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METHODOLOGICAL ARTICLE

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Creating a digital approach for promoting physical activity in pediatric pulmonary hypertension: A framework for future interventions

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Abstract

Children with pulmonary hypertension (PH) often demonstrate limited exercise capacity. Data support exercise as an effective nonpharmacologic intervention among adults with PH. However, data on exercise training in children and adolescents are limited, and characteristics of the optimal exercise program in pediatric PH have not been identified. Exercise programs may have multiple targets, including muscle deficits which are associated with exercise limitations in both adult and pediatric PH. Wearable accelerometer sensors measure physical activity volume and intensity in the naturalistic setting and can facilitate near continuous data transfer and bidirectional communication between patients and the study team when paired with informatics tools during exercise interventions. To address the knowledge gaps in exercise training in pediatric PH, we designed a prospective, single arm, nonrandomized pilot study to determine feasibility and preliminary estimates of efficacy of a 16-week home exercise intervention, targeting lower extremity muscle mass and enriched by wearable mobile health technology. The

exercIse Training in pulmONary hypertEnsion (iTONE) trial includes (1) semistructured exercise prescriptions tailored to the participant's baseline level of activity and access to resources; (2) interval goal setting fostering self-efficacy; (3) real time monitoring of activity via wearable devices; (4) a digital platform enabling communication and feedback between participant and study team; (5) multiple avenues to assess participant safety. This pilot intervention will provide information on the digital infrastructure needed to conduct home-based exercise interventions in PH and will generate important preliminary data on the effect of exercise interventions in youth with chronic cardiorespiratory conditions to power larger studies in the future.

KEYWORDS

actigraphy, exercise, informatics, pediatric pulmonary hypertension, physical activity

EXERCISE LIMITATIONS AND PHYSICAL INACTIVITY IN PEDIATRIC PH

In pediatric PH, pulmonary vascular disease predisposes infants, children, and teenagers to right ventricular (RV) heart failure and death. Hemodynamics, symptoms, and survival can improve with aggressive pulmonary vasodilator therapy. However, exercise intolerance is nearly universal and markedly impacts quality of life.[1,2] Children with PH engage in less physical activity than peers,[3] but higher levels of physical activity are associated with better functional status.[4] Furthermore, adult data support exercise as a non-pharmacologic therapy.[5,6] Exercise training safely improves aerobic capacity and quality of life in adults with PH[7–16] and in one pediatric study.[17] Despite adult data, therapeutic exercise has not been widely adopted in pediatric PH due to limited data, fear of adverse events, lack of resources, or physician restriction. The mechanisms by which exercise interventions have a clinical effect are unclear; they may target cardiopulmonary reserve, skeletal muscle performance, endothelial function, or psychosocial factors. As skeletal muscle abnormalities are associated with worse exercise performance in both adults and children with PH[18–20] improving the peripheral muscle pump and augmenting RV stroke volume could improve exercise tolerance in pediatric PH.

The characteristics of the optimal pediatric PH exercise program are not clear. Many adult programs have been hospital-based, some with additional at-home components; but duration has varied; and programs vary with the time dedicated to aerobic, resistance, and respiratory exercise training. Further, patient adherence has been inconsistently assessed. In youth, practical concerns of developmental differences, correct performance of activities, access to facilities or equipment, and parental time commitment must be considered. Supervised home programs are critical to avoiding missed school and workdays. Wearable activity sensors provide new opportunities for remote supervision during home exercise programs. Tri-axial accelerometers measure the total volume of activity and differentiate activity intensity (sedentary, light, moderate to vigorous activity [MVPA]). Key technological advancements in research-grade accelerometers, low-energy wireless transmission protocols (Bluetooth), cell phone data network-connected mobile devices, and two-way messaging between participant and study team facilitate implementation of naturalistic activity monitoring into research protocols. While hip-worn devices have been used to assess physical activity in pediatric PH over limited time periods,[3] young patients may find newer research-grade smartwatches more acceptable for prolonged wear. The near-continuous monitoring by wearable activity sensors provides a critical opportunity to assess trial participants in the home setting.

To further advance these knowledge gaps, we designed the exercIse Training in pulmONary hypertEnsion (iTONE) trial, a prospective, single arm, nonrandomized pilot intervention sponsored by the NIH (K23HL150337 to C. M. A, ClinicalTrials.gov #NCT05442671). The first aim is to determine the feasibility of a 16-week home exercise program, targeting lower extremity muscle mass and enriched by wearable mobile health technology, in pediatric PH (Figure 1). The second aim is to assess preliminary estimates of efficacy by assessing the change in MVPA (min/day) from baseline over the course of the intervention (primary outcome of aim 2) and to compare pre-to-postintervention changes in muscular and functional status

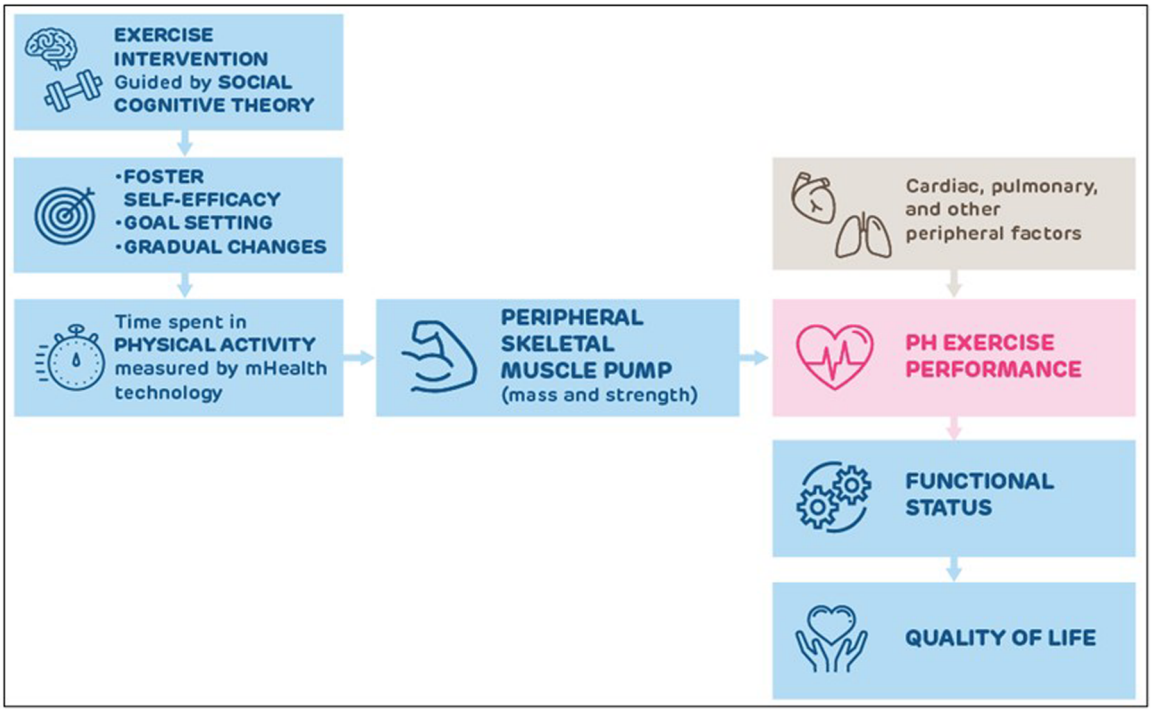

FIGURE 1 Study schematic. An exercise intervention, guided by Social Cognitive Theory and enriched by mobile health technology, could increase physical activity and enhance skeletal muscle mass and strength, leading to better exercise performance, functional status, and quality of life in youth with PH and other cardiac diseases.

by densitometry (DXA)-derived leg lean mass *Z*-score (a surrogate for skeletal muscle mass as most skeletal muscle is in the legs), upper and lower extremity muscle strength, quality of life summary scores, and standard of care 6-min walk test distance (secondary outcomes of aim 2).

STUDY DESIGN

The trial is recruiting 20 ambulatory patients ages 8–18 years with World Symposium of PH diagnostic groups I–IV and World Health Organization functional class I or II. Additional inclusion criteria include mean pulmonary to systemic arterial pressure ratio <0.75 on last cardiac catheterization, completion of a treadmill or bike cardiopulmonary exercise test (CPET) within 3 months of enrollment, stable PH medication regimen for 3 months before enrollment, and home Wi-Fi access. Patients will be excluded for single ventricle physiology, moderate to severe renal or hepatic impairment, current pregnancy, or significant developmental delay/inability to comply with verbal instructions as determined by the study team. The study is approved under Children's Hospital Institutional Review Board protocol #20-018168.

After informed consent, participants will undergo preintervention (visit 1) procedures including anthropometric assessment (weight, height, sitting height), pubertal status questionnaire, PedsQL health related quality of life questionnaire, DXA measures of whole body and leg lean mass, measurement of forearm strength by handgrip dynamometer, and measurement of leg strength by biodex dynamometer (Table 1). Relevant clinical data including most recent standard of care 6-min walk distance (typically performed every 3–6 months per clinical practice and anticipated to be obtained at visit 1 in most participants since research visits will be coordinated with clinical care as much as possible) will be abstracted from the medical record.

Participants will have a 1-h introductory session with a clinical exercise physiologist. After stretching and warm-up aerobic exercise on the treadmill or stationary bike, participants will complete a circuit of light resistance exercises with resistance bands, at least 75% of which will concentrate on the legs. The exercise physiologist will choose the resistance most appropriate for the participant's age, size, strength, and developmental status (very light, light, or medium) from three band types. Correct use of resistance bands will be demonstrated. They will complete up to 15 repetitions/min, using the correct lifting and breathing technique to avoid the Valsalva maneuver. They will grade the difficulty of each exercise (easy, medium, hard). Vital signs will be monitored at the start, 30 min through, and at the end of the session. They will end with cool-down stretching.

TABLE 1 Schedule of study procedures.

Study procedure	Visit 1	After visit 1	Weeks 1–16	Visit 2	Follow-up record review
Review inclusion/exclusion criteria	X				
Informed consent/assent	X				
Demographics, PH history, standard of care clinical testing including 6MWT	X			X	X
Anthropometry	X			X	
Tanner questionnaire	X			X	
Pregnancy test (females)	X			X	
PedsQL questionnaire	X			X	
Handgrip dynamometer	X			X	
Lower extremity Biodex	X			X	
Whole body DXA	X			X	
CPET[a]	X				
Introductory session with the exercise physiologist	X				
Wear smartwatch for 7-day baseline observational period		X			
Home exercise program including aerobic exercise and light resistance exercise			X		
Wear smartwatch throughout intervention			X		
Wear armband heart rate monitor when exercising			X		
Weekly communication (call, text, email)			X		
Adverse event assessment			X	X	

Abbreviations: 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; DXA, densitometry; PH, pulmonary hypertension.

[a]If the participant has not had a clinical one in the prior 3 months.

The exercise physiologist will screen for symptoms. After the session, the exercise physiologist will give the participant written instructions for the home aerobic and light resistance exercises.

A fully charged and initialized ActiGraph GT9X Link smartwatch and Polar OH1 armband heart rate monitor will be given to the participant at visit 1. Written instructions on use of the technology and visual guides will also be provided. The family will be given a data hub to plug into their home Wi-Fi modem to enable syncing of activity and heart rate data from the smartwatch to the ActiGraph CentrePoint cloud-based database. The data hub is a home-based communication gateway that enables transmission of raw data from the GT9X Link activity monitor to CentrePoint via an internet connection. After visit 1, participants will wear the smartwatch on the nondominant wrist for 7 days to measure baseline MVPA. Thereafter, the participant will receive personalized exercise plans via email and continue to wear the smartwatch for the length of the intervention. Postintervention (visit 2) procedures including anthropometric, pubertal, and quality of life assessments, DXA, and upper and lower extremity strength will be repeated after the exercise intervention. Follow-up clinical data including functional class, echocardiographic parameters, brain type natriuretic peptide level, and 6-min walk test distance will be recorded for 6 months after completion of the intervention.

ANTHROPOMETRIC, MUSCULAR, AND FUNCTIONAL ASSESSMENT

These procedures will be performed pre- and postexercise intervention.

Anthropometry and tanner staging

Weight will be measured to the nearest 0.1 kg on a digital scale. Heights and sitting height will be measured to the nearest 0.1 cm with a wall-mounted stadiometer and a

sitting platform without shoes or hair adornments. Leg length will be calculated as height minus sitting height. Pubertal status will be assessed by a Tanner stage self-assessment questionnaire explained to the participant (with or without a parent present) in advance and then completed in private.

Health-related quality of life

The PedsQL questionnaire will be administered to assess physical, emotional, social, and school functioning.[21] A total summary score and physical and psychosocial health subscores will be generated.

DXA-determined measures of lean mass

Body composition will be measured using a Hologic Horizon fan-beam bone densitometer in array mode operating in Apex software on supine participants wearing scrubs to minimize scan variability. A urine pregnancy test will be performed in female participants before DXA. Regional and whole-body measurement of bone mineral content and density, fat mass, fat free mass, lean body mass, percent body fat, and fat distribution will be obtained. Whole body and leg lean mass will be converted to sex- and race-specific *Z*-scores, relative to age using data from >2000 healthy, typically developing children from multiple ethnic groups enrolled in the Bone Mineral Density in Childhood Study,[22,23] a multicenter longitudinal DXA study. Body composition measures are highly correlated with height and pediatric PH patients often have impaired linear growth.[24] Therefore, the whole-body lean mass *Z*-scores will be adjusted for height *Z*-score, and leg lean mass *Z*-scores will be adjusted for leg length *Z*-score.[25]

Measures of muscle strength

Handgrip strength will be measured by the Smedley III Digital Grip Strength hand-held device.[26] The subject will stand upright with arms extended, grip the dynamometer, and exert full force. Three trials will be performed with each hand. Force production (kgf) will be digitally displayed. Dominant and nondominant handgrip strength will be converted to age-, sex-, and race-specific *Z*-scores.[27] Leg strength will be measured with the Biodex Dynamometer.[28] Participants will warm up with 5 min of treadmill walking, if a 6-min walk test was not yet performed that day. For the knee, peak quadriceps muscle torque (ft-lbs) will be measured in knee flexion and extension. Participants will sit with their thighs at an angle of 110° to the trunk. The tested knee will be positioned at 90° flexion, and the mechanical axis of the dynamometer will be aligned with the lateral epicondyle of the knee. The trunk and both thighs will be stabilized with belts for a knee range of motion of 90° (90–0° of flexion). Each participant will perform 10 concentric contractions at 120° (flexion and extension) of both sides, and the highest value will be recorded. For ankle, peak calf muscle torque (ft-lbs) in dorsiflexion and plantar flexion will be measured in triplicate with the foot placed in 20° of plantar flexion, and the highest value recorded. As reference data are not published for lower extremity biodex, only unadjusted values will be reported.

EXERCISE PRESCRIPTION

After the baseline MVPA assessment, personalized exercise schedules will be manually generated by the primary investigator and study team based on MVPA and maximum heart rate on CPET. The weekly schedules for the entire program will be sent to the participant's parent via email. The schedules will aim to sequentially increase average daily MVPA from their baseline MVPA estimate during each of the first 4 weeks for a total increase of 10 min by the end of Week 4. This goal will be sustained or increased for the remaining 12 weeks of the intervention. If the participant is already averaging >20 min of MVPA per day, the schedule will increase gradually from a 20-min baseline. The gradual nature of the intervention with interval goal setting will foster self-efficacy, in line with the key behavioral constructs of Social Cognitive Theory.[29,30]

During the 16-week intervention, participants will be asked to perform aerobic exercise 4 days per week and light resistance exercises 3 days per week, per American College of Sports Medicine, Guidelines for Training and Exercise Prescription.[31] Participants will wear a Polar OH1 armband heart rate monitor while exercising. The heart rate monitor syncs with the ActiGraph via Bluetooth, and heart rate will be visible to the participant on the watch face. Aerobic sessions will start with stretching followed by walking, biking, or light jogging, depending on access to facilities/equipment and weather. For instance, a participant may use a stationary bike, treadmill, recreation center track, or even the stairs or halls in their home. Heart rate goals for aerobic exercise sessions will vary between 50% and 80% maximum CPET heart rate to correspond to the prescribed amount of MVPA. Participants will also be given resistance bands to perform the same light resistance exercises at the same resistance, intensity, and with the same technique learned in the introductory session. These sessions will also begin and end with stretching. Again, ≥75% of the exercises will concentrate on the lower limbs; the

remainder will concentrate on the upper limbs and torso to maintain body habitus. Participants will be advised to avoid exceeding heart rate thresholds.

PHYSICAL ACTIVITY ASSESSMENT

Participants will be asked to wear the smartwatch as much as possible during the intervention, ideally during both waking and sleeping hours. The watch is water-resistant and can be worn while bathing or showering or for any water activity at ≤3 feet of depth and for ≤30 min. The smartwatch will be programmed to record triaxial activity data at a frequency of 30 Hz. Families will be instructed to connect the smartwatch to their home data hub after each exercise session to upload activity and heart rate data to the ActiGraph CentrePoint Version 2 cloud-based database (Figure 2). The older CentrePoint Version 2 is required to upload both activity data and the heart rate data from the paired Polar heart rate monitor. A published activity intensity cutpoint that is available in CentrePoint Version 2 will be applied to the activity data in CentrePoint to determine minutes spent in various levels of activity intensity.[32] Using the Freedson cutpoint, 0–99 counts per minute corresponds to sedentary activity; 100–1951 counts per minute corresponds to light activity; 1952–5724 counts per minute corresponds to moderate activity; and 5725–9498 counts per minute corresponds to vigorous activity. Moderate and vigorous activity will be combined to determine MVPA.

ACTIGRAPH TO REDCAP INTEGRATION

Daily summaries of smartwatch wear time, step counts, vector magnitude counts per minute, time spent in sedentary, light, and moderate to vigorous activity will be transferred from CentrePoint to a Research Electronic Data Capture (REDCap) database via automation using CentrePoint (V2) Application Programming Interface (API) once every 24 h. API pulls will be automated using the R statistical programming language. The REDCapR package will be used to help facilitate the data transfer between the CentrePoint and REDCap APIs.[33] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.[34,35] Any heart

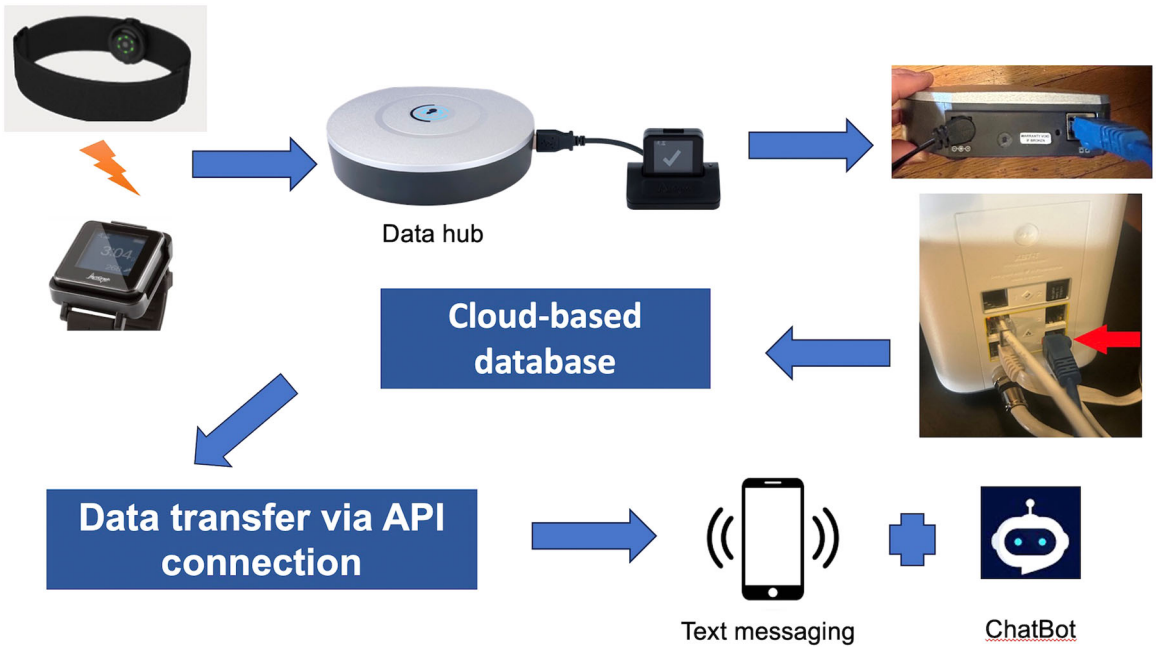

FIGURE 2 Activity tracker and informatics tools. When worn, the heart rate monitor communicates with the smartwatch via Bluetooth, and the participant heart rate is visible on the watch screen. When the watch face is docked and connected to the home data hub (disc shaped object) via a USB port and the hub is connected to the participant's home Wi-Fi modem via an ethernet cord, heart rate and activity data are uploaded to a cloud-based database. Activity intensity cutpoints are applied and daily activity summaries are transferred to the center's database via an automated API connection. Participant feedback can be provided via text messaging. A URL-based ChatBot enables communication between the participant and study team.

rate ≥80% the maximum CPET heart rate will be flagged in CentrePoint and indicated in REDCap. Weekly REDCap reports will be generated from the daily summaries to assess participant progress, ensure participants are not exceeding heart rate goals, and create REDCap logic for messaging participants regarding achievement of weekly goals.

TEXT MESSAGING

REDCap will send up to four types of text messages—wear time/syncing, heart rate, surveys, and goal achievement—to participants using Twilio messaging platform, a third-party cloud communications platform that is integrated within REDCap (Twilio). REDCap uses Twilio's collection of APIs to send Short Message Service (SMS) messages to study participants.[36] If smartwatch wear time is <8 h on a given day or if it has been >24 h since a data sync, REDCap will send a text message to the participant's or parent's cell phone or mobile device to remind the participant to wear the device and upload data or contact the study team with difficulties. If heart rate exceeds 80% CPET maximum, REDCap will message the participant to remind them to adhere to heart rate goals and stay beneath maximum threshold. REDCap will message the participant weekly with a brief survey to report resistance exercise sessions (as resistance activity may be challenging to capture with smartwatch accelerometer) and to report any symptoms with exercise. Selection of red flag symptoms (chest pain, palpitations, presyncope, syncope) will generate a text message alert to the principal investigator. Finally, once a week, participants will receive a brief text message congratulating them on meeting the prior week's study goals or encouraging them to try again the coming week. Our general expectations are that messages will be sent to the parent's cell phone for participants 8–13 years of age and to the participant's cell phone (if they have one) for participants 16–18 years of age. For participants 13–15 years of age, we will decide the best option on a case-by-case basis depending on device access, family preference, and participant maturity level. In all cases, we will keep records of messaging difficulties. If a family does not have access to a mobile device, the alert information will be communicated via phone call to the family home.

MONITORING FOR ADVERSE EVENTS

If participants experience symptoms or adverse events, they will have access to multiple resources to report issues and contact the study team. In addition to the symptom assessment via text messaging, participants can access a simple, rules based ChatBot that can answer some preprogrammed questions and enable the participants to contact the study team directly as needed for urgent scenarios. Participants can text "help" from a mobile device to a fixed phone number and choose from a menu of items regarding exercise prescription, symptoms, smartwatch issues, and more. The ChatBot will alert the study team to contact the participant immediately for urgent scenarios. Screening for adverse events will also occur during weekly telephone calls from the study coordinator to participants.

Study-related safety events requiring hospital evaluation will be reported expeditiously to the Data Safety and Monitoring Board (DSMB) Chair and NHLBI program office within 2 business days of the principal investigator learning of the event.

STATSITICAL ANALYSES

The first aim is to determine the feasibility of the home exercise program. Feasibility will be measured by the number of participants who complete the intervention. We will also keep records on challenges with technology that impact consent or completion of the study. Intervention adherence will be measured by the number of weekly reported exercise sessions, weekly smartwatch syncs, and average daily smartwatch wear time.

The second aim is to assess preliminary estimates of efficacy of the exercise program. The primary outcome of aim 2 is change in MVPA over the course of the intervention. Secondary outcomes of aim 2 are PedsQL quality of life scores, leg lean mass *Z*-score, handgrip *Z*-score, lower extremity strength by biodex, and standard of care 6-min walk distance. Baseline and postintervention variables will be summarized by standard descriptive statistics (mean/standard deviation, median/interquartile range, frequencies/percentages). Linear mixed modeling will be employed to capture changes on average daily MVPA from baseline over the course of the intervention and changes in adherence over time (e.g., initial adoption and subsequent drop off in adherence and decline in MVPA). Paired *t*-tests or Wilcoxon signed rank tests will be conducted to assess within-subject changes in secondary outcomes pre/postintervention. The correlations between MVPA, lean mass *Z*-score, muscle strength, 6-min walk test distance, and quality of life scores pre- and postintervention will be determined toward preliminary exploration of whether change in muscle strength, functional capacity, or quality of life are reflective of change in physical activity. All analyses will be conducted

in SAS 9.4 with two-sided tests of hypotheses and a $p < 0.05$ as the criterion for clinical significance.

Using published data from Zijlstra et al.[3] and assuming a median (IQR) preintervention MVPA of 13.3 (7.5–25) min/day in PH survivors, a sample size of 20 participants can detect a pre/postintervention MVPA difference effect size of 0.7 or higher with at least 80% power and significance level 0.05. In real-world terms, this would translate to a difference of approximately 10 units with an estimated standard deviation of approximately 13. This pilot study will also generate necessary preliminary data on effect of the home exercise intervention on muscle outcomes, exercise performance, and quality of life to power a larger study in the future.

From prior studies in training, we estimate that approximately 20% of participants will fail to complete the intervention and provide a postintervention measurement of MVPA. We will recruit up to 25 patients, to have 20 evaluable participants with primary and secondary outcomes. However, even those who fail to complete the intervention will have serial 6-min walk tests in clinical testing. We will also evaluate the smartwatch wear time and the number of exercise sessions reported while in the program as measures of feasibility in those who fail to complete the intervention. Therefore, we will still obtain useful data from participants who start but do not complete the intervention.

The DSMB will meet via teleconference at least two times per year during the intervention. Review of interim data analyses will occur after 1 year of the trial.

FRAMEWORK FOR FUTURE INTERVENTIONS

Five characteristics of this study provide a framework for future exercise interventions in pediatric PH and other pediatric heart and lung diseases: (1) semistructured exercise prescriptions consistent with ACSM guidelines but tailored to the participant's baseline level of activity and access to resources; (2) gradual nature of the intervention's increase in time spent exercising with interval goal setting fostering self-efficacy; (3) real time monitoring of activity in the home-setting via wearable devices; (4) digital platform enabling communication and feedback between study team and participant; (5) multiple avenues to assess participant safety. While the aims of this nonrandomized pilot study are to test the feasibility and preliminary estimates of efficacy of this intervention, future studies should identify the ideal characteristics of a home exercise program with remote monitoring in pediatric PH. Using frameworks for building and evaluating mobile health interventions such as Multiphase Optimization Strategy (MOST),[37] candidate components can be identified, refined, and confirmed in a standard randomized trial.[38] Eventually, future trials should test whether an increase in physical activity can increase cardiorespiratory fitness and decrease risk of serious events in pediatric PH.

This trial design may introduce bias as families without home internet access are not eligible. At the time of study initiation, there was no wrist-worn ActiGraph smartwatch that measured activity and displayed heart rate, which was necessary to execute the gradual exercise schedules and to monitor participants. The solution was to use the Polar OH1 armband heart rate monitor during planned exercise. When the Polar heart rate monitor and the ActiGraph GT9X Link communicate via Bluetooth, the participant heart rate is visible on the watch screen. However, this prevents also enabling a Bluetooth connection between the smartwatch and an app on a mobile device that would facilitate transfer of data to CentrePoint and REDCap. The data hub is required to transfer raw data via an internet connection.

However, we are confident that this pilot trial experience, coupled with advances in wearable technologies and analysis of activity data, will support more equitable approaches in future trials. Newer multi-sensor devices are anticipated to measure heart rate, sleep, activity, and other biometrics within a single device and sync with mobile applications without needing a data hub. Some devices may even transmit data directly to the cloud via widespread cellular connections, eliminating the need for a mobile app, which would allow any participant to connect from anywhere. These technologies are critical to the widespread delivery of home-based interventions to all interested families.

The API connection established in this pilot study may later enable raw data to be pulled into a computational environment for processing with open-source algorithms such as the "MIMS-unit (Monitor Independent Movement Summary-unit) algorithm."[39] The MIMS-unit algorithm can be applied to large actigraphy data sets such as in the National Health and Nutrition Examination Survey (NHANES) and can enable creation of physical activity percentiles, progressing beyond intensity cutpoints and increasing standardization of data acquisition and analysis.

CONCLUSION

The iTONE trial will explore whether a home exercise intervention, guided by Social Cognitive Theory and enriched by mobile health technology, can increase

physical activity and enhance skeletal muscle quality, leading to better exercise performance, functional status, and quality of life in children and teenagers with PH. This pilot intervention will generate important preliminary data on the effect of exercise interventions in youth with chronic cardiorespiratory conditions to power larger studies in the future.

AUTHOR CONTRIBUTIONS

Catherine M. Avitabile designed the trial and crafted the manuscript. Jena P. Mota, Kiley M. Yeaman, Sybil J. Andrieux, Lara Lechtenberg, Emma Escobar, John Chuo, John Chuo, Shannon M. O'Malley, Elizabeth Ford, and Michael G. McBride provided collaboration in study design and execution and edited the manuscript. Walter Faig provided statistical methods and edited the manuscript. Stephen M. Paridon, Jonathan A. Mitchell, and Babette S. Zemel provided senior mentorship in study design and execution and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Not applicable for the methods paper. The trial is approved by Children's Hospital Institutional Review Board protocol #20-018168.

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