A Mobile Health Intervention in Pulmonary Arterial Hypertension Protocol

Date: 6 August 2019

Version: 4.3

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Confidential Information

Protocol Summary

OBJECTIVES:

The primary objective of this study is to test the feasibility of a mobile health (mHealth) intervention to increase mean daily step counts in patients with pulmonary arterial hypertension (PAH) after 12 weeks.

Secondary objectives include:

- Change from baseline of six minute walk test distance (meters) at week 12.
- Change from baseline of RV free wall longitudinal strain at week 12 (RV Strain).
- Assess the frequency that the daily step target was achieved over 12 weeks (Daily goal attainment).
- Change in minutes of activity per day between week 12 and baseline (Daily aerobic time).
- Change in survey score between week 12 and baseline (emPHasis-10 Quality of Life survey)
- Change in survey score between week 12 and baseline (SF-36 Quality of Life Mental Component Score).
- Change in Borg Dyspnea Score between week 12 and Baseline.
- Change in heart rate between week 12 and Baseline (Resting heart rate).
- Change from baseline insulin resistance at week 12 (HOMA-IR).
- Change from baseline B-type natiurectic peptide level at week 12 (BNP).
- Change in SF-36 score between week 12 and Baseline (SF-36 Physical Component Score).
- Change in minutes between week 12 and baseline in minutes of moderate-vigorous activity.
- Change in fat volume between week 12 and baseline (visceral fat volume).

STUDY DESIGN:

Randomized, single-blinded, parallel group, Phase II study of 50 subjects with PAH. Eligible subjects will be randomly assigned to receive the mHealth intervention or not for twelve weeks.

STUDY POPULATION:

Inclusion criteria:

- Adults aged 18 or older.
- Diagnosed with idiopathic, heritable, or associated (connective tissue disease, drugs, or toxins) pulmonary arterial hypertension (PAH) according to World Health Organization consensus recommendations.
- Stable PAH-specific medication regimen for three months prior to enrollment. Subjects with only a single diuretic adjustment in the prior three months will be included.
- Subjects must own a Bluetooth capable modern smartphone capable of receiving and sending text messages.
- Forced vital capacity >65% predicted with no or minimal interstitial lung disease based on reviews of imaging studies by PI and medical monitor.

Exclusion criteria:

- Prohibited from normal activity due to wheelchair bound status, bed bound status, reliance on a cane/walker, activity-limiting angina, activity-limiting osteoarthritis, or other condition that limits activity.
- Pregnancy
- Diagnosis of PAH etiology other than idiopathic, heritable, or associated
- Functional class IV heart failure
- Requirement of > 1 diuretic adjustment in the prior three months
- Preferred form of activity is not measured by an activity tracker (swimming, yoga, ice skating, stair master, or activities on wheels such as bicycling or rollerblading)

PRIMARY ENDPOINT:

- Change from baseline mean daily step count at week 12.

SECONDARY ENDPOINTS:

- Change from baseline of six minute walk test distance (meters) at week 12.
- Change from baseline of RV free wall longitudinal strain at week 12 (RV Strain).
- Assess the frequency that the daily step target was achieved over 12 weeks (Daily goal attainment).
- Change in minutes of activity per day between week 12 and baseline (Daily aerobic time).
- Change in survey score between week 12 and baseline (emPHasis-10 Quality of Life survey)
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- Change from baseline insulin resistance at week 12 (HOMA-IR).
- Change from baseline B-type natriuretic peptide level at week 12 (BNP).
- Change in SF-36 score between week 12 and Baseline (SF-36 Physical Component Score).
- Change in minutes between week 12 and baseline in minutes of moderate-vigorous activity.
- Change in fat volume between week 12 and baseline (visceral fat volume).

- **OBSERVATIONS:**
- Subjects will be evaluated in person at screening, baseline, 12 weeks.
- Subjects will have telephone follow-ups at 2, 4, 6, 8, and 10 weeks.
- BNP levels, other biomarkers will be assessed at baseline and 12 weeks.
- Subjects will have six minute walk testing at baseline and 12 weeks.
- Subjects will have a transthoracic echocardiogram at baseline and 12 weeks.

- Subjects will have a Dual-Energy X-ray Absorptiometry (DEXA) at baseline and 12 weeks.
- Subjects will answer quality of life questionnaires at baseline and 12 weeks.

SAMPLE SIZE AND POWER:

A total of 50 subjects will be enrolled with 1:1 randomization to either mHealth intervention or no intervention. [redacted]

[redacted]

[redacted]

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ABSTRACT

Patients with pulmonary arterial hypertension (PAH) have impaired exercise capacity and reduced quality of life. Current therapies only modestly improve exercise capacity and are often prohibitively expensive, highlighting the need for additional, cost-effective interventions. [redacted] Moreover, cardiopulmonary rehabilitation is not reimbursed by insurance companies or Medicare in the United States underscoring the need for alternatives to promote physical activity. [redacted]

We propose a randomized trial of step tracking with smart texts versus tracking without smart texts for 12 weeks to increase step counts in 50 men and women with PAH.

1.0 Background & Significance

1.1 Morbidity, mortality, and limitations of medical therapy in pulmonary arterial hypertension.

[redacted]

1.2 Functional impairment and efficacy of exercise.

[redacted]

1.3 Mechanisms of the beneficial effects of physical activity in PAH.

[redacted]

1.4 Mobile health tools to promote behavioral change.

[redacted]

[redacted]

2.0 Objectives and Specific Aims

2.1 Objectives

This is a Phase II, single center, randomized, parallel group trial to demonstrate the efficacy of a mHealth intervention in PAH

2.2 Specific Aims

Primary Aim:

1. To determine whether a mHealth intervention affects mean daily step counts at week 12 in patients with PAH.

Secondary Aims:

- Change from baseline of six minute walk test distance (meters) at week 12.
- Change from baseline of RV free wall longitudinal strain at week 12 (RV Strain).
- Assess the frequency that the daily step target was achieved over 12 weeks (Daily goal attainment).
- Change in minutes of activity per day between week 12 and baseline (Daily aerobic time).
- Change in survey score between week 12 and baseline (emPHasis-10 Quality of Life survey)
- Change in survey score between week 12 and baseline (SF-36 Quality of Life Mental Component Score).
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- Change from baseline B-type natiurectic peptide level at week 12 (BNP).
- Change in SF-36 score between week 12 and Baseline (SF-36 Physical Component Score).
- Change in minutes between week 12 and baseline in minutes of moderate-vigorous activity.
- Change in fat volume between week 12 and baseline (visceral fat volume).

[redacted]

3.0 Screening, Subject Selection, and Randomization

3.1 Recruitment of Study Sample

Patients will be recruited from the Center for Pulmonary Vascular Disease (CPVD) at Vanderbilt University Medical Center. Potentially eligible subjects will be pre-screened and informed about that study to determine if they have an interest in enrolling. After the initial pre-screening, the subject will provide informed consent before any study procedures are performed.

3.2 Inclusion/Exclusion Criteria

Inclusion criteria:

1) Adults (aged 18 or older)
2) Diagnosed with idiopathic, heritable, or associated (connective tissue disease, drugs, or toxins) pulmonary arterial hypertension (PAH) according to World Health Organization consensus recommendations
3) Stable PAH-specific medication regimen for three months prior to enrollment. Subjects with only a single diuretic adjustment in the prior three months will be included
4) Subjects must have a Bluetooth capable modern smartphone capable of receiving and sending text messages and an active data plan. Study staff will provide a temporary smartphone with data plan in the event that a participant is otherwise qualified but does not own a smartphone
5) Forced vital capacity >65% predicted with no or minimal interstitial lung disease based on reviews of imaging studies by PI and medical monitor.

Exclusion criteria:

1) Prohibited from normal activity due to wheelchair bound status, bed bound status, reliance on a cane/walker, activity-limiting angina, activity-limiting osteoarthritis, or other condition
2) Pregnancy
3) Diagnosis of PAH etiology other than idiopathic, heritable, or associated
4) Functional class IV heart failure
5) Requirement of > 1 diuretic adjustment in the prior three months
6) Preferred form of activity is not measured by an activity tracker (swimming, yoga, ice skating, stair master, or activities on wheels such as bicycling or rollerblading)

3.3 Study Arm Assignment, Randomization, and Subject Retention

Participants will be assigned to either the intervention or no intervention arms after the run-in period in a random manner until 25 participants are enrolled into each arm. Permuted block randomization stratified by functional class (I/II vs. III) will be used to ensure approximate balance of treatment groups within each stratum over time. [redacted]

Randomization will be performed in small blocks, which vary in size. Investigators will be unaware of the size or order of the blocks. [redacted]

The group randomization code will be maintained by the research coordinator. The code is to be broken only if knowledge of group assignment for that subject is required to initiate appropriate therapy of an adverse event (AE) or if the safety of the subject is at serious risk without knowledge of the group assignment. The decision to unmask will be made by the PI and the Medical Monitor. The Data Safety Monitoring Board will be notified as soon as possible.

4.0 Study Designs

4.1 Overview

We propose a randomized trial to examine the feasibility of a mHealth intervention to improve step counts in patients with PAH. Subjects will be randomized to step tracking plus smart texts versus tracking with usual activity for 12 weeks.

4.2 Monitoring Device

The Fitbit Charge HR tri-axial accelerometer will be used to continuously gather data on physical activity, heart rate, and sleep. This device provides feedback in units of activity (steps, stairs climbed, activity time, and exercise time) and heart rate (per second when active, per 5 seconds when inactive). [redacted]

4.3 Fitbit Application and Data Management

[redacted]

[redacted]

Our HIPPA compliant texting platform is linked to the Fitbit Application Program Interface. Real time activity data will be transmitted from the subject's smartphone to our mHealth platform via cellular network. Subjects assigned to the texting arm will receive 3 texts/day in sync with their preferred morning, lunch, and evening [redacted]

Subjects in both study arms may receive additional texts during the day for reminders about charging, syncing, and the Fitbit Charge HR. Subjects will receive weekly email reminders about the importance of wearing their device from a secure email address created for this study. Subjects can email this account with study questions. If there is loss of data transmission for a full day, subjects will be emailed with a reminder to wear their device and/or reestablish a connection with their phone. After 3 days of absent data, another email reminder will be sent and the study coordinator will call the subject to determine the cause. If subjects have regularly scheduled clinic visits with their treating physician, they will be counseled not to reveal their group assignment.

4.5 Run-in Period and Step Count Targets

We will use a two-week run-in period, which will improve our ability to identify a true baseline step count and reduce dropout after randomization. Participants will wear the Fitbit Charge 3 HR device 24 hours a day for seven days a week (with the option to remove device during showering or bathing) to determine their baseline daily step count. [redacted]

[redacted]

The initial daily step target Weeks 1-4 for the intervention group will be 20% higher than the run-in baseline value. [redacted] Average daily step counts during Week 4 will be calculated and used to define the target (20% above the Week 4 average) for Weeks 5-8. The daily target for Weeks 9-12 will be calculated in the same manner. New targets will be communicated with patients via text message. If [redacted]

[redacted]

5.0 Data Collection

5.1 Consent

Written consent will be obtained for enrollment from participants. For each consent process, study personnel will discuss over the phone or in person the details of the study, the risks and benefits, and the subject's rights and responsibilities if they choose to participate in the trial and their right to refuse to participate. It will be made clear that their clinical care will not be affected by their decision.

The subject consent process will be conducted either by phone, in person at the Vanderbilt Pulmonary Clinic or at the Vanderbilt Center for Translational and Clinical Research, or by using a REDCap-based electronic consent form. The eConsent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. If the subject chooses to complete the electronic consent through REDCap, then a link will be emailed to the subject. Subject self-initiated accessing of the REDCap consent form may occur via smartphone, computer, or other electronic device. If the subject does not have access to a computer, then a phone consent will be offered. If the subject prefers to have a hard copy of the consent to review instead of an emailed PDF, it will be mailed to the subject.

[redacted]

5.2 Study Visits and Contacts

This study will consist of two visits, baseline and week 12. The baseline and week 12 visits will take approximately 4 hours. The subject will be offered the option of eConsent through a web link to REDCap, or the option of verbal phone consent. Subjects will have the option to be consented in the Pulmonary Vascular Disease Clinic, the Clinical Research Center, or the Vanderbilt Translational and Clinical Cardiovascular Research Center by the PI or a clinical research coordinator [redacted]

5.2.1 *Screening*

At time of initial phone or in-person screening, all subject questions are adequately answered. After consenting, subjects will be mailed or given the Fitbit device and the application will be uploaded to their smartphone. The subject will be asked to continue wearing the device for 14 days and the application password will be concealed during the screening period. The following will be reviewed at time of screening:

- Informed consent
- Review inclusion/exclusion criteria
- Review of medical history
- Demographic data
- Review of current medications
- WHO functional class
- Education on FitBit device

5.2.2 *Study Day – Visit 1 (Baseline)*

Baseline testing will take place over 1 day at the Clinical Research Center. The visit will last approximately 4 hours. Baseline information will be used to characterize the participants and to compare the experimental groups with regards to demographics and other variables. Eligibility criteria will be confirmed prior to randomization to treatment group. The following procedures will be performed:

- Transthoracic Echocardiography
- Six Minute Walk Test
- Dual Energy X-ray Absorptiometry (DEXA)
- Blood collection
- Quality of Life Questionnaires (SF-36 and emPHasis-10)
- Vital signs

- Physical exam
- Interim medical history
- Review current medications

[redacted] The subject will complete the SF36 and emPHasis-10. The investigator or research nurse will take a history/interim history and perform a physical examination including checking vital signs, and review current medications. The subject will perform the six minute walk test. Echocardiography and DXA bone density scan will be performed.

All inclusion/exclusion criteria will be confirmed by an investigator before the subject can be formally randomized. The subject will be randomized to a treatment group using a web-based database.

5.2.3 *Phone Calls (Week -1, 2, 4, 6, 8, 10)*

The research coordinator will call the subject. Symptoms and potential side effects will be assessed and changes in medications will be reviewed and recorded. Study compliance will be assessed and reinforced.

5.2.4 *Study Day – Visit 2 (Week 12)*

All tests done at baseline will be repeated at the Week 12 Visit. The following procedures will be performed:

- Transthoracic Echocardiography
- Six Minute Walk Test
- Dual Energy X-ray Absorptiometry (DEXA)
- Blood collection
- Quality of Life Questionnaires (SF-36 and emPHasis-10)
- Vital signs
- Physical exam
- Review current medications

After fasting research labs have been drawn, the subject will have the opportunity to eat a snack. The subject will complete the SF36 and emPHasis-10. The investigator or research nurse will take a history/interim history and perform a physical examination including checking vital signs, and review current medications. The subject will perform the six minute walk test. Echocardiography and DXA bone density scan will be performed. Subjects will be asked to continue wearing the activity monitor for another 21 days. Subjects who have preferred to receive a money payment as compensation for their participation will be given a prepaid envelope to return the activity monitor 21 days.

5.3 Study Schedule of Endpoints and Procedures

The table below summarizes the study endpoint assessments and procedures.

Table 2. Study Procedures

	Screening	Run-In		Treatment Period								Wash Out
	Week -2 to -4	Week -2	Week -1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 15	Week 17
Visit #				1						2		
Telephone Call #			1		2	3	4	5	6		7	8
Day#	(-14 to -30 days to Study Hour 0)	-14 to -30	-7 to -23	0	14 ± 3	28 ± 3	42 ± 3	56 ± 3	70 ± 3	84 ± 3	105 ± 3	119 ± 3
Informed Consent	X											
Run-In		X	X									
Randomization				X								
Wash-Out											X	
Follow-Up												X
History And Physical Exam				X						X		
Medical History	X			X						X		
Symptom Assessment				X	X	X	X	X	X	X	X	X
Medications	X			X	X	X	X	X	X	X	X	X
Vital Signs				X						X		
Physical Exam				X						X		
WHO Functional Class	X			X						X		
Testing												
Phlebotomy				X						X		

Glucose & Insulin				X						X		
Fatty Acid & Acylcarnitine Profiles				X						X		
NT-proBNP				X						X		
DXA				X						X		
Six Minute Walk Test				X						X		
SF-36, emPHasis-10				X						X		
Echocardiogram				X						X		
Urine Pregnancy Test (women only)	X											
Study Procedures												
Adverse Events					X	X	X	X	X	X		X
Compliance		X	X		X	X	X	X	X	X	X	

6.0 Assessments of Efficacy and Outcome Measures

6.1 Assessments of Efficacy

Primary Outcome Measure(s): Daily Step Count (Time Frame: 12 weeks)

Secondary Outcome Measure(s):
There are several secondary objectives of this study. They include:

- To assess the effect of a mHealth intervention on frequency of daily goal attainment at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on daily aerobic time at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on total daily activity at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on 6MWD at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on Borg Dyspnea Score at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on resting heart rate at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on the SF36 and emPHasis-10 at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on RV free wall longitudinal strain at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on tricuspid annular plane systolic excursion (TAPSE) at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on tricuspid annular velocity (S') at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on HOMA-IR at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on BNP at week 12.

- To assess the effect of a mHealth intervention vs. no intervention on skeletal muscle and fat mass at week 12.
- To assess the effect of a mHealth intervention vs. no intervention on WHO functional classification for PAH at week 12.
- To assess the fidelity of data collection and text transmission of a mHealth intervention over 12 weeks.
- To assess the effect of a mHealth intervention vs. no intervention on patient satisfaction at week 12
- To assess the effect of a mHealth intervention vs. no intervention on dropout rates over 12 weeks.
- To assess the effect of a mHealth intervention vs. no intervention on PAH-related hospitalizations over 12 weeks.
- To assess the effect of a mHealth intervention vs. no intervention on medication regimen escalation/reduction over 12 weeks.
- To assess the effect of a mHealth intervention vs. no intervention on incidence of death over 12 weeks.

6.1.1 *Step Counts and Physical Activity*

Wearable accelerometers can provide accurate measurements of steps and activity in three dimensions.

[redacted]
Step counts and physical activity will be measured using the Fitbit Charge HR monitor, a lightweight device that has a three-axis acceleration sensor, altimeter, vibration motor, and optical heart rate monitor. This device provides feedback in units of activity (steps, stairs climbed, activity time, and exercise time) and heart rate (per second when active, per 5 seconds when inactive[redacted] Step counts will be (1) tracked by the Fitbit Charge HR device, (2) transmitted to the participant's smartphone via Bluetooth, and (3) finally transmitted from the subject's smartphone to our mHealth platform via cellular network.

Subjects will begin wearing the Fitbit on the day of their screening visit and will wear it for the next 17 weeks. Participants will wear the Fitbit Charge HR device 24 hours a day for seven days a week (excluding only bathing/showering and charging), starting on the day after the screening visit and for the next 17 weeks. In addition to absolute step counts, we will assess frequency of goal attainment, daily aerobic time (total time spent walking continuously for > 10 minutes without breaking for > 1 minute), and total daily activity (time spent above 3 metabolic equivalents)

6.2 Secondary Outcome Measures

6.2.1 *Six Minute Walk Distance*

[redacted]

[redacted][9-15].The 6MWT will be performed at baseline and 12 weeks. The subject will be instructed to wear comfortable clothing and shoes. The test will be performed at approximately the same time of day at each visit. In addition, Borg dyspnea Score, oxygen saturation, and heart rate will be recorded at the beginning and conclusion of each test.

6.2.2 *Transthoracic Echocardiographic Measures*

We will assess RV free wall longitudinal strain and other parameters as secondary endpoints via transthoracic echocardiography. [redacted]

[redacted] *Fidelity of Data Collection and Text Transmission*

[redacted]

6.2.4 *The Borg Dyspnea Score*

In order to assess exercise capacity, the Borg score for dyspnea and overall fatigue will be recorded before and after subjects complete the six-minute walk, performed at baseline and week 12. This score is a measure of the physical activity intensity level based on the subject's perceived exertion. Subjects will rate at resting and peak exercise.

6.2.5 *Resting Heart Rate*

Resting heart rate will be monitored regularly using the activity tracking device (per second when active, per 5 seconds when inactive). In addition, subject's heart rate will be measured will be recorded before and after subjects complete the six-minute walk test. This will provide resting and peak exercise heart rate at baseline and week 12.

6.2.6 *Quality of Life Questionnaires (SF36 & emPHasis–10)*

The SF36 is one of the most widely used generic measures of subjective health status. The SF36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical and emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Subjects will complete the SF36 at baseline and each subsequent clinic visit during the therapy phase of the study.

The emPHasis-10 is a pulmonary hypertension-specific questionnaire to assess health related quality of life. It covers breathlessness, fatigue and lack of energy, social restrictions, and concerns regarding effects on patient's significant others, such as family and friends[50]. Each item is scored on a semantic differential six-point scale (0-5), with contrasting adjectives at each end. A total emPHasis-10 score is derived using simple aggregation of the 10 items. emPHasis-10 scores range from 0 to 50, higher scores indicate worse quality of life[50].

6.2.7 *Dual Energy X-ray Absorptiometry (DEXA)*

[redacted] Body composition will be assessed at baseline and 12 weeks for changes in relative lean muscle and body fat mass.

6.2.8 *Blood Biomarkers*

a. Plasma NT-proBNP

[redacted] BNP will be assessed at baseline and 12 weeks.

b. HOMA-IR

Insulin resistance will be quantified using the homeostasic model assessment of insulin resistance (HOMA-IR), which estimates insulin resistance through fasting plasma insulin and glucose ratios, at baseline and 12 weeks.

[redacted]

6.2.9 *WHO Functional Class*

The WHO functional classification for PAH has been modified from the well-known New York Heart Association functional classification. This functional classification is based on symptoms, with Class I being defined by no symptoms, Class II as having mild limitation in physical activity, Class III as having markedly limited physical activity and Class IV as being unable to perform any physical activity. The WHO functional class will be assessed at every visit.

6.2.10 *Other Feasibility Endpoints*

a. Drop Out Rates

[redacted]

6.2.11 *Medication* Regimen *Escalation/Reduction*

[redacted]

Hospitalization for PAH progression or right-sided heart failure

[redacted]

Death

[redacted]

7.0 Statistical Considerations

[redacted]

[redacted]

7.5 Interim Monitoring Guidelines

We have not planned a formal interim analyses for efficacy and therefore there are no stopping rules for efficacy for this trial. This is a Phase II trial which will be useful in supporting future studies of the intervention even if null. This project will have a DSMB who may consider whether to stop the trial or not if there is an increased risk of adverse events or toxicity.

[redacted]

8.0 Study Risks and Discomforts

8.1 Activity Tracking

Digital activity tracking and text messaging do not present any obvious medical risk. Participants will be told that the text messaging system does not substitute interaction with health care providers and cannot address emergency situations. The PI will report in a timely fashion to the IRB any unanticipated problem or major study deviation.

8.2 Echocardiography

There are no risks to this ultrasound procedure aside from minor discomfort related to placement of the ultrasound probe on the chest.

8.3 Venipuncture

The protocol requires patients to have blood drawn for research purposes. The risks of drawing blood are uncommon and may include bleeding, minor infection and bruising. Commonly, having blood drawn is painful, and rarely can lead to infection at the site of the blood draw. The amount of blood drawn is small, and represents an exceedingly small percentage of the amount of the total blood volume and will not represent a significant risk to the patient.

[redacted]

[redacted]

9.0 Quality Control

Design strategies and monitoring activities throughout the study will ensure the integrity and high quality of the data. Design strategies include randomization of treatment assignment and training and certification of personnel. The rigorous monitoring program includes data queries and performance monitoring over the time of the trial.

9.1 Personnel Training

Prior to randomization of the first subject in the study protocol, each site PI will ensure that staff has completed appropriate training and that all documentation including IRB approval (and local IRB approvals, if required) is completed and available. The purpose of training is to ensure that study personnel are carrying out the protocol in a consistent way and are adhering to good clinical practice guidelines. Staff will have current Human Subjects Training Certification on file. Before enrollment begins, study coordinators and research assistants who will perform the outcome assessments will be trained in all procedures, including completion of case-report forms (CRFs).

9.2 Data Quality

The PI and study coordinator will constitute the first line of monitoring of the safety of the human participants. They will perform continuous monitoring of data quality and completion of CRFs. Surveillance for AEs will consist of questioning subjects about potential AEs at every study contact, having subjects report any adverse event to the study team, and having subjects undergo vital sign checks and physical exams during each study visit. The research team will create computer modules to identify discrepancies and incomplete data. These reports are tracked until each problem is resolved and corrected in the database.

All study personnel are required to read the consent form and protocol.

10.0 Data and Safety Monitoring and Reporting

10.1 Consent

Written consent will be obtained for enrollment from participants. For each consent process, study personnel will discuss the details of the study, the risks and benefits, and the subject's rights and responsibilities if they choose to participate in the trial and their right to refuse to participate. It will be made clear that their clinical care will not be affected by their decision. Subjects will be permitted to provide verbal consent over the phone prior to being scheduled for a screening visit. Documentation of verbal consent will be noted. Written consent will be obtained at the screening visit or before.

10.2 Designated Medical Director

[redacted] will serve as the medical director for this trial. [redacted] She will attend weekly meetings with the PI and study personnel. She will be available to discuss adverse events with the PI and respond to safety concerns from subjects or study personnel.

10.3 Monitoring

During bi-weekly phone calls, study personnel will review a checklist of signs or symptoms to detect any evidence of over-exertion or disease progression. Subjects will also be given a list of symptoms with definitions in lay language that may be related to overexertion and will be instructed to contact study personnel if symptoms arise. The list will include questions about excessive breathlessness with exertion, dizziness, presyncope/syncope, excessive fatigue, muscle soreness, increased use of as needed diuretics, orthopnea, and paroxysmal nocturnal dyspnea. Any positive responses will be reviewed with the medical director who will discuss these concerns with the subject to determine whether the symptoms are related to the intervention. If symptoms are likely attributable to the intervention, we will record it as an adverse event and decrease the step count goal to a tolerable level, depending on the severity of the symptoms and the judgement of the medical director. All serious adverse events will be reported to the DSMB, Vanderbilt Institutional Review Board, and NIH as described in Section 10.5.4.

10.4 Data Safety Monitor Board (DSMB)

An independent Data Safety Monitor Board (DSMB) will monitor the trial. The aims of the DSMB are to safeguard the interests of the trial's participants, potential participants, and investigators, to ensure the safety of the trial's interventions, to monitor the trial's overall conduct, and protect the trial's validity and credibility. The DSMB membership consists of 5 individuals. Members have been chosen because of their experience in clinical trials and/or clinical expertise, and have been approved by the PI and the team of Co-Investigators. The members are independent of the trial (e.g., not be involved with the trial in any other way or have any involvement that could impact the trial).The members of the DSMB are [redacted]

10.5 Safety and Adverse Events

10.5.1 *Definitions*

- **Unanticipated Problem (UP**): Any incident, experience, or outcome that meets **all** of the following criteria:
    1. unexpected (in terms of nature, severity, or frequency) given a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and b) the characteristics of the subject population being studied;
    2. related or possibly related to participation in the research *(Possibly related to participation in the research means there is a reasonable possibility that the AE, experience, or outcome may have been caused by the procedures involved in the research*); and
    3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

- **Adverse Event (AE)**: Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:
    - results in study withdrawal
    - is associated with a serious AE
    - is associated with clinical signs or symptoms
    - leads to additional treatment or to further diagnostic tests
    - is considered by the investigator to be of clinical significance

- **Serious Adverse Event (SAE):** Adverse reactions are classified as serious or non-serious. A *serious adverse event* is any AE that is:
  - fatal
  - life-threatening
  - requires or prolongs hospital stay
  - results in persistent or significant disability or incapacity
  - a congenital anomaly or birth defect
  - an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All AEs that do not meet any of the criteria for serious should be regarded as ***non-serious AEs***.

- **Suspected Adverse Reaction:** Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For reporting purposes, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/investigational product and the adverse event.

10.5.2 *Classifying AEs*

Severity

The intensity of the AE is classified according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAEv4.0). Grade refers to the severity (intensity) of the AE:

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

CTCAEv4 Grade 1: **mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4 Grade 2: **moderate**; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv4 Grade 3: **severe** or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: **life-threatening** consequences; urgent intervention is indicated.

CTCAEv4 Grade 5: **death** due to an AE.

In this grading system, severity is not equivalent to seriousness. For example, a SAE would be any event which was life-threatening or disabling (Grade 4) or fatal (Grade 5) or was moderate-severe (Grade 2-3) and required or prolonged hospitalization.

Expectedness

AEs must be assessed as to whether they were expected to occur or were unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label.

Expected: an AE known to be associated with the intervention or condition under study.

OHRP defines an **unexpected AE** as any AE occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and b) other relevant sources of information, such as product labeling and package inserts; or
2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.
3) **Relatedness**

   1) Definite: the AE is clearly related to the research procedures
   2) Probably: the AE is likely related to the research procedures
   3) Possible: the AE may be related to the research procedures
   4) Unlikely: the AE is doubtfully related to the research procedures
   5) Unrelated: the AE is clearly not related to the research procedures

Possibly related to participation in the research: There is a reasonable possibility that the adverse event, experience, or outcome may have been caused by the procedures involved in the research.

For each identified AE, an AE entry on the appropriate form will be completed using the above classifications as soon as possible, updating as necessary. Reporting procedures should be started immediately (within 24 hours) upon learning of a SAE or UP.

10.5.3 *Interpretation of Definitions*

AE and UP Reporting Period
The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 21 days following the last administration of study treatment (week 15 phone call).

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Post-study AE
All unresolved SAEs or AEs that are possibly, probably, or definitely related to the study or study drug should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
Laboratories will not be drawn unless clinically indicated. A clinical laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

AEs and SAEs which do not fall under the expedited reporting procedure requirements will be reported by the investigator to the IRB during yearly renewals and to the DSMB and NHLBI at scheduled or ad hoc meetings upon request. The Investigator/designee should keep originals or photocopies of all relevant documentation, including facsimile confirmations, and file them in the participant's file. The Investigator should ensure that all routine AE(s) are reported to ensure the IRB has accurate data for periodic or annual reporting requirements.

10.5.4 *Expedited Reporting Procedures*

The Investigator should notify the IRB, DSMB and NHLBI, in an expedited manner, of those events listed in the table below related to study participation.

Expedited Reporting Process

The PI will report the following information to the IRB for initial assessment and subsequent reporting will occur as outlined on the table.

- Protocol name and number
- Subject identifiers
- Demographic data
- Nature of the event
- Severity of the event
- Probable relationship (causality) of AE to study procedure
- Date and time of AE onset
- Date and time of AE resolution, if available
- Concomitant medications that the participant was taking for an underlying medical condition or disease and the therapeutic agents used for the treatment of the adverse event
- Clinical assessment of participant conducted at time of SAE/AE
- Results of any laboratory and/or diagnostic procedures, and treatment
- Follow-up plan
- Outcome
- Autopsy findings (if appropriate)

The IRB will communicate to the PI if the event requires revisions to the informed consent form or other measures. The PI will also report any qualifying events to the DSMB and NHLBI as noted in the schedule. The PI will file copies of all correspondence with the IRB in the appropriate section of the Trial Master File or site study regulatory file.

What Event is Reported	Event	By Whom is Event Reported	To Whom is Event Reported	When is Event Reported
Fatal or life threatening unexpected, suspected serious adverse reactions	Event	Investigator	• IRB	Within **24 hours** of initial receipt of information
	IRB determination	IRB	• Investigator	Within **3 business days** of IRB determination
	All events	Investigator IRB	• NHLBI, DSMB	Within **7 calendar days** of investigator's initial receipt of information
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Event	Investigator	• IRB	Within **24 hours** of initial receipt of information
	IRB determination	IRB	• Investigator	Within **3 business days** of IRB determination
	All events	Investigator IRB	• NHLBI, DSMB	Within **15 calendar days** of investigator's initial receipt of information

Unanticipated Problem that is not an SAE	Event	Investigator	• IRB	Within **2 business days** of initial receipt of information
	IRB determination	IRB	• Investigator	Within **3 business days** of IRB determination
	All events	Investigator IRB	• NHLBI, DSMB	Within **14 calendar days** of investigator's initial receipt of information
All Unanticipated Problems	All Events	IRB	• OHRP	Within **30 days** of the IRB's receipt of the report

Other Reportable Events:

The following events are also reportable to the IRB:

- Any AE that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of the research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

10.5.5 *Subject Withdrawal*

A subject has the right to withdraw from the study entirely at any time for any reason without prejudice to future medical care by the investigator or other physician. The investigator also has the right to withdraw subjects from the study in the event of concurrent illness, AEs, or other reasons deemed to be in the subject's best interest.

A subject should be withdrawn from the study if there is:

- Withdrawal of consent
- PI determination that the subject should be withdrawn for safety

In order to preserve the integrity of the intention-to-treat analysis, even if the subject is withdrawn from the treatment portion of the protocol (either due to subject, physician, or investigator decision), it is imperative to continue with the scheduled follow-up assessments both for the safety of the subject and for completeness of data collection.

This will be explained to potential subjects at the time of informed consent. The importance of compliance with study visits will be reinforced throughout the trial.

10.5.6 *Unblinding of Intervention Assignment*

Unblinding of the PI for a specific subject will be considered, prior to the formal study unblinding, only if the following circumstances are met: 1) knowledge of the treatment assignment is required to initiate appropriate therapy for an AE or 2) if the safety of the subject is at serious risk if the treatment is continued without the knowledge of treatment assignment. The decision to unmask will be made by the Investigator and Medical Monitor. The DSMB must be notified of the decision as soon as possible.

11.0 Confidentiality of Study Data

In this study, each patient will be assigned a unique Participant ID number (PID) when his/her demographic and race/ethnicity information is entered for the first time. Follow-up data are subsequently entered as needed when a patient has a clinic visit. The unique PID number remains with each patient permanently and is matched with all new data entered. The PID number and patient identifiers are directly linked in the study database.

The study coordinator will also generate a Global Unique Identifier (GUID) for each subject using a NIH tool client. This is an identifying code assigned to a single research participant so that data can be compiled between research studies without using personally identifiable information (PII), even if the data are collected at different locations or by different studies. The GUID is created using PII (including, current name, legal given name given at birth (first, middle, and last), date of birth, city of birth, state of birth, country of birth, and physical sex at birth). Data including the GUID (without other identifiers) is considered de-identified by the NIH and OHRP. Personal identifying information used to generate the GUID will be erased by the study staff after the GUID is created at the end of the study.

The potential for data sharing has been included in the informed consent. Data releases to investigators for approved research purposes and analyses (after review and approval by the Publications and Presentations Committee and approval by IRB and execution of a Data Use Agreement) will be stripped of identifiers using a “Safe Harbor” approach. If an approved investigator has conducted a separate study in which a shared participant has also consented to the use of a GUID then this will be retained in the data release; however, for all other data releases the GUID will be removed.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Several mechanisms will be in place to maintain confidentiality. All of the data will be reported in aggregate. Each subject in all phases of the study will be assigned a unique study Participant Identification (PID) number to be used on all data forms, study records, and blood samples. A list of patient names and code numbers will be maintained separately in locked file cabinets or on password protected computers. Only the investigators and project staff will have access to this information. No other personally identifiable information will be available. We will also obtain a Certificate of Confidentiality from the NIH for this study before consent of the first patient.

11.1 Privacy/Confidentiality Issues

Consent forms, medical history data, and study data are stored in secured files, either in locked file cabinets or in a locked room separate from medical records and coded such that all subject identifiers have been removed. As an additional precaution all HIPAA regulated information is stored in an electronic file separate from other study data. Only approved study staff (determined by the PI) will be given authorization to access the database. Bio-specimens are processed and labeled with barcode labels that include the subjects electronically generated study code and date of sample collection. The bio-specimens are stored in locked freezers in the study Laboratory; only approved study staff has access to the keys for each freezer. Access to the electronic freezer inventory of the specimens is kept on a secure password protected computer.

[redacted]