.[10] Distance achieved in 6MWT increased by an average of 7.1% (36.2 ± 9.1m) from baseline to midpoint (12 weeks), exceeding published minimal clinically important differences (MCID) of 30[38] to 35m[39] in COPD. No MCID for 6MWT has been published in LAM. Average daily steps after 12 weeks of training increased by 30% compared to the run-in period, exceeding the increase of 9.8% achieved after 12 weeks of training in the 'Exercise & Fatigue in LAM' study,[10] and supporting adequate statistical power of the pilot study.

Given the LAM*Fit* cohort's similar age demographics and disease status as the 'Exercise & Fatigue in LAM' cohort,[10] comparable changes in exercise capacity, physical activity, quality of life, and fatigue after 12 weeks of participation support the fidelity of the evidence-based exercise intervention that was offered within LAM*Fit*. Training effects were similar at 12 weeks, even after implementing multiple adaptations to become a fully-remote program with no in-person study visits and collection of digital endpoints only. Adapting to become a fully-remote program allowed for higher participant enrollment (n=25) than the 'Exercise & Fatigue in LAM' study (n=15)[10], low to no participant travel burden or cost, and a more diverse representation of patients with LAM from multiple geographic regions of the United States.

Our patient-centered approach to the design, testing, and implementation of the LAM*Fit* digital technology platform likely helped to enhance participant usability and acceptance of technology features. We sought to minimize the number of smartphone apps, complicated setup and troubleshooting steps, and devices required for remote monitoring wherever possible. Unfortunately, we could not identify any one existing smartphone app or digital health platform that could support all of our remote monitoring needs. Instead, we co-designed and rapidly iterated certain technology features to support LAM*Fit's* unique needs, in close collaboration with platform developers and individuals with LAM. Our co-design methods, no doubt, optimized the accuracy of remote testing data collected, as well as the resulting platform usability. One key innovation within LAM*Fit* was the custom development of a remote 6MWT for self-administration in the home setting, digital endpoint collection, and aerobic exercise prescription. While we did not perform a formal validation study of the remote 6MWT prior to use, the test instructions adhered to ATS guidelines[23] and an evidence-informed tape measure method[24] was used to optimize the accuracy of self-reporting. The addition of an orientation video for the remote 6MWT in the instructional materials may help reduce the number of

cancelled and repeated test attempts and improve the standardization of the testing protocol. Further validation testing is needed, and planned for future studies, to permit comparison of distance achieved in remote 6MWT to distance achieved in standardized 6MWT in clinic.

LAM*Fit* did not utilize weekly check-ins and active coaching like the 'Exercise & Fatigue in LAM' study[10] did, but instead employed in-app personal goal achievement data visualizations, automatic rules for nudge reminder notifications, and group accountability features. The simultaneous application of multiple technology-enabled nudges within the LAM*Fit* digital platform limited our ability to study the effectiveness of any one nudge in particular. Nevertheless, the comprehensive benefit of the nudges appears to be comparable to the accountability benefits that were provided by active weekly check-ins with a coach in the prior 'Exercise & Fatigue in LAM' study.[10] Other studies have shown that wearing a consumer-grade fitness tracker with preprogrammed automatic nudges can on its own increase physical activity, reduce sedentary behaviors, and provide behavioral accountability.[40–43] Our results suggest that the combination of custom, program-specific nudges with a consumer-grade fitness tracker may reduce the amount of active personnel support needed to operate a digital fitness program like LAM*Fit*. A growing body of literature supports the use of behavioral nudges in health care[41,44] and recommends that nudges be thoughtfully designed, personalized with rules based on patient needs and preferences, and seek to minimize nudge / notification fatigue.[45,46]

Required pre-enrollment steps, including outpatient visits for medical screening, completion of in-person clinical exercise testing (e.g., 6MWT or CPET), and provider attestation of medical appropriateness, were demonstrated to be feasible for referring providers and program participants to complete. The previously published, expert consensus LAM*Fit* exercise preparticipation screening tool[18] was successfully utilized by community-based providers across the United States to prescreen all LAM*Fit* pilot study participants. One interested patient with

LAM and cardiac arrhythmia was screened out by a medical provider due to higher risk of cardiovascular event during exercise; instead of enrollment in LAM*Fit,* the preparticipation screening algorithm suggested patient referral to supervised outpatient rehabilitation with real-time cardiac monitoring. The absence of serious or nonserious study-related adverse events during the pilot study supports the ongoing use of the exercise preparticipation screening tool prior to LAM*Fit* enrollment. It also motivates efforts to further disseminate the screening tool and instructions for provider use to pulmonologists that regularly see patients with LAM, especially those that practice at designated LAM Centers of Excellence.

Instead of transitioning LAM*Fit* participants to a maintenance program after 12 weeks like many center-based PR programs do, at midpoint, we chose to recommend completion of another 12 weeks of exercise training with the same parameters. The midpoint 6MWT helped participants update their personalized target HR threshold to guide aerobic exercise during weeks 15-26. Our results show that the addition of a second 12-week exercise program helped participants to minimize the loss of health benefits, which is often seen after completion of center-based PR.[3] In fact, distance achieved in 6MWT continued to increase after the second 12 weeks compared to baseline, as did HRQoL (ATAQ-LAM total score) and control of dyspnea in daily life (mMRC dyspnea). On the other hand, improvements in physical fatigue that were reported at midpoint (MFI-20 total score, physical fatigue, reduced activity subscales) nearly reverted to baseline during the second 12 weeks. Fatigue is a poorly understood phenomenon in LAM[34,47], but fatigue research in other chronic diseases suggests that the experience of fatigue symptoms stems from both physical and psychological factors[48–50], as well as activity avoidance behaviors[51]. It may be that in the second 12 weeks, participants had similar expectations for the magnitude of improvement in fatigue symptoms as was experienced in the first 12 weeks. But, because their exercise capacity and physical activity behaviors had drastically changed, their

perceptions of fatigue had also changed. Perceptions of physical fatigue may be relative to what one expects fatigue to be based on their prior experiences, current physical activity status, and expectations.

In addition to digital endpoint and survey completion, we also tracked several key process metrics and participant support needs (Table 4.4), which can be used to estimate the number of person-hours required per user to operationally support the LAM*Fit* program moving forward. Within digital health interventions, it can be tempting to maximize the number of low-cost, automatic technology features and minimize the number of higher-cost, active support tasks required. However, excessive use of automated technology features may lead to less participant accountability to the health care team, a reduced ability of providers to deliver patient-centered care, and undetected events during exercise. To preserve accountability to the health care team and minimize risks, a delicate balance must be struck between the use of passive technology features and active management.

LAM*Fit* is the first digital fitness program of its kind in chronic respiratory disease. The program fully embraces the digital transformation of health care that was accelerated by the COVID-19 pandemic and is now increasingly accepted by major professional associations, health systems, and payors as a lasting disruption to traditional health care delivery models.[5,16,19,52,53] LAM*Fit* responsibly seeks to balance risks of event during unsupervised exercise with the proven benefits of exercise training in LAM. The utilization of a digital health platform for program delivery opens up opportunities to expand access nationally and internationally to more individuals with LAM.

Next Steps

Now that the LAM*Fit* digital fitness program has been designed and pilot tested, scaling access can be accomplished with low cost and minimal barriers. In our next phase, we plan to adapt the LAM*Fit* program website, recruitment materials, instructional handouts, and provider prescreening logistics to be self-sustaining and facilitate handoff of operations to a designated LAM*Fit* program manager. Active support tasks are likely to include communicating with interested participants and connecting them to educational resources, sending LAM*Fit* prescreening materials to providers, ensuring provider attestation of medical appropriateness, participant enrollment, technology troubleshooting, and digital endpoint database maintenance. We will then confirm adapted program feasibility and intervention fidelity over 12 months in a larger cohort of individuals with LAM. The final version of LAM*Fit* will be optimized to sustain indefinitely under community-based management by The LAM Foundation, independent of an academic institution.

Limitations

This study has some limitations. First, primary outcomes were digital platform feasibility and safety-focused, not effectiveness-related. We did examine a few secondary effectiveness outcomes, but without a control group. Consequently, effect sizes could not be measured by comparison to a meaningful control. As discussed earlier, multiple nudges and behavioral change strategies were implemented together; thus, we cannot attribute effectiveness outcomes to any one specific change intervention. We also did not perform a formal assessment of exercise intervention fidelity, as it was beyond the scope of this initial pilot study. Future studies of LAM*Fit* should consider evaluating intervention fidelity using the NIH Behaviour Change Consortium (BCC)'s Treatment Fidelity Framework, which has five domains for the design,

training, delivery, receipt, and enactment of an intervention and has been used to measure the fidelity of other physical activity promotion programs.[54,55]

Our patient-centered research and development approach led to a decision to change the user-facing smartphone app for fitness tracking from Fitrockr HUB to GarminConnect after the midpoint study visit. Participants immediately perceived the change of apps as positive, but data variables like total METs*minute / exercise session and average METs / minute were not congruent between the apps. Thus, we were unable to compare some physical activity metrics between the first and second 12 weeks of the study. In our analyses, we focused on physical activity metrics collected during the first 12 weeks in order to compare LAM*Fit* outcomes to the 12-week 'Exercise & Fatigue in LAM' study[10] and previous publications of traditional, center-based or inpatient PR programs in LAM.

The LAM*Fit* exercise preparticipation screening tool successfully identified one person with higher cardiovascular risk of event, but we did not follow up with them after referral to an outpatient rehabilitation program to learn whether exercising within a supervised setting did in fact reduce the occurrence rate of an adverse event. Other studies have shown that overly cautious preparticipation screening tools may overestimate the true risks of events[56–58] and unnecessarily reduce patient access to exercise training. In future studies of LAM*Fit*, efforts should be made to follow up with patients who are deemed medically inappropriate to participate, track whether or not they subsequently attend an outpatient rehabilitation program, and compare safety and effectiveness outcomes of center-based PR in LAM to those of LAM*Fit*. As more individuals with LAM gain access to and participate in LAM*Fit*, we will also be able to catalogue and track longitudinally provider decisions about risk stratification and actual occurrence rates of events during exercise, which will help experts to refine future practice guidelines for exercise preparticipation screening in LAM.

The sample size for the pilot study was low and restricted to individuals with LAM living in the United States. Recruitment was primarily done through online patient webinar, interest survey, word of mouth, and advertisements facilitated by The LAM Foundation, resulting in a convenience sample of individuals with LAM that were already connected to the patient advocacy group. We did attempt to increase the representativeness of our cohort by using blocked, randomized sampling from an interest pool and were able to achieve wider racial/ethnic and geographic representation than in the 'Exercise & Fatigue in LAM' study.[10] These study results are still limited in their generalizability beyond patients with mild to moderate LAM disease severity living in the US that are technology literate, have a relatively high level of education, report a household income above the federal poverty level[59], and are willing and able to participate in a remote, unsupervised exercise program. In future efforts to scale LAM*Fit*, we will seek to recruit more broadly, facilitate equitable access for individuals with LAM from all backgrounds, and investigate opportunities to adapt and implement the program internationally.

4.7 INTERPRETATION

The pilot study of LAM*Fit* demonstrated that a fully-remote, digital technology-enabled approach to delivering an exercise program is feasible and safe in LAM. Study results support our future plans to scale access to the LAM*Fit* program nationally and internationally, to more individuals with LAM that are medically appropriate to participate.

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4.9 Supplemental Material

Physician Attestation of Exercise Preparticipation Screening and LAMFit Eligibility

LAM*Fit* Study Description: At least twenty-five patients with LAM will enroll in a 6-month pilot study of **LAM*Fit*,** a LAM-specific, home-based, asynchronously monitored physical activity program that incorporates daily activity goal setting, reminder messaging, and LAM-specific social connection.

Investigators: Mary Beth Brown, PT, PhD (**mbbrown1@uw.edu**) and Claire E. Child, DPT, MPH (**cechild@uw.edu**)

Exercise Preparticipation Screening

Patient's Full Name: _____

Date of Birth (DOB): _____

Please complete the following form to attest that you have completed the **LAMFit Exercise Preparticipation Screening Tool** for the above patient.

Check the box if the statement is TRUE:

☐ The patient has been screened using the LAM*Fit* Exercise Preparticipation Screening Tool.

☐ The patient was demonstrated to be medically stable in an in-person clinical exercise test [e.g., six-minute walk test (6MWT) or cardiopulmonary exercise test (CPET)] within the last 3 months.

☐ The patient has a diagnosis of LAM, as confirmed clinically by biopsy or high-resolution CT scan of the chest.

☐ The patient has adequate knowledge of the level of supplemental oxygen they should use during exercise, if any, and how to read their pulse oximeter for pacing and self-monitoring.

Inclusion/Exclusion Criteria

I attest that the patient meets ALL of the inclusion criteria below.
☐ Yes ☐ No

LAMFit Inclusion Criteria:

Inclusion Criteria

1) Diagnosis of LAM (confirmed via biopsy or high-resolution CT scan of the chest)

2) Age ≥18 yrs at enrollment

3) In stable medical condition

4) Able to titrate supplemental oxygen and/or exertional intensity to maintain appropriate oxygen saturation levels

I attest that the patient meets NONE of the study exclusion criteria below.

☐ Yes ☐ No

LAM*Fit* Exclusion Criteria:

Exclusion Criteria

1) Unstable medical condition

2) Musculoskeletal or other conditions which would limit exercise participation

3) Non-compliance with medical therapies

4) High risk for cardiovascular event (as defined by the 2012 AACVPR Stratification Algorithm for Risk of Cardiovascular Event)

5) Severe resting pulmonary hypertension

6) Pneumothorax in the last 4 weeks

7) Prior lung transplantation

8) Known current pregnancy

In my professional judgment, the patient is medically appropriate to enroll and participate in LAM*Fit*.

☐ Yes ☐ No

Physician Name:

Physician Signature:

Clinic Name and Location:

Email:

Phone Number:



Welcome to LAM*Fit*!

A Digital Fitness Program for LAM

LAM*Fit* Program Guide

Components of the Monitoring Kit

1. Garmin Vívosmart 5 Fitness Tracker
    - For use during the entire LAM*Fit* program
    - Set up using the Fitrockr Hub app

2. MIR Spirobank Smart Spirometer
    - For use during home spirometry at baseline, midpoint and final timepoints
    - Set up and use within the patientMpower app

3. Nonin BLE 3230 Pulse Oximeter
    - For use during six-minute walk tests (6MWT) at baseline, midpoint, and final timepoints.
    - For use during exercise session monitoring
    - Set up and use within the patientMpower app

4. Water Bottle

5. Small Cones
    - For the six-minute walk test (6MWT) course at baseline, midpoint, and final timepoints.

6. *KSEIBI* 20 Meter Tape Measure
    - For the six-minute walk test (6MWT) course at baseline, midpoint, and final timepoints.

7. Hand Tally Counter
    - For use during six-minute walk tests (6MWT) at baseline, midpoint, and final timepoints.

8. Yellow Padded Mailing Envelope
    - For return shipment of the Nonin Pulse Oximeter at the end of the LAM*Fit* pilot study

Digital Platform Setup Instructions

LAM*Fit* is a home-based, remotely monitored exercise program that incorporates daily activity goal setting, reminder messaging, and social connection.

Overview

The LAM*Fit* program uses remote monitoring devices and smartphone applications. Your remote monitoring kit includes 1) a Garmin vívosmart 5 device, 2) a Nonin 3230 fingertip pulse oximeter, and 3) an MIR Spirobank Smart home spirometer. These devices will be paired with your smartphone to collect data for the LAM*Fit* study. This handout will help you set up the remote monitoring device and platform.

About the Garmin Device

You will be equipped with a Garmin vívosmart 5 device that is going to automatically record your health and activity data. To support this process, please follow these rules:

– **Wear the device day and night** (device is waterproof, this means that you can also wear it during shower or swimming but not for diving).

– **Charge the device regularly** (at least every 4-5 days).

– **Sync the device daily** (see section below on sync process).

– **Do not connect the Garmin device to any other app** or Internet service other than instructed by the study protocol. Particularly, do not connect the Garmin device to “Garmin Connect” unless specifically instructepd to do so.

– **Follow instructions received through push notifications**.

– **Immediately complete questionnaires when received**.

Set Up Garmin Device

Your Garmin device needs to be paired with your smartphone to allow data synchronization.

Pair with the Fitrockr Hub smartphone app

To pair the Garmin device with the "Fitrockr Hub" app, follow these steps:

(1) Download the "Fitrockr Hub – Garmin Sync" app from the Google Play or iOS Apple store.
(2) Approve all access requests by the app (such as camera access, etc.).
(3) Scan the QR code that you received from LAM*Fit* study personnel.
(4) Follow pairing instructions in the app to connect the Garmin device.

If pairing fails, try again. If the issue cannot be resolved, contact the study team at **lamfit-study@uw.edu**.

Sync Garmin Device

Your Garmin device will record all your activity and health information and store it on its internal storage. To provide researchers access to the data, you need to synchronize the Garmin device daily. It is no problem if you forget to synchronize it on a day. Just synchronize it on the next day.

Participant sync via Fitrockr Hub

To synchronize the Garmin device, you need to open the Fitrockr Hub app on your smartphone. The synchronization will start automatically. Wait until the synchronization has finished. Then minimize or close the app.

If the sync fails, try again. If the issue cannot be resolved, contact the study team at **lamfit-study@uw.edu**.

Notifications & Questionnaires

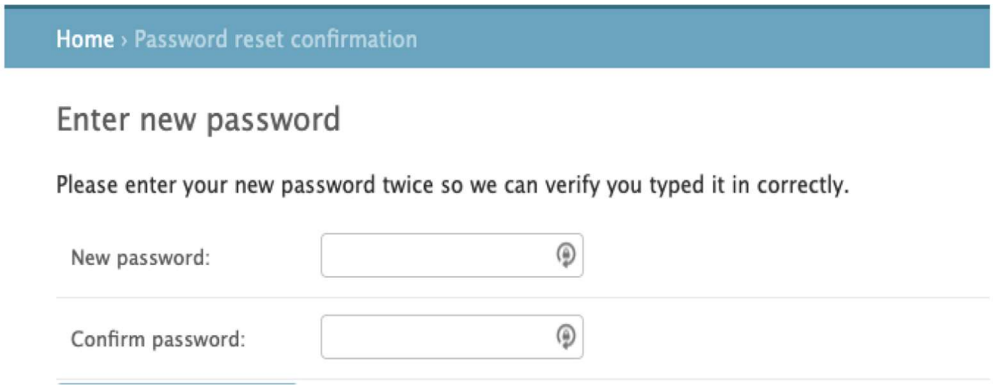
During the data collection period, you will receive push notifications and questionnaires in the Fitrockr Hub app. Notifications must be allowed for the Fitrockr Hub app. Please follow instructions given through notifications and immediately complete any questionnaires that you receive.

About the Nonin Pulse Oximeter and MIR Spirosmart Home Spirometer

You will be equipped with a Nonin 3230 BLE pulse oximeter and an MIR Spirosmart home spirometer that will automatically record your health data within the patientMpower app.

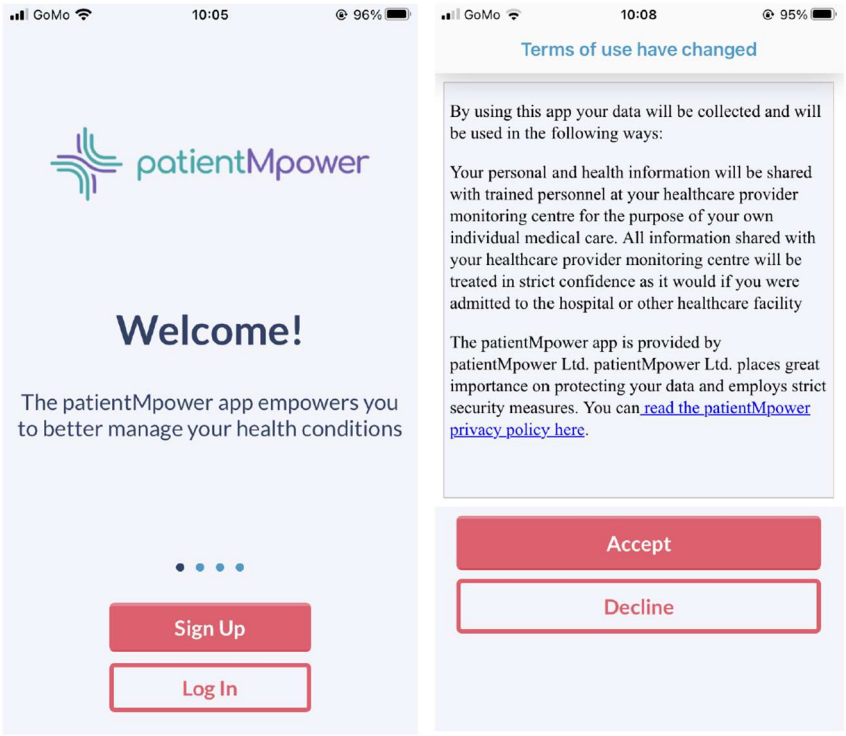
Download the patientMpower app

(1) Open your enrollment email from info@patientmpower.com
(2) Click on the first link to set your password.
(3) The password should have the following:
    a. At least 8 characters in length
    b. Contain one uppercase letter
    c. Contain one lowercase letter
    d. Contain one number



(4) Return to the email and select the second link to download the application.
(5) Download the app from the Google Play or iOS Apple Stor on a smartphone device. Make sure the “patientMpower” app is selected.
(6) ***Log in*** to the app using your email and the new password you have created.

(7) Read the terms of use policy. If you agree, click Accept. If you do not agree, click Decline and contact the study team at **lamfit-study@uw.edu**.



Set Up Nonin and MIR Spirosmart Devices

Nonin Pulse Oximeter:

(1) Open the box and remove the device and the 2 AAA batteries
(2) Slide down to open the pulse oximeter battery door
(3) Insert both batteries
(4) Slide the battery door back on
(5) Place device on your finger to turn on



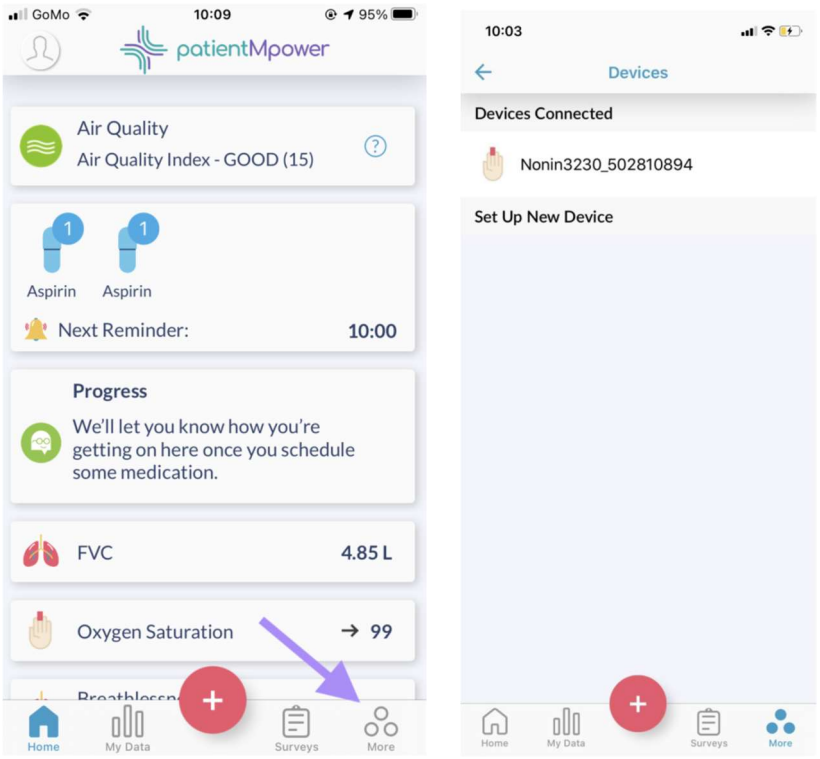
MIR Spirosmart Home Spirometer:

(1) Open the box and remove the device and the 2 AAA batteries
(2) Slide down to open the spirometer battery door
(3) Insert both batteries
(4) Slide the battery door back on



Pairing Bluetooth devices

(1) Before pairing, turn on Bluetooth for your smartphone.
(2) Select “More” in the navigation bar at the bottom of the screen on the opening page of the app.



(3) Select “Bluetooth Devices”
(4) You should see the device appear, e.g. Nonin3230_502810894
(5) Click this and press pair in the pop-up window
(6) Once paired, you will see a success message

Bluetooth Troubleshooting

(1) Make sure that Bluetooth is turned on for your smartphone.
(2) Remove the batteries from the monitoring device and place them back in. Try to re-pair the device via Bluetooth.
(3) Ensure the device is not paired to any other smartphones or tablets in the patient’s surroundings. If it has connected with another device, it will need to be unpaired before it can connect to your smartphone and the patientMpower app.
(4) If the Bluetooth pairing fails, try again. If the issue cannot be resolved, contact the study team at **lamfit-study@uw.edu**.

Notifications & Questionnaires

During the data collection period, you will receive push notifications and questionnaires in the patientMpower app. Notifications must be allowed for the patientMpower app. Please follow instructions given through notifications and immediately complete any questionnaires that you receive.

Facebook LAM*Fit* Community Group

During the LAM*Fit* study, you are invited to participate in a private LAM*Fit* Community Group (hosted by Facebook) with other study participants that are also choosing to become more active. Participation in this group is optional, not required. The Group Forum will include weekly discussion topics consisting of semi-structured questions and scenarios proposed by individuals with LAM and members of the study team.

After study enrollment, you will receive an email invitation to enroll in the private LAM*Fit* Community Group on Facebook. You may also follow this link and request an invitation from the Group administrator(s).

https://www.facebook.com/groups/225105903887007/

Third Parties Involved

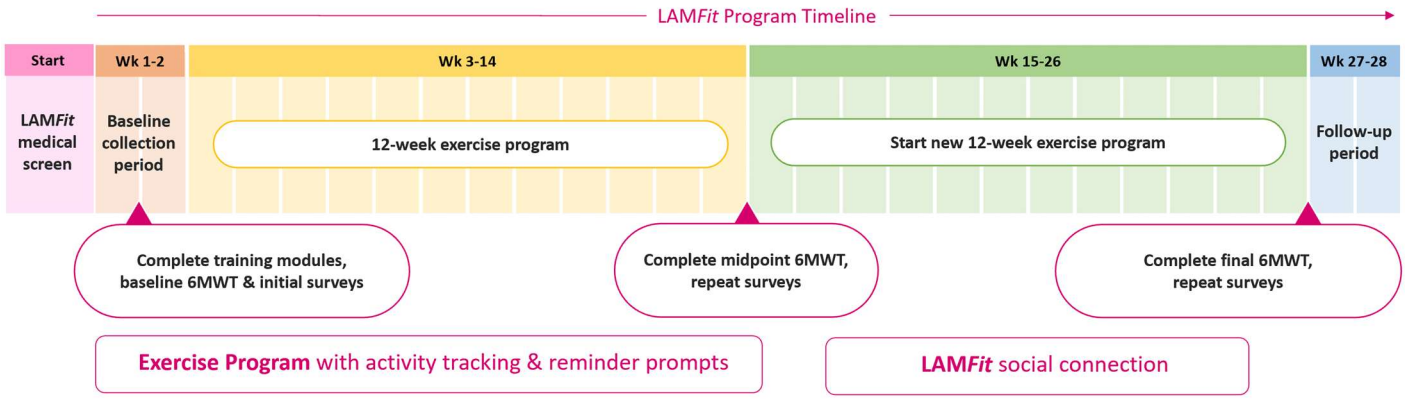
There are third parties involved in the research process. They will have access to parts of your data and have signed strict data processing agreements or independent controller-controller agreements.

During the data collection phase, Fitrockr Health Solutions (a Germany-based Software company) will obtain the Garmin research data and surveys administered via the Fitrockr Hub app for us. PatientMpower (an Ireland-based Software company) will obtain Nonin pulse oximetry, remote six-minute walk test, and MIR home spirometry research data and surveys administered via the patientMpower app for us. Facebook may also obtain information about you and your online activity. Please read all third party privacy policies prior to use of the digital platform.

Weekly Program Instructions

LAM*Fit* is a home-based, remotely monitored exercise program that incorporates daily activity goal setting, reminder messaging, and social connection.

LAM*Fit* Program Timeline



Funded by an Established Investigator Award from The LAM Foundation

Weeks 1-2

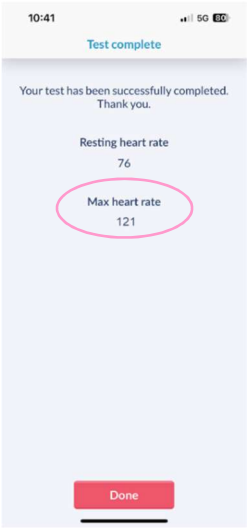
Complete the steps of the LAM*Fit* Digital Platform Setup.

Wear the Garmin device for 2 weeks for a baseline collection period. Do not change your routine daily amounts of physical activity during this time.

<u>Baseline Assessment</u>

Complete the following tasks in the patientMpower app:

- ☐ Baseline six-minute walk test (6MWT) on a 20-meter course
- ☐ Home spirometry
- ☐ Multidimensional Fatigue Inventory (MFI-20)
- ☐ A Tool to Assess Quality of Life in LAM (ATAQ-LAM)



Record the highest heart rate value (Max HR) shown on 6MWT.

Max HR on baseline 6MWT: _____

Weeks 3-14

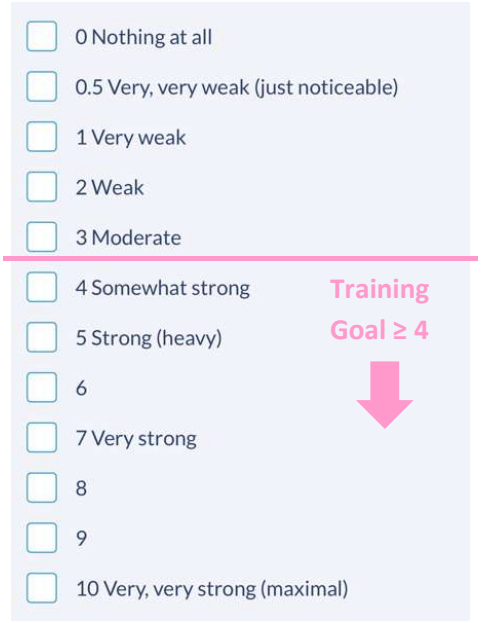
Goals of the first 12-week program:

- ☐ Intentional aerobic exercise training at least 4 times/week for 30 minutes/day or longer
- ☐ Achieve at least 30 minutes of moderate-to-vigorous physical activity (MVPA) on most days of the week
- ☐ Resistance exercise of major limb and core muscle groups at least 2 times/week
- ☐ Participate at least 1 time/week in the LAM*Fit* Community Engagement Forum *(optional)*

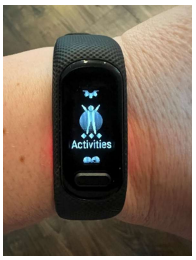
Use your own Max HR on 6MWT or ≥ 4 on the Rating of Perceived Exertion (RPE) scale as the goal training threshold.

HR Training Goal: _____
(Max HR on baseline 6MWT)

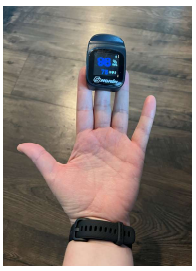
Rating of Perceived Exertion Scale



Record each exercise training session as an “Activity” on your Garmin watch. Sync your Garmin device with the Fitrockr app at least every 2 days. Recorded activities will be saved and synced with the Fitrockr app.



Monitor all exercise sessions using the Nonin 3230 fingertip pulse oximeter worn on your second or third finger. Record your pulse oximetry during an exercise session at least 1 time/week in the patientMpower app, but you are welcome to do it more often.



You will receive a notification to complete the following surveys 1 time/week in the Fitrockr app:

- ☐ Shortness of Breath survey
- ☐ Fatigue Severity survey

Week 14

<u>Midpoint Assessment</u>

Complete the following tasks in the patientMpower app:

- ☐ Midpoint six-minute walk test (6MWT)
- ☐ Home spirometry
- ☐ Multidimensional Fatigue Inventory (MFI-20)
- ☐ A Tool to Assess Quality of Life in LAM (ATAQ-LAM)

Record the highest heart rate value (Max HR) shown on 6MWT.

You will use <u>this HR</u> or ≥ 4 on the <u>Rating of Perceived Exertion (RPE) scale</u> as an updated goal training threshold during weeks 15-26.

Max HR on midpoint 6MWT: _____

Weeks 15-26

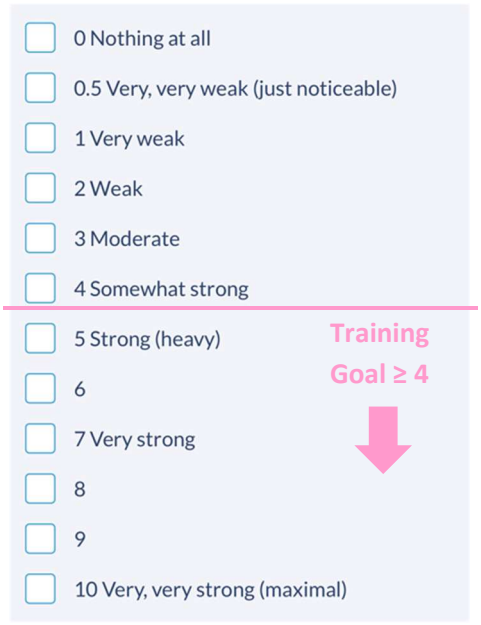
Goals of the second 12-week program:

- ☐ Intentional aerobic exercise training at least 4 times/week for 30 minutes/day or longer
- ☐ Resistance exercise of major limb and core muscle groups at least 2 times/week
- ☐ Achieve at least 30 minutes of moderate-to-vigorous physical activity (MVPA) on most days of the week
- ☐ Participate 1 time/week in the LAM*Fit* Community Engagement Forum *(optional)*

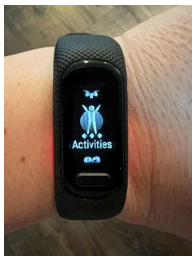
Use your own Max HR on 6MWT or ≥ 4 on the Rating of Perceived Exertion (RPE) scale as the goal training threshold for moderate intensity.

HR Training Goal: _____
(Max HR on midpoint 6MWT)

Rating of Perceived Exertion Scale



Record each exercise training session as an “Activity” on your Garmin watch. Sync your Garmin device with the Fitrockr app at least every 2 days. Recorded activities will be saved and synced with the Fitrockr app.



Monitor all exercise sessions using the Nonin 3230 fingertip pulse oximeter worn on your second or third finger. Record your pulse oximetry during an exercise session at least 1 time/week in the patientMpower app, but you are welcome to do it more often.



You will receive a notification to complete the following surveys 1 time/week in the Fitrockr app:

- ☐ Shortness of Breath survey
- ☐ Fatigue Severity survey

Weeks 27-28

<u>Final Assessment</u>

Complete the following tasks in the patientMpower app:

- ☐ Final six-minute walk test (6MWT)
- ☐ Home spirometry
- ☐ Multidimensional Fatigue Inventory (MFI-20)
- ☐ A Tool to Assess Quality of Life in LAM (ATAQ-LAM)

Record the highest heart rate value (Max HR) shown on 6MWT.

Use <u>this HR</u> or ≥ 4 on the <u>Rating of Perceived Exertion (RPE) scale</u> as a goal training threshold during Weeks 27 and 28, and beyond.

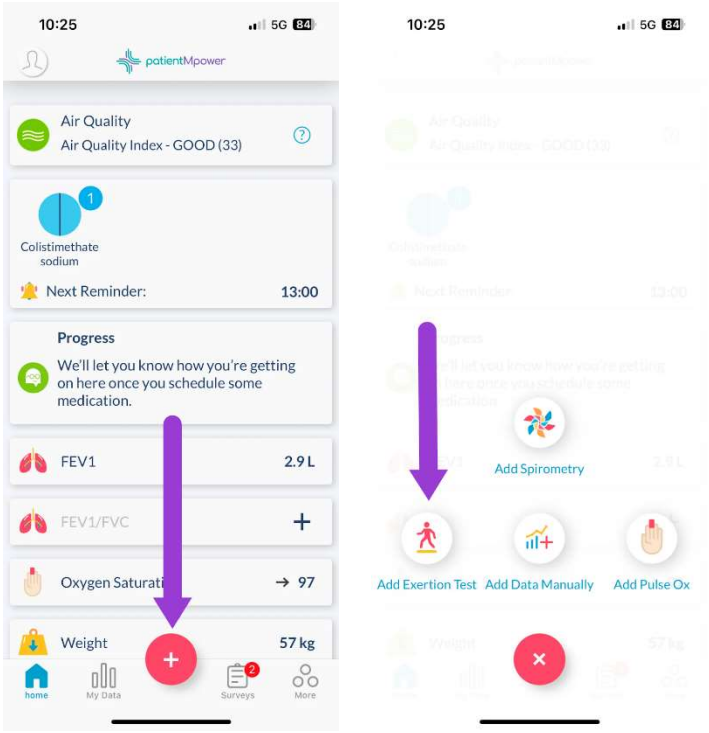
Max HR on final 6MWT: _____

Wear the Garmin device during Weeks 27 and 28. You are encouraged to keep up the same exercise routine and daily amounts of physical activity during this time.

Six-Minute Walk Test (6MWT) in the patientMpower app

Test Instructions

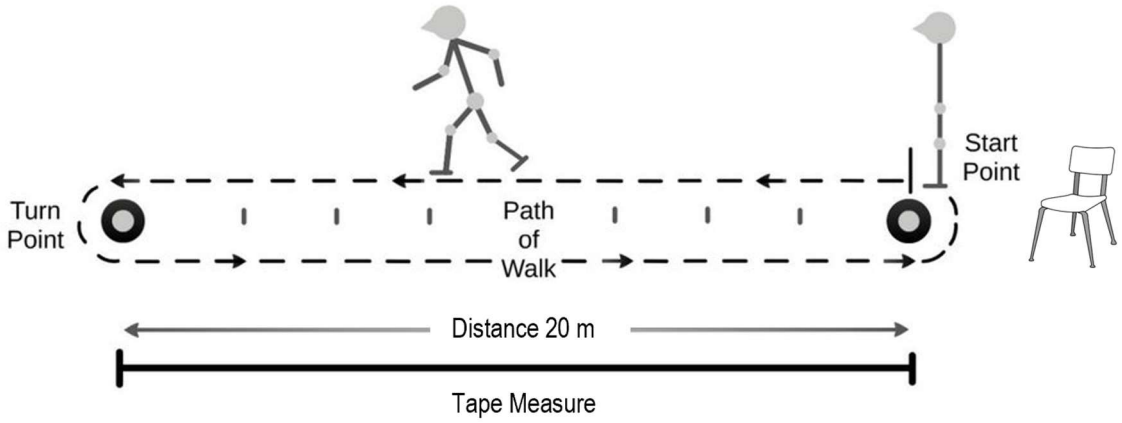
1. Open the patientMpower app on your phone. Click the red + button at the bottom of the screen and select **Add Exertion Test**.



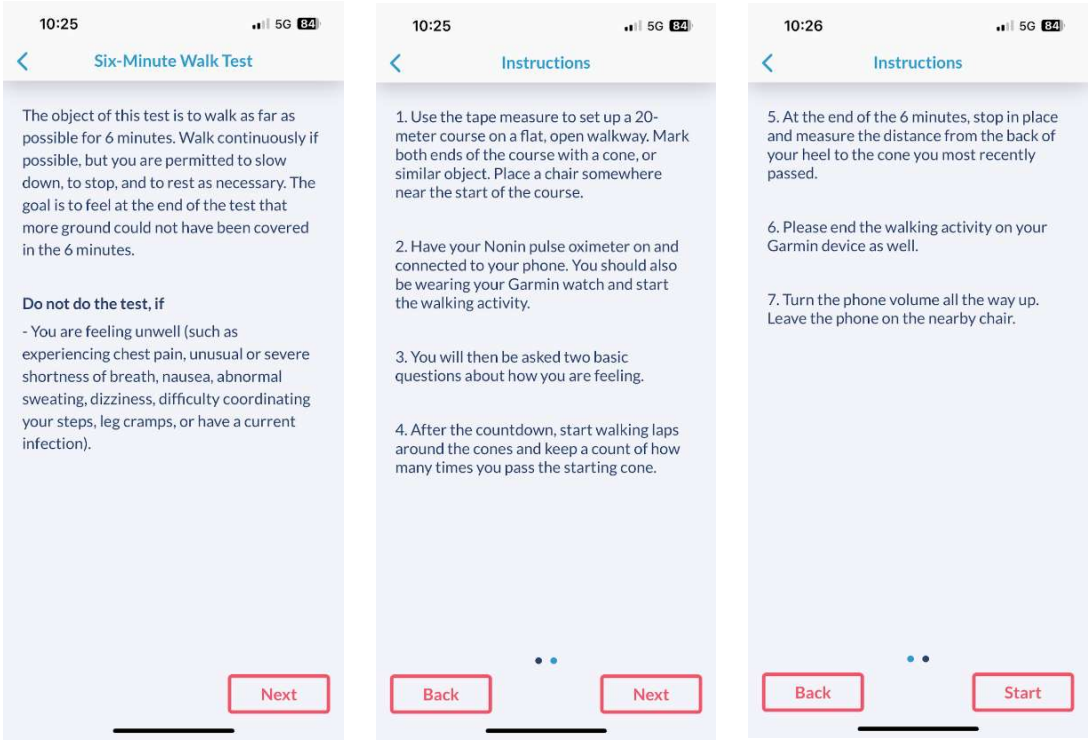
2. Read through the instructions provided in the app. Use the tape measure to set up a 20-meter (m) course on a flat, open walkway. Mark both ends of the course with a cone similar to the diagram below. Place a chair near the start of the course. Turn your phone's volume all the way up and place it on the chair, or in your pocket.

   Place the lap counter on your finger. Plan to press the lap counter each time you pass the starting point.

   Once ready, press the **Start** button.



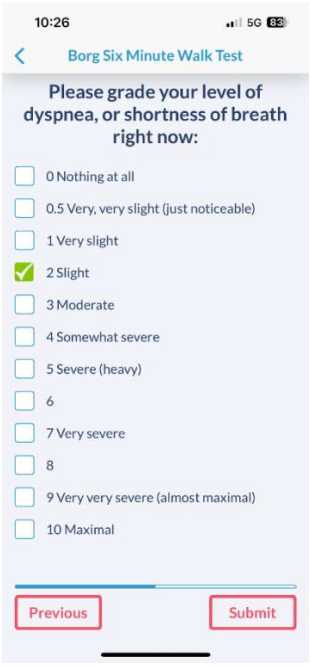
Adapted from Benavent-Caballer



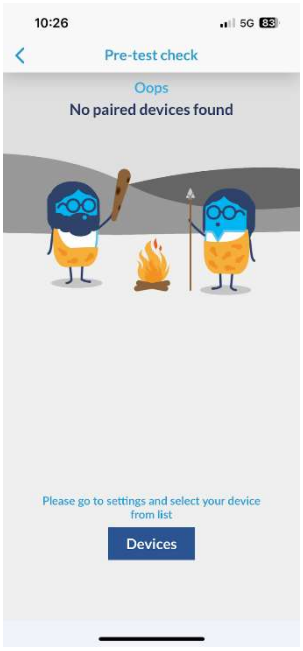
3. You will first be asked to grade your level of perceived exertion, or effort on a scale of 0 to 10. Once selected, click the **Next** button.

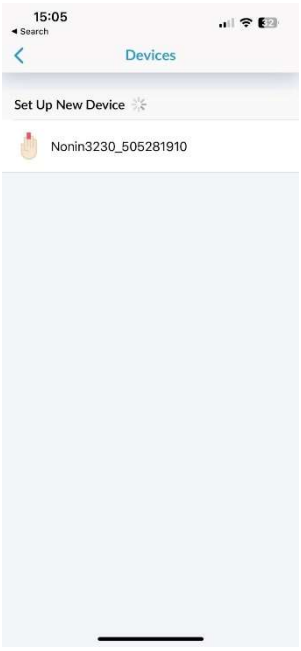


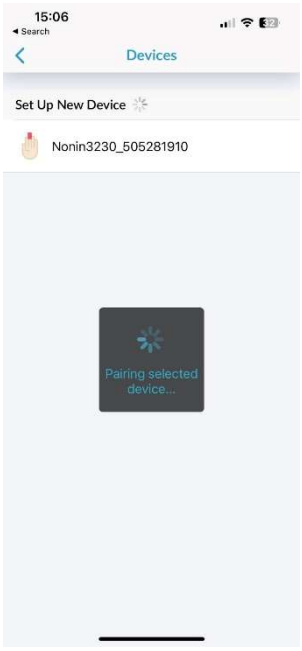
4. You will then be asked to grade your level of dyspnea, or shortness of breath on a scale of 1 to 10. Once selected, click the **Submit** button.



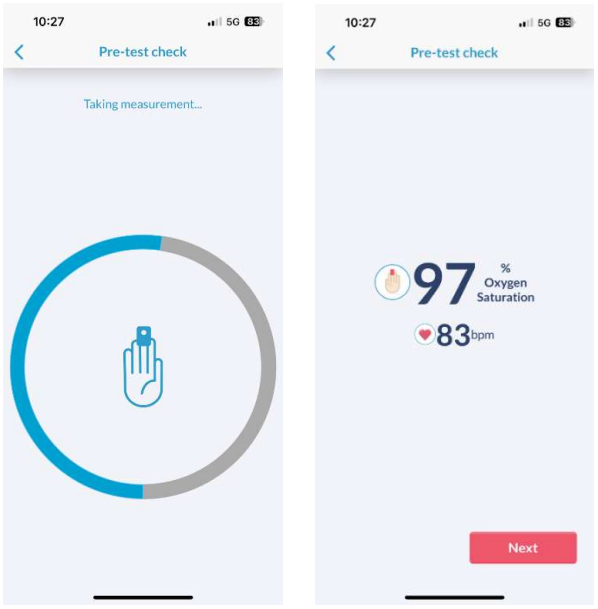
5. You will then take a pre-test pulse oximetry reading. If you haven't already, please pair your pulse oximeter device to the app. To do this, click on the **Devices** button. Place the device on the tip of your middle finger, with your palm and the device screen facing you. The screen should then light up and the device should appear on the app as Nonin3230_XXXXX. Click on this to start pairing.



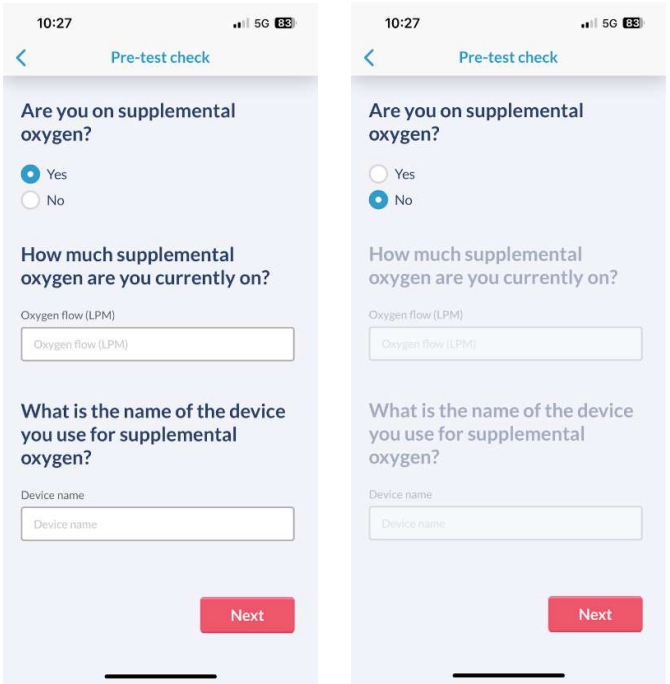




6. Once the device is paired, the app will start taking your pulse oximetry measurement. Remain still while the measurement is being taken. Your results will appear on the screen. Click the **Next** button to continue.

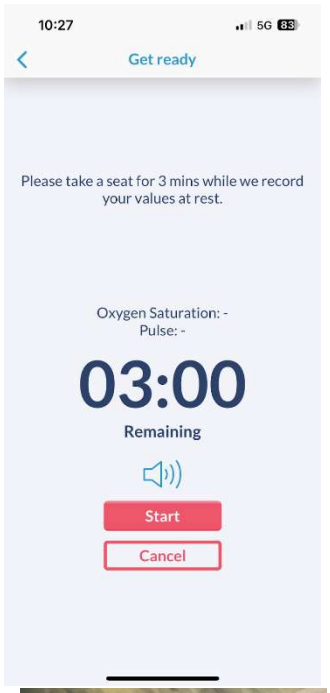


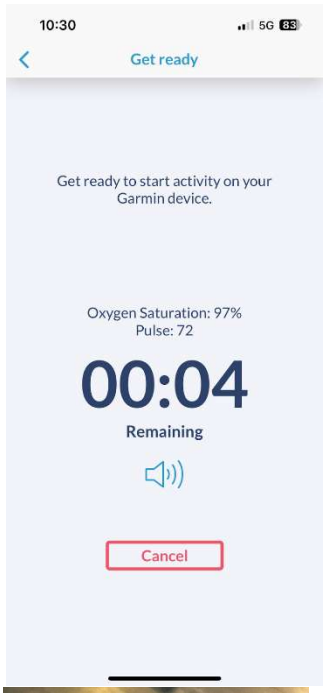
You will then be asked if you are currently taking supplemental oxygen. Answer this question and click on the **Next** button to proceed. If you are taking supplemental oxygen, enter how much oxygen you are using (in liters per minute) and the name of the device you use.

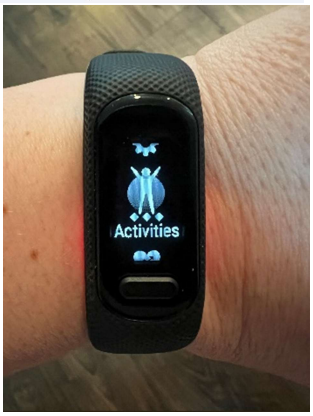


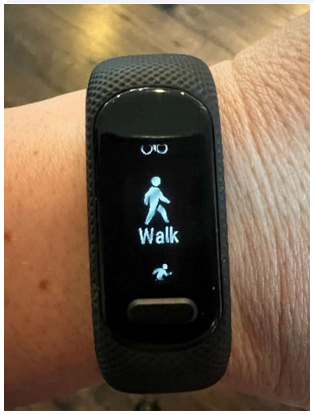
7. Next, take a seat for 3 minutes while the app records your pulse and oxygen saturation levels <u>at rest</u>. Once ready, click the **Start** button. Please keep the pulse oximeter on your finger for the full 3 minutes. Remain still on your chair.

   Towards the end of the 3 minutes, get ready to start a “Walk” activity on your Garmin wristworn device.

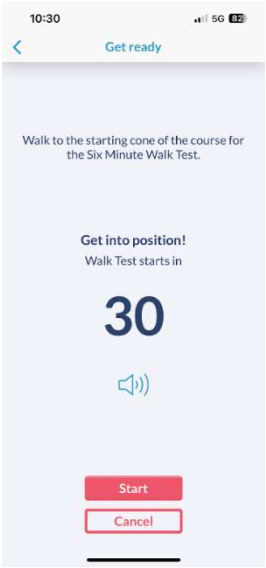




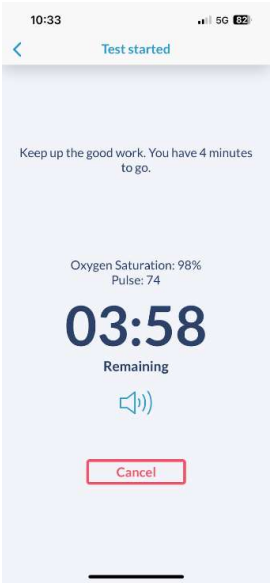




8. It is now time to start your Six Minute Walk Test. Keep the pulse oximeter device on your finger for the duration of the test. Click the **Start** button and a timer will count down from 30 seconds to give you time to prepare. Leave your phone on the chair with the volume turned up full. Audio instructions will play during the test to let you know how long you have left. Walk to the starting cone of the course. If you need more time, you can click the **Reset** button.

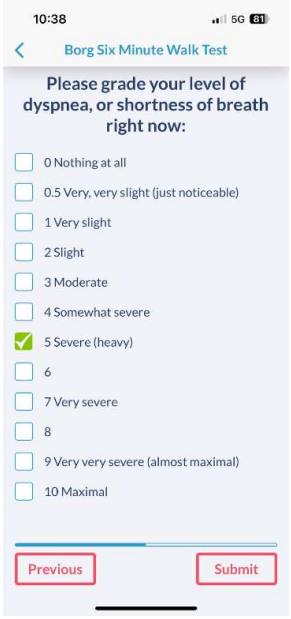


9. Once the timer hits zero, the test will begin and you can start your laps. Remember to keep track using your counter of how many laps you complete around the starting cone.

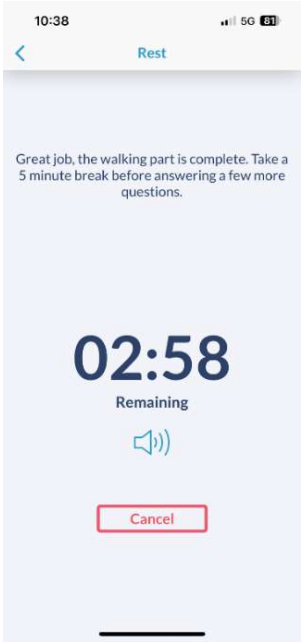


10. Once the test is complete, take a seat and catch your breath. Stop and save the “Walk” activity on your Garmin device. Open the patientMpower app and answer the 2 questions on the screen. Grade your level of perceived exertion, or effort, and your level of dyspnea, or shortness of breath on a scale from 1 to 10. Answer these questions and click the **Submit** button.

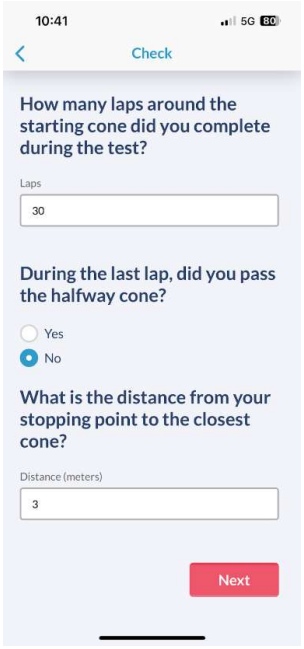




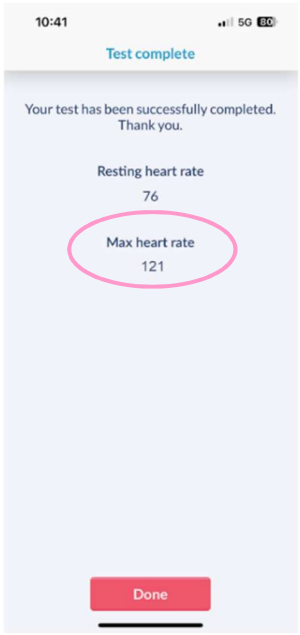
11. Continue to recover while sitting in a chair. A timer will count down from 3 minutes. Keep the pulse oximeter on your finger.



12. At the end, you will answer 3 more questions. Record the number of laps you completed around the starting cone. Record 1) if you passed the halfway cone during the last lap and 2) the distance from your stopping point to the closest cone.



13. The test is now complete. Your resting heart rate and max heart rate will appear on screen. Take a screenshot on your phone and write down your highest heart rate achieved (Max HR) on 6MWT. Click **Done** to return to the home screen.



How to Pace Exercise Intensity

LAM*Fit* is a home-based, remotely monitored exercise program that incorporates daily activity goal setting, reminder messaging, and social connection.

How to Pace Using Heart Rate

During each 12-week program, you will be asked to pace your exercise sessions using a personalized goal training intensity.

Prior research has validated the use of the highest heart rate (HR) achieved on six-minute walk test (Max HR on 6MWT) as a target HR intensity for aerobic exercise prescription in other cardiopulmonary diseases. Max HR on 6MWT will be remotely measured at different timepoints during LAM*Fit*. This HR value may help LAM*Fit* participants to personalize and update their own goal training intensity over the program duration.

After each remote 6MWT is performed (at baseline, midpoint, and final program timepoints), please record the highest heart rate value (Max HR) shown on 6MWT in the pink box on the LAM*Fit* Program Instructions. Use this HR value as your target HR training level during aerobic exercise sessions. During your exercise sessions, train at or above this HR value.

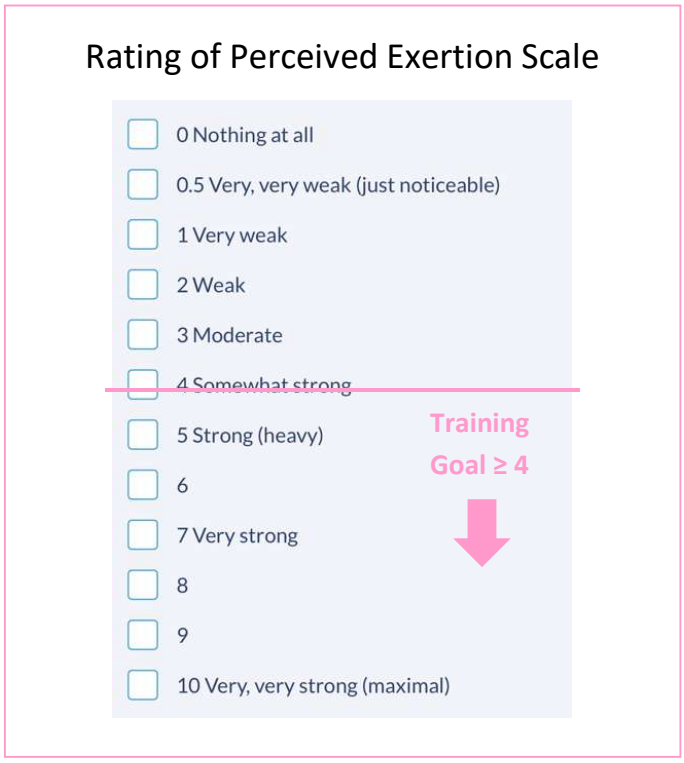
Max HR on 6MWT: _____

How to Pace Using Perceived Exertion (RPE)

Due to the effects of some medications (e.g., medications used to control blood pressure), HR may be a less accurate estimate of training intensity for some individuals with LAM. If you take medication(s) to control your blood pressure, or you otherwise notice that your highest HR value achieved on the 6MWT does not match well with your perceived effort level, please use the Borg Rating of Perceived Exertion (RPE) scale (0-10).

While you exercise, think about how hard you are exerting yourself, or how much effort you are putting forth. Then, pick the number and words on the scale that best show how you feel at that time.

Try to keep your exertion, or effort level <u>at a 4 ("Somewhat strong") or greater</u> during exercise training.

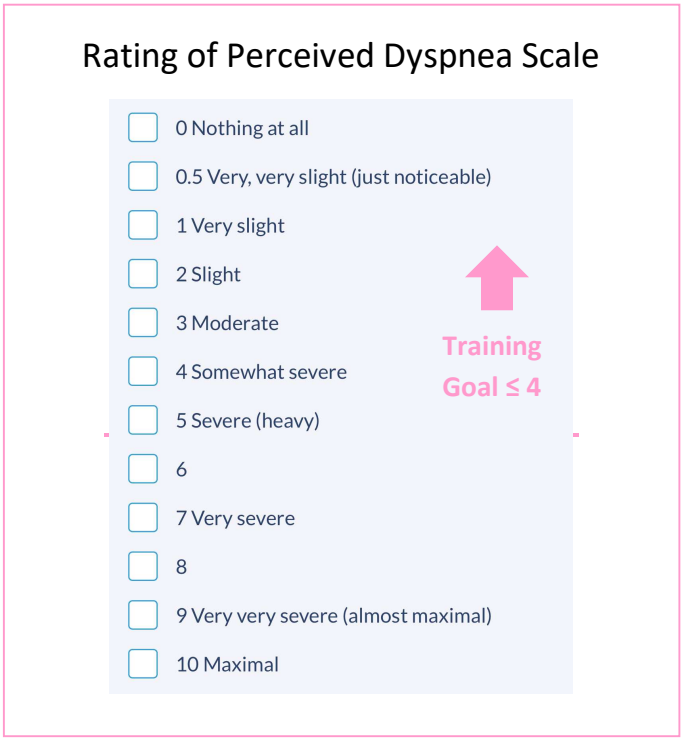


How to Pace Using the Dyspnea Scale

The Dyspnea Scale measures shortness of breath. You can also use the Dyspnea Scale to help guide your exercise intensity.

While you exercise, think about how short of breath you feel. Be aware of how hard you are working to breathe. Then, pick the number and words on the scale that best show how you feel at that time. If your shortness of breath is very slight, you're at level 1. If you feel severely short of breath, you're at level 5. If you can't breathe at all, you're at level 10 ("Maximal").

Use this scale to help pace your exercise sessions. Try to keep your dyspnea level less than or equal to 4 ("Somewhat severe") during exercise training.



Symptoms of Exercise Intolerance

If you experience any of the following symptoms during exercise, stop exercising.
Find a place to sit down and rest. Continue to monitor how you are feeling.

- Chest, left arm, jaw, back or lower neck pain or pressure
- Unusual or severe shortness of breath
- Abnormal sweating
- Cold and clammy skin
- Dizziness/vertigo, difficulty coordinating your steps, confusion
- Leg cramps, intermittent or continuous
- Severe fatigue
- Generally feeling unwell

If you develop mild symptoms of exercise intolerance, sit down and rest.

If your symptoms do not improve after 2 minutes of rest in a sitting position, take another 5 minutes of rest and keep monitoring your symptoms.

If your oxygen saturation (SpO_2) drops below 85% and persists beyond 2 minutes duration while resting, first, increase the amount of supplemental O2 you are receiving (if you have home supplemental O_2 prescribed by your doctor) until your SpO_2 is ≥90% on your pulse oximeter. If you do not have supplemental oxygen at home and your saturation level dips below 85%, or if low SpO_2 readings persist beyond 2 minutes, call and talk with your primary care provider**.**

If your symptoms seem severe and are not improving, and your oxygen saturation (SpO_2) remains low, ***call 911*** *and seek immediate medical attention.*

For more emergent symptoms, ***call 911*** *and seek immediate medical attention.* These include:

- New onset of chest, left arm, jaw, back or lower neck pain or pressure
- Abnormal sweating
- Dizziness/vertigo, difficulty coordinating your steps
- New onset of confusion
- Syncopal (fainting) event
- Significant heart rhythm change

For nonurgent questions about exercise pacing, contact the study team at **lamfit-study@uw.edu**.

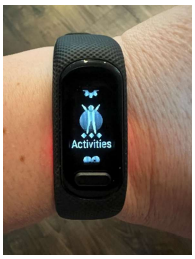
Safety tip: You are advised to have someone at home (i.e. partner, caregiver) who can help in the event that emergent symptoms occur during exercise.

Adapted From: Swain, D. P. (2014). *ACSM's resource manual for Guidelines for exercise testing and prescription.* 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Exercise Session Monitoring with Pulse Oximetry in the patientMpower app

Monitoring Instructions

You will be provided with a Garmin wrist-worn activity/heart rate monitor that is yours to keep. Use this watch to record each exercise training session as an “Activity”.



For monitoring of blood oxygen saturation during exercise in the LAMFit program, you will be provided with a medical grade pulse oximeter capable of continuous monitoring and Bluetooth transmission of values.

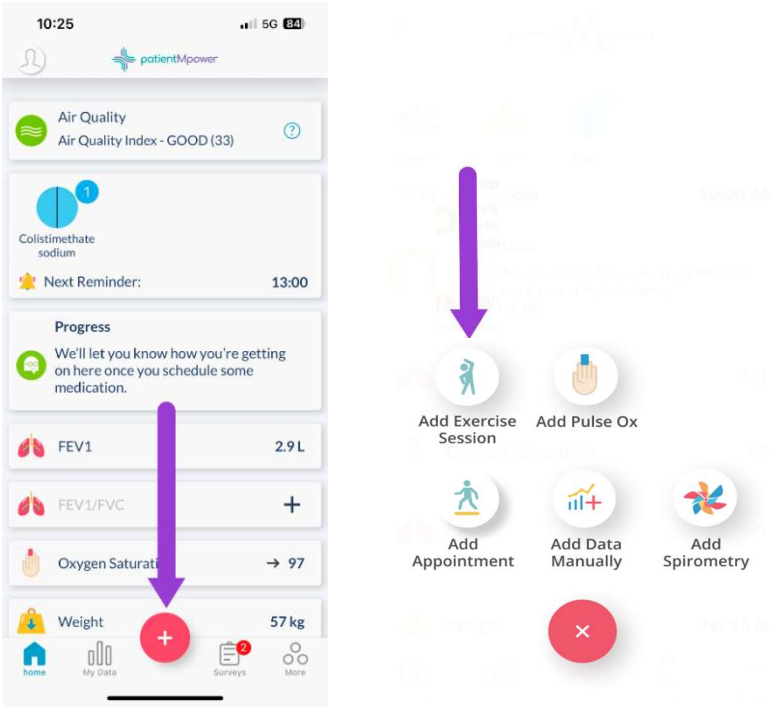


Monitor all exercise sessions using this fingertip pulse oximeter, worn on your second or third finger. Record your pulse oximetry during an exercise session at least 1 time/week in the patientMpower app. Follow the guidance provided in the handout on “How to Pace Exercise Intensity,” as well as any specific guidance you have received from your medical provider.

Note: You can perform exercise session monitoring more often in the patientMpower app, but it is not required.

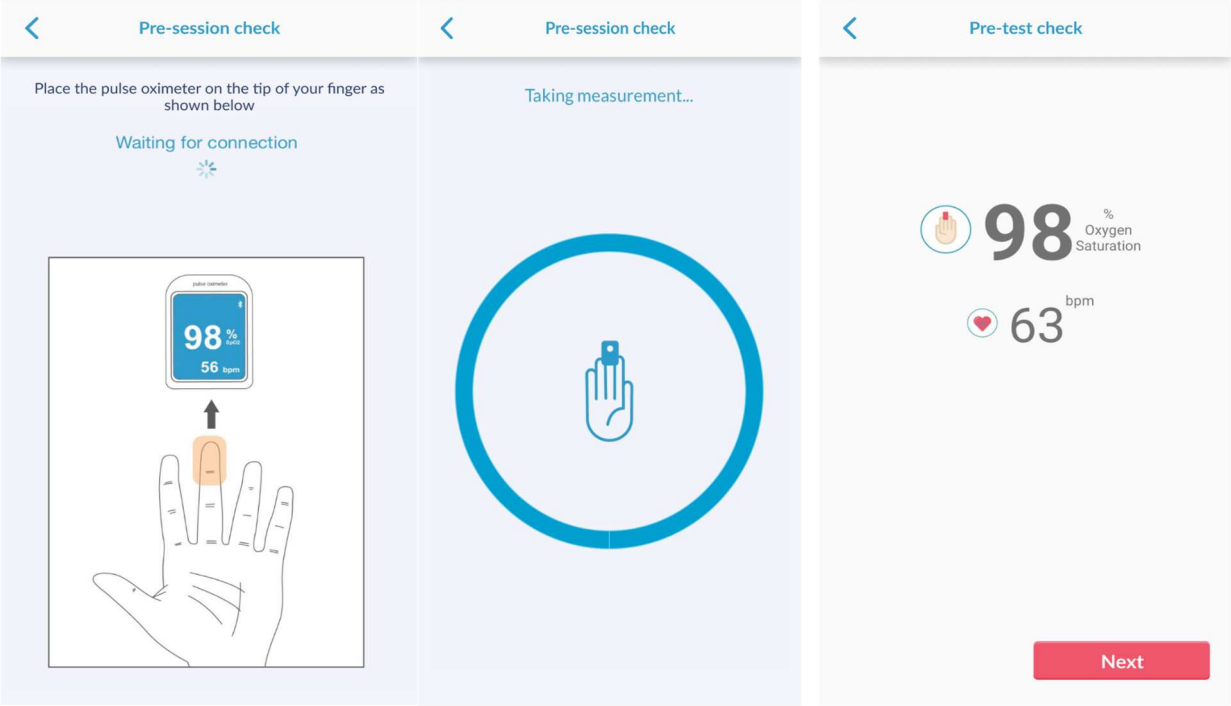
Recording Pulse Oximetry During Exercise

1. Open the patientMpower app on your phone. Make sure that your pulse oximeter is paired prior to starting your exercise session.
2. Click the red + button at the bottom of the screen and select **Add Exercise Session**.

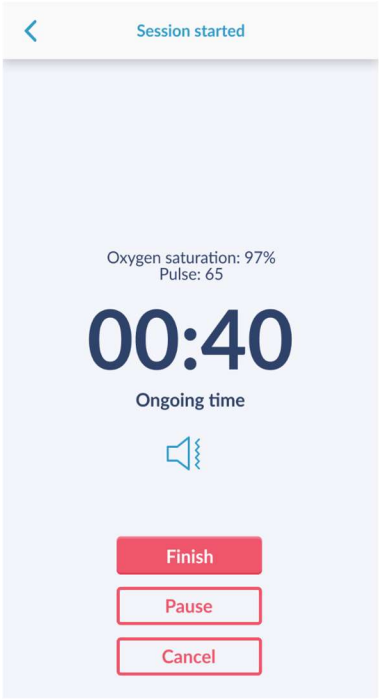


3. Read through the instructions provided in the app.

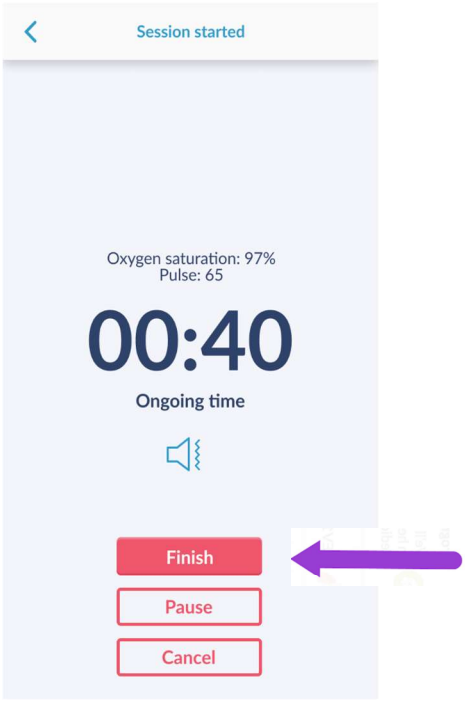
4. Complete a pre-session check of your pulse oximeter.



5. Start the timer when you begin your exercise session. The timer allows you to track the length of your exercise session. You can also view your current pulse rate and oxygen saturation (SpO_2) values on this screen.



6. If you can see the pulse oximetry data in the app, then your data is transmitted to the study portal automatically.
7. Press the **Finish** button at the end of your exercise session. Thank you for recording your pulse oximetry during exercise!



Home Spirometry in the patientMpower app

Home Spirometry Instructions

Home spirometry is a method of pulmonary function testing outside of the clinical setting that measures the flow and volume of air entering and leaving the lungs. Remote monitoring of pulmonary function via home spirometry has been studied in a number of different lung conditions, and tends to match well with clinical measures of pulmonary function. It may provide early detection of lung infection and other changes.

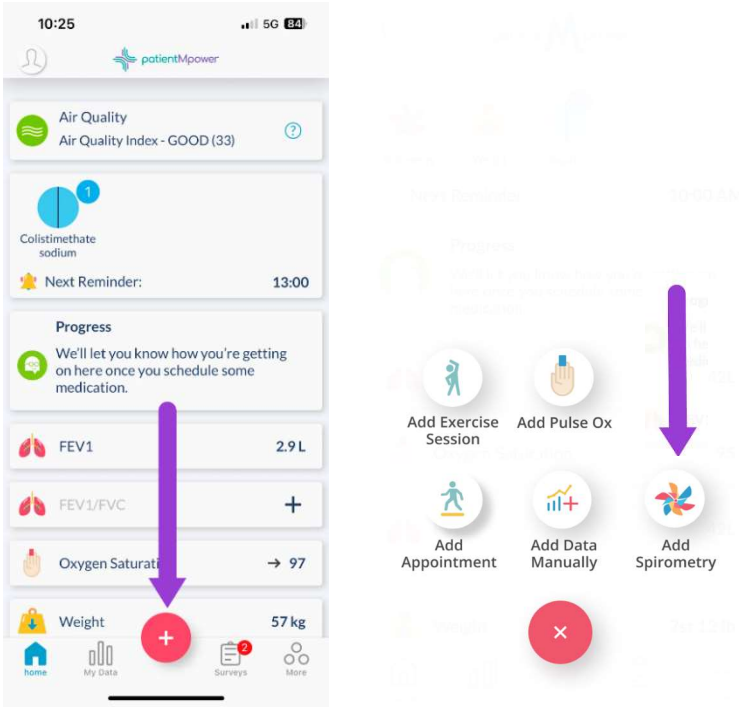
During LAM*Fit,* we will explore the usefulness of home spirometry among individuals with LAM by asking you to perform home spirometry testing at baseline, midpoint, and final timepoints.

Connecting the Spirobank Smart Spirometer

1. Log in to the patientMpower app and click on “More”
2. Go to “Bluetooth devices”
3. You will see the name “Spirobank Smart” followed by a string of numbers. Click this device.
4. This will prompt a text that reads "PatientMpower would like to Use Bluetooth." Select OK. You should see a confirmation on the app that the spirometer has been paired successfully.

Taking a Spirometry Measurement

1. Open the patientMpower app on your phone. Click the red + button at the bottom of the screen and select **Add Spirometry**.



2. Read through the instructions provided in the app.
3. You will be prompted to perform different breathing maneuvers, similar to clinical pulmonary function testing.
4. If you can see the data in your mobile app, then your data is transmitted to the study portal automatically.
5. Perform 3 repetitions of spirometry testing at least 2 days over the course of 1 week – at baseline (weeks 1-2), midpoint (week 14), and final (week 27-28) timepoints.

Note: You are welcome to perform spirometry testing more often during the program, but it is not required.

Example Month from the Program Calendar & Written Exercise Log

LAMFit Program Calendar

January 2024

Instructions for Use: Number each week (starting with Week 1) based on when you start the LAM*Fit* program. Follow the LAM*Fit* Exercise Program Instructions Handout to know which tasks to perform each week. During weeks 3-14 and 15-26, record the days you complete each goal (exercise sessions, daily physical activity, resistance training, and LAM*Fit* Community Forum).

Note: Use of this paper exercise log is optional, not required. You do not need to return the exercise log to the study team.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week _____	1	2	3	4	5	6
7 Week _____	8	9	10	11	12	13
14 Week _____	15	16	17	18	19	20
21 Week _____	22	23	24	25	26	27
28 Week _____	29	30	31			
Notes:						

GOALS

EXERCISE SESSIONS
Perform aerobic exercise training sessions 4 or more times per week for ≥ 30 minutes/day

PHYSICAL ACTIVITY
Achieve ≥ 30 minutes of moderate-to-vigorous physical activity (MVPA) on most (≥ 4) days of the week

RESISTANCE TRAINING
Perform resistance (strengthening) exercises of major limbs and core muscle groups ≥ 2 times/week

LAM*Fit* COMMUNITY
Participate at least 1 time/week in the LAMFit Community Engagement Forum (optional)

4.10 Acknowledgements

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The co-authors affirm that the first author Dr. Child conceived and designed the study under the supervision of senior author Dr. Brown, and took the lead role in the analysis and interpretation of study data. Dr. Child alone drafted the manuscript.

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The Authors declare that there is no conflict of interest.

Chapter 5 – Conclusion

5.1 Summary of the Dissertation

This dissertation documents a successful, patient-centered process for designing and testing a remote, unsupervised exercise program specifically for individuals with lymphangioleiomyomatosis (LAM). LAM*Fit* is an innovative digital fitness program that embraces the ongoing digital transformation of health care and seeks to empower individuals with the rare lung disease LAM to use technology to enhance access the health benefits of exercise. Our program carefully weighs the negative effects of physical inactivity, low access to pulmonary rehabilitation, LAM-specific risks of events during unsupervised exercise, and evidence of the benefits of exercise training in LAM observed during the previous 'Exercise & Fatigue in LAM' study.

Exercise training in LAM is not without any risk. The 'Exercise & Fatigue in LAM' study required participants to travel to Seattle, WA for completion of in-person baseline and final study visits,[1] similar to a hybrid model of pulmonary rehabilitation that begins with an in-person clinical assessment, supervised exercise testing, and exercise prescription before transitioning to home-based exercise training.[2] To successfully scale up access during LAM*Fit*, it was important to minimize barriers to program participation, like travel, but also implement prescreening methods that would help the study team to maximize safety during exercise in the context of possible physiological risks in patients with LAM. We sought to answer the research question of which exercise preparticipation screening steps are necessary to determine whether a patient with LAM is medically appropriate to participate in a remote, unsupervised exercise program.

Tools for population-based exercise preparticipation screening have been developed and disseminated,[3–5] but are less specific to chronic respiratory diseases like LAM and ILD. Prior to

the Aim 1 study of this dissertation, there was no consensus regarding unique risks of events during exercise that patients with LAM encounter. We conducted a two-round modified Delphi study to synthesize expert opinions and develop a consensus exercise preparticipation screening tool specifically for patients with LAM for use during the LAM*Fit* pilot study. Experts in LAM and ILD felt that it was essential for patients with LAM to first to conduct an in-person medical screening by a licensed medical provider, with clinical exercise test to ensure adequate home supplemental oxygen availability during exercise. All participants in the Aim 3 LAM*Fit* pilot study were prescreened by their own medical provider using the consensus LAM*Fit* exercise preparticipation screening tool developed in Aim 1. Participants also completed supervised, in-clinic exercise testing prior to enrollment to ensure adequate availability of home supplemental oxygen during aerobic exercise training. Medical providers electronically attested with signature that their patients were medically appropriate to participate in the fully-remote LAM*Fit* program.

In chapter 3, we present the results of the Aim 2 study, a secondary analysis of a combined sample of n=29 individuals with ILD [n=15 patients with LAM, n=14 patients with idiopathic pulmonary fibrosis (IPF)] that previously participated in similar studies of a 12-week, home-based exercise program. We sought to answer the research question of how best to prescribe aerobic exercise intensity using a target HR threshold or HR zone in higher-functioning individuals with ILD, in the absence of a recent maximal CPET. In traditional pulmonary rehabilitation (PR) settings, guidelines exist for exercise specialists to calculate a percent (%) of VO_2max obtained on CPET[6,7] or 6MWT[8] to prescribe treadmill-based walking speed, cycling speed, duration of exercise sessions, and exercise progression for patients with chronic respiratory diseases. However, constant treadmill walking or cycling speed at a %VO_2max is not easily adaptable to real-world, free-living environments where individuals often exercise using

different modalities than in center-based PR. The use of a target HR threshold or HR zone for exercise prescription is attractive as it is more intuitive for patients to use than a %VO_2max and translates more easily to other accessible exercise modalities like brisk overground walking and outdoor hiking.

Identification of an individual's heart rate at first ventilatory threshold (VT1) on CPET ($HR_{VT1onCPET}$) is the criterion standard for delineating between slight and moderate exercise intensities,[6] and exercising above this threshold stimulates aerobic metabolism.[9,10] Studies have validated the use of peak HR on 6MWT ($HR_{peak6MWT}$) to estimate VT1 on CPET and guide aerobic exercise prescription in medically stable patients with COPD[11] and cystic fibrosis.[12] However, no prior studies have compared $HR_{peak6MWT}$ to $HR_{VT1onCPET}$ to determine the utility of $HR_{peak6MWT}$ to guide aerobic exercise prescription in ILD.

We used multiple statistical methods to compare physiologic data collected during standardized 6MWT and CPET protocols completed during baseline, in-person study visits for these 29 individuals with ILD and determine the validity of $HR_{peak6MWT}$ in estimating the true aerobic exercise intensity, or the $HR_{VT1onCPET}$. We identified a 'ceiling effect' at or above a cut-off of 85% predicted 6MWT distance, which impacts the predictive utility of $HR_{peak6MWT}$ for aerobic exercise prescription among individuals with ILD. In the absence of incremental CPET, individuals with ILD and lower cardiorespiratory fitness that walk 6MWT distance <85% predicted may use $HR_{peak6MWT}$ to estimate the true HR threshold for aerobic exercise intensity. For those that walk ≥85% predicted 6MWT distance, the use of $HR_{peak6MWT}$ to estimate moderate intensity aerobic exercise is not appropriate.

Chapter 4 summarizes the Aim 3 study of the dissertation, which had 2 objectives: 1) to design a custom, patient-centered digital technology platform with wearable fitness devices and

medical grade pulse oximetry monitoring, and 2) to determine the feasibility and safety of the fully-remote LAM*Fit* program over a 6-month pilot study period. A custom LAM*Fit* technology platform with remote monitoring was created and user-tested to capture all digital study endpoints. Enrolled participants were shipped a remote monitoring kit that included a wristworn fitness tracker, medical grade pulse oximeter, instructional handouts, and materials for a remote 6MWT course. The study team co-designed the LAM*Fit* program logo, recruitment website (www.lamfit.org), and online community engagement forum in collaboration with patient representatives with LAM and a graphic designer. Participants received a 30-min training video and instructional handouts about how to use a personalized target HR, perceived levels of exertion, dyspnea, and oxygen saturation (SpO_2) to self-monitor and adjust exercise intensities as appropriate. All handouts and a monthly calendar were user-tested for clarity, printed, shipped to participants in remote monitoring kits, and posted online for viewing and download on a secure, web-based participant portal.

The LAM*Fit* pilot study was conducted from January to October 2024. Recruitment was relatively easy due to very high interest from the LAM patient community. Completion of in-person medical screening and provider attestation of medical appropriateness was slightly more burdensome, but feasible. Several key process metrics were documented to estimate the person-hours required to support LAM*Fit.* The LAM*Fit* exercise preparticipation screening tool was successfully used to screen out one person with LAM who had a diagnosis of Wolff-Parkinsonian White syndrome, and who was recommended instead to enroll in a supervised outpatient rehabilitation program with real-time cardiac monitoring. High program completion and aerobic exercise program adherence was achieved, with all 25 participants (100%) completing the first 12-week exercise program, including baseline and midpoint study visits.

Twenty-two participants (88%) completed the second 12-week program and final study visit, with 3 discontinuations for reasons unrelated to the intervention. Completion of digital endpoints was high. No serious or non-serious study-related adverse events occurred. Group goal achievement was high for >30 daily minutes of moderate-to-vigorous physical activity (MVPA), and participants reported feeling motivated by the addition of group accountability features. Distance achieved in 6MWT increased by an average of 7.1% from baseline to midpoint (12 weeks), and 8.5% from baseline to final (24 weeks). Symptoms of fatigue, dyspnea, and health-related quality of life significantly improved after 12 weeks of participation. Participants expressed a high level of satisfaction and acceptability of the LAMFit digital fitness program. We concluded that a fully-remote approach to delivering LAM*Fit* is feasible and safe for individuals with LAM that have been deemed medically appropriate to participate.

5.2 Retrospective Evaluation of the HR-based Exercise Prescription Used in LAM*Fit*

When the Aim 3 pilot study of LAM*Fit* began, the Aim 2 statistical analyses were not yet completed. An intentional decision was made by the study team to take a more conservative approach to aerobic exercise prescription during the pilot study so as to minimize unnecessary risks. No LAM*Fit* participants had recently completed a maximal CPET. Thus, based on available evidence,[11,12] all were recommended to use $HR_{peak6MWT}$ as a goal HR threshold for aerobic exercise training. We then learned from our Aim 2 analyses that there is a 'ceiling effect' for using $HR_{peak6MWT}$ to estimate moderate intensity aerobic exercise among higher functioning patients with ILD that achieve a 6MWT distance ≥85% predicted. Use of $HR_{peak6MWT}$ to estimate moderate intensity was likely appropriate for lower functioning LAM*Fit* participants (with a 6MWT distance <85% predicted, n=7), but higher functioning participants (with a 6MWT distance ≥85% predicted, n=18) may have been aerobically undertrained.

Using our detailed LAM*Fit* workout session and outcomes data, we decided to investigate retrospectively whether functional exercise capacity gains of higher functioning participants, as measured by % improvement in 6MWT distance, were the same or different than gains observed in lower functioning participants. Our data showed that higher functioning participants demonstrated a greater % improvement in 6MWT distance over the first 12 weeks than lower functioning participants, with a p value approaching significance at $\alpha = 0.05$ (7.0% vs. 3.8% increase, p=0.1105; Figure 5.1). This was somewhat surprising given our concern for undertraining higher functioning participants.

We then examined whether higher functioning participants stayed at or near their baseline $HR_{peak6MWT}$ during workouts, or whether they self-adjusted to a higher training intensity. Using Pearson correlation analyses, we observed that while lower functioning participants demonstrated a very strong correlation between average METs on baseline 6MWT and average METs during workouts in the first 12 weeks (r=0.89, p=0.045), there was no such correlation for higher functioning participants (r=0.35, p=0.321; Table 5.1).

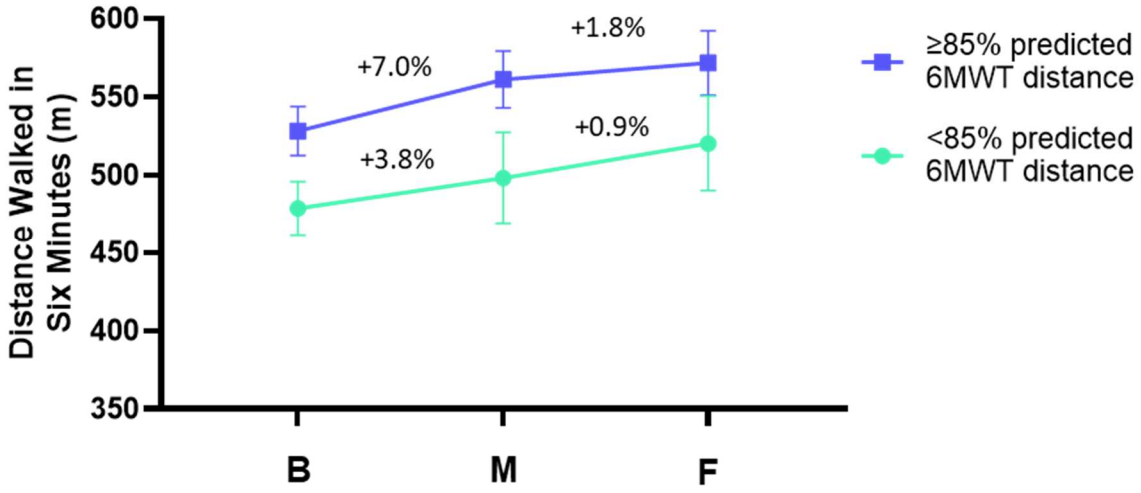


Figure 5.1: Subgroup Differences in Percent (%) Improvement in 6MWT Distance, using 85% predicted 6MWT distance at baseline as a cutoff.

Table 5.1: Subgroup Differences in Exercise Intensity Achieved During the First 12 Weeks

	Avg METs During Workouts (Exercise Weeks 1-12)	
6MWT distance ≥85% pred. (n=18)	**r**	**p**
Baseline 6MWT Peak HR	0.44	0.133
Baseline 6MWT Avg METs	0.35	0.321
Baseline 6MWT distance (m)	0.47	0.056
Baseline 6MWT distance (% pred.)	0.22	0.401
6MWT distance <85% pred. (n=7)	**r**	**p**
Baseline 6MWT Peak HR	0.12	0.852
Baseline 6MWT Avg METs	**0.89**	**0.045**
Baseline 6MWT distance (m)	0.76	0.133
Baseline 6MWT distance (% pred.)	0.73	0.165

Further analysis of exercise workouts showed that higher functioning participants began the first week of exercise with an average HR >8 bpm higher than their baseline $HR_{peak6MWT}$ (8.7±13 bpm, p=0.059; Figure 5.2), suggesting that these participants were immediately comfortable self-pacing their aerobic workouts above $HR_{peak6MWT}$. Conversely, lower functioning participants were observed to begin the first week of exercise with an average HR nearly 12 bpm lower than their $HR_{peak6MWT}$ (-11.9±19 bpm, p=0.120) and slowly ramp up their average HR training intensity in the first 3 weeks until they achieved the recommended training threshold of $HR_{peak6MWT}$ (Figure 5.2). On average over the first 12 weeks, higher functioning participants trained 7.1±11 bpm above their $HR_{peak6MWT}$ and lower functioning participants trained -7.0±15 bpm below their $HR_{peak6MWT}$, with a significant between-subgroup difference of 14.2±6 bpm (p=0.040) average HR during training.

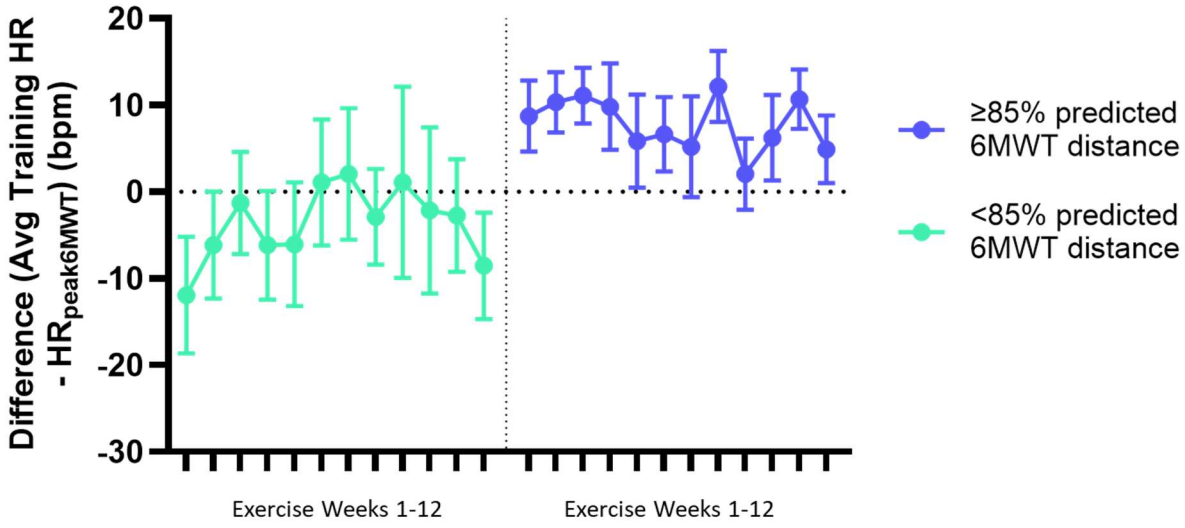


Figure 5.2: Subgroup Differences between Average Training HR during Weeks 1-12 and Peak HR During the Baseline 6MWT ($HR_{peak6MWT}$), using 85% predicted 6MWT distance at baseline as a cutoff.

Despite the study team recommending a relatively conservative HR-based training threshold based on 6MWT data to all participants, higher functioning participants in LAM*Fit* demonstrated the ability to self-adjust their exercise intensity to be higher during aerobic exercise workouts. It is possible that these participants chose to use a 'moderate' rating of perceived exertion (RPE) threshold instead of HR, as the LAM*Fit* training video and handouts advised participants to do if they felt that the recommended HR threshold based on 6MWT did not match their own "moderate" level of perceived exertion.

It is vexing that this subgroup of higher functioning individuals with LAM cannot reliably use a HR-based exercise prescription without completion of a maximal CPET. Many commercially-available wearable fitness devices automatically calculate HR-based training zones for users using the age-predicted max HR + heart rate reserve (APMHR+HRR) method,[13] but our analyses have shown that this method is not always appropriate in LAM. In the Aim 2 analyses, the APMHR+HRR method moderately correlated with the true HR at VT1 on CPET

for higher functioning patients with ILD, but a very large positive bias on Bland Altman analysis indicated a high risk for overestimating the true HR at VT1. High physiological variability[14] and the influence of multiple factors on HR in LAM[15] also confound the utility of HR-based methods for individualized exercise prescription in LAM. Given these limitations, it is reassuring that higher functioning participants in LAM*Fit* were able to self-adjust their exercise intensity to be higher and still achieved meaningful improvements in functional exercise capacity with no exercise-related adverse events.

5.3 Contributions to the Literature

LAM*Fit* is the first digital fitness program of its kind in chronic respiratory disease. The three innovative studies in this dissertation produced immediately applicable recommendations and clinical tools that will help 1) LAM medical providers to safely prescribe and 2) patients with LAM to safely participate in remote, unsupervised exercise training. The results of the Aim 1 modified Delphi study were recently published in *CHEST Journal* as a clinical practice guideline for 'Unsupervised Exercise in ILD', with a specific disease focus on lymphangioleiomyomatosis (LAM).[16] Similar guidelines are needed in other chronic cardiopulmonary conditions that have little available published research about risk of events during unsupervised exercise in the home and community. With low access to center-based cardiopulmonary rehabilitation in the United States, and substantial uptake of consumer-grade wearable devices and smartphones, more patients living with cardiopulmonary diseases are going to have questions for their own providers about how they can safely exercise on their own, outside of a supervised rehabilitation setting. Our research approach demonstrates one very successful strategy for developing consensus prescreening guidelines for unsupervised exercise, even for rare cardiopulmonary diseases and conditions.

The manuscript for the Aim 2 study, which identified the presence of a 'ceiling effect' for using peak HR on 6MWT to guide moderate intensity aerobic exercise in higher functioning patients with ILD, is formatted for planned submission to the *Archives of Physical Medicine & Rehabilitation (APMR)*. These results are immediately useful in clinical settings for prescribing aerobic exercise using peak HR on 6MWT for lower functioning patients with ILD. This manuscript also demonstrates the need for additional research to optimize exercise prescription and prescription of short-term, exertional supplemental oxygen for higher functioning patients with ILD, in the absence of a CPET.

The LAM*Fit* pilot study (Aim 3) is the first study of a fully-remote, asynchronously monitored exercise program in chronic respiratory disease conducted entirely using digital endpoints collected via decentralized study visits, wearable fitness trackers, remote monitoring devices, and patient-reported outcome measures. Our findings demonstrate that a fully-remote approach to delivering a structured exercise program is feasible and safe for individuals with LAM that are medically appropriate to participate. In the coming weeks, we will format the manuscript for the LAM*Fit* pilot study for planned submission to *CHEST Journal.* Key research innovations within LAM*Fit* included 1) building of a strong academic-community partnership with The LAM Foundation, 2) reliance on attestation of medical appropriateness by the patient's own LAM care provider, 3) co-design of a remote 6MWT and user-centered digital health platform for collection of digital endpoints, and 4) the implementation of multiple technology-facilitated change strategies to successfully promote physical activity behavior change. In addition to creating a scalable program for LAM, our innovative research approach can be used to create novel, disease-specific fitness programming in other rare disease communities.

5.4 Future Directions

Now that the LAM*Fit* digital fitness program has been designed and pilot tested, scaling access to the LAM*Fit* program can be accomplished with low cost and minimal barriers. Using preliminary data from the LAM*Fit* pilot study, our team recently applied for and was awarded the 2025 Clinical Research Award from The LAM Foundation (Principal Investigator: Dr. Child, Co-Investigator: Dr. Brown). In our next phase, we plan to adapt LAM*Fit* program technology components, provider screening and educational materials to be self-sustaining, to enable handoff of LAM*Fit* program operations to a designated LAM community-based program manager. We also plan to create and user test patient-generated remote six-minute walk test (6MWT) and exercise session performance reports that LAM*Fit* participants can securely download from the digital platform and share with their LAM care providers, in order to facilitate shared decision making around exercise and supplemental oxygen use. Finally, we will launch a scaled-up, self-sustaining version of LAM*Fit* with a larger cohort of patients with LAM to confirm feasibility metrics. The final version of LAM*Fit* will be optimized to sustain indefinitely under community-based management by The LAM Foundation, independent of an academic institution. Ultimately, our multi-phased research approach may serve as an implementation blueprint for expanding access to evidence-based exercise interventions for more individuals living with rare diseases in the United States and internationally.

Several questions remain to be answered in this area of health care innovation and specific line of research inquiry. Commercially available fitness trackers are affordable and effective devices for motivating physical activity behavioral change. However, the majority of fitness trackers have not been validated against clinical criterion standards for medical diagnostic capabilities like 12-lead electrocardiogram, maximal cardiopulmonary exercise test with expired

gas analyses, or research-grade accelerometers like Actigraph. Most commercially available fitness trackers use proprietary algorithms for estimation of VO_2max, MET levels, and detection of irregular heart rhythms. They are marketed to the public for health and wellness purposes only and have achieved significant consumer uptake without needing to pursue FDA clearance for their health screening functions. It remains unclear whether the data obtained from different wrist-wearable devices are comparable, thus limiting the ability to perform larger, population-based studies and meta-analyses across studies. Validation studies conducted by third-party researchers are needed.

We have shown in our recent intervention studies that commercially available fitness trackers can be used to safely and effectively pace a home-based exercise program for individuals living with chronic respiratory diseases. The addition of a medical grade pulse oximeter for remote monitoring helps to increase the safety of unsupervised exercise in patients with ILD, including LAM. In the LAM*Fit* pilot study, participants demonstrated the ability to self-pace and maintain a recommended target HR threshold, adjust exercise intensity higher when necessary, and titrate home supplemental oxygen as needed to maintain safe ranges of oxygen saturation during exercise. Positively, continuous, medical grade pulse oximeters are now available for purchase over-the-counter, without a medical prescription. Despite high retail costs (>$300), direct patient accessibility of higher quality medical grade pulse oximeters significantly improves the feasibility of scaling up access to a home-based program like LAM*Fit*.

However, noninvasive, medical grade pulse oximeters that use photoplethysmography (PPG) also have some limitations. They are not validated or optimized for use during exercise, and are therefore rather sensitive to motion artifact. Despite their limitations, they are frequently used during clinical exercise stress testing (e.g., 6MWT and CPET) in ILD to determine

respiratory limitations and medical need for short-term, exertional supplemental oxygen. In acute and intensive care hospital settings, continuous, noninvasive pulse oximetry monitoring guides major medical, surgical, and anesthesiologic decisions. Recent studies have revealed that dark skin pigmentation influences the accuracy and performance of noninvasive pulse oximeters devices, resulting in overestimations of SpO_2 and increased incidence in the risk for occult hypoxemia.[17] Nearly all of these studies have been conducted in acute and intensive care settings on patients that are being monitored at rest, with no additional exercise stress.[17] Further research is needed to investigate health risks associated with dark skin pigmentation on pulse oximetry performance during movement and exercise. Post-processing algorithms that help minimize the effects of motion artifact also need to be optimized for user differences in skin pigmentation.

Individuals with LAM and other ILDs rely heavily on pulse oximetry readings to make decisions about pacing and titration of supplemental oxygen during routine activities of daily living, habitual physical activity, and exercise training. We have heard from many individuals with ILD that the current pulse oximetry device wear experience is poor. A change in location from wearing on the fingertip to a more stable, proximal location on the upper arm, trunk, earlobe, or forehead may help decrease the effects of motion artifact and improve the device wear experience during exercise. Using industry-academic partnerships, clinically meaningful innovations in wearable fitness trackers and medical grade pulse oximeters are within reach and highly feasible to accomplish in the near term.

We envision a reality in the not-too-distant future where all individuals living with cardiopulmonary diseases, regardless of age, diagnoses, geographical location, skin pigmentation, or socioeconomic background will be able to access evidence-based exercise interventions in their own homes and communities, even if they live far from a cardiopulmonary

rehabilitation center. Exercise preparticipation screening algorithms will help providers to make more evidence-informed decisions about patient referrals. The digital health technology and health care expertise necessary to implement programs like LAM*Fit* into at-risk patient populations already exists. Patient-centered improvements in devices and software platforms will continue to enhance safety and feasibility of unsupervised exercise training. Decentralized digital fitness programs like LAM*Fit* will never completely replace the need for supervised, exercise-based cardiopulmonary rehabilitation for some higher risk individuals. However, innovative digital fitness programs like LAM*Fit* can certainly help to fill in access gaps for the >95% of individuals with respiratory diseases that currently do not participate in pulmonary rehabilitation programs,[2] despite being eligible. Patients are the ultimate beneficiaries; whether it is through a center-based program like cardiopulmonary rehabilitation, or through a digital fitness program like LAM*Fit*, more patients will gain the well-documented, positive health benefits of exercise training as an additional method of disease self-management.

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Appendix A

Statement of Co-Authorships

As co-authors of the manuscript entitled "Unsupervised Exercise in Interstitial Lung Disease: A Delphi Study to Develop a Consensus Preparticipation Screening Tool for Lymphangioleiomyomatosis" that had been prepared for submission to *CHEST Journal*, we confirm that Claire Child was the primary contributor to the study in each of the following areas:

- Design of the study
- Data collection
- Data analysis and interpretation of the findings
- Writing of the manuscript and critical appraisal of the content

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As co-authors of the manuscript entitled "Identification of a 'Ceiling Effect' Limitation to Use of 6MWT for Aerobic Exercise Prescription in Higher Functioning Persons with Interstitial Lung Disease" that had been prepared for submission to *Archives of Physical Medicine & Rehabilitation*, we confirm that Claire Child was the primary contributor to the study in each of the following areas:

- Design of the study
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