HEART CAMP CONNECT: A FEASIBILITY STUDY

NCT05985395

26 DEC 2023

HEART Camp Connect: A Feasibility Study

Protocol Number: 0914-21-FB

National Clinical Trial (NCT) Identified Number: NCT05985395

Principal Investigator: Windy Alonso, PhD, RN

Sponsor: GP IDeA CTR/UNMC

Grant Title: HEART Camp Connect: A Feasibility Study

Grant Number: NA

Funded by: NA

Version Number: v.1

26 December 2023

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Table of Contents

STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: 12/26/2023

Name: Windy Alonso

Title: Assistant Professor

Investigator Contact Information
Affiliation: University of Nebraska Medical Center College of Nursing
Address: 985330 Nebraska Medical Center, Omaha, NE 689198-5330
Telephone: 402-559-8342
Email: windy.alonso@unmc.edu

1 PROTOCOL SUMMARY

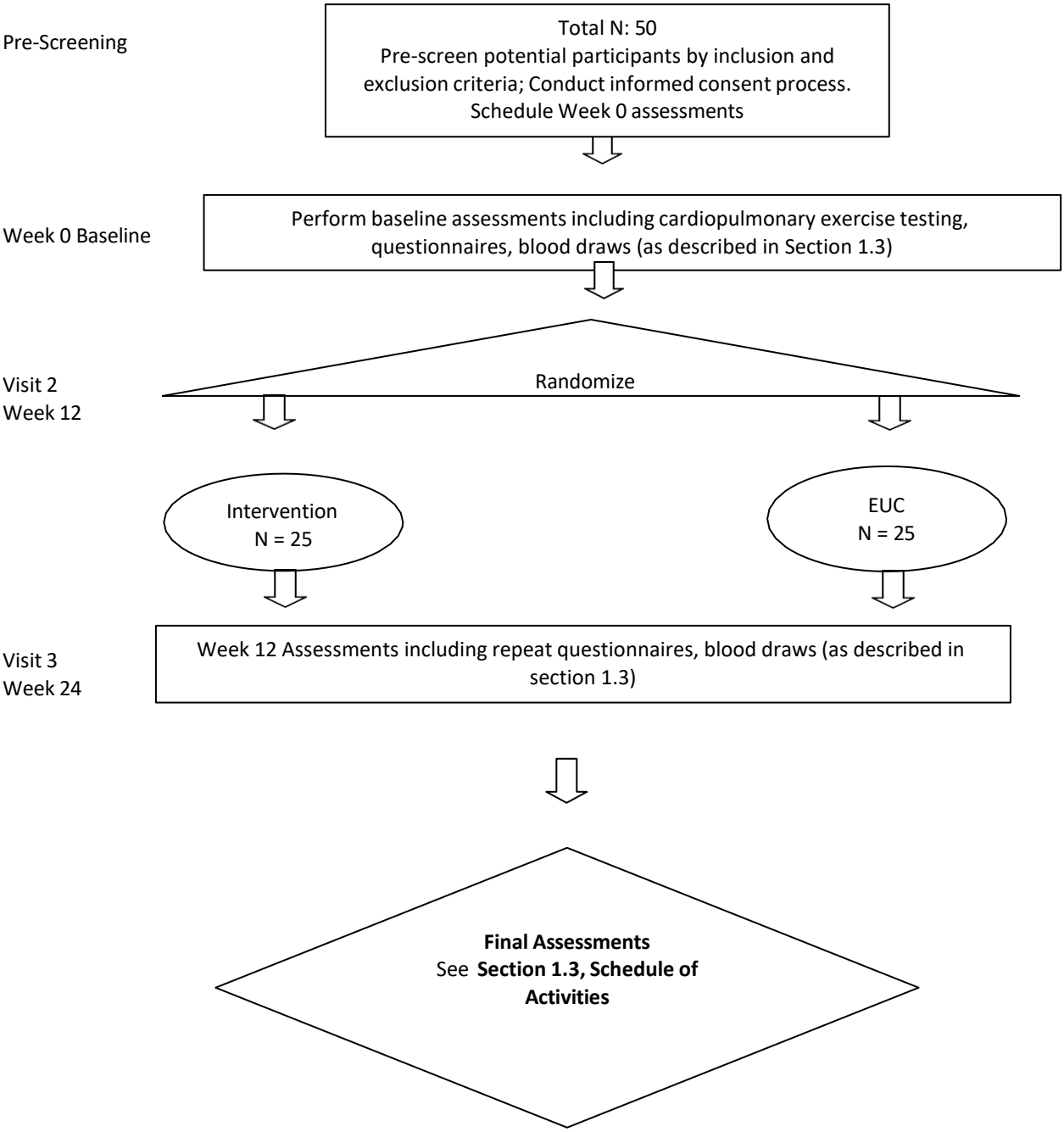
1.1 SYNOPSIS

Title:	HEART Camp Connect: A Feasibility Study
Grant Number:	*NA*
Study Description:	The proposed study uses a technology-facilitated, theory-based intervention to help patients with HFpEF start and continue an exercise program over time. This feasibility, pilot study will give us data to refine the intervention and allow us to gather preliminary data for a competitive application to a federal funder.
Objectives:	Our overall objectives for this study are to: (1) evaluate the feasibility of a virtual, theory based exercise training and coaching intervention in adults with HFpEF; and (2) examine the preliminary effects of this intervention on adherence to exercise, physical function, key inflammatory markers, and patient-reported outcomes.
Endpoints:	Primary Endpoint: 3 months Secondary Endpoints: 6 months
Study Population:	We will enroll 25 participants with heart failure with preserved ejection fraction 19 years of age or older from Nebraska Medicine in Omaha, Nebraska.
Phase:	Feasibility
Description of Sites/Facilities Enrolling Participants:	Single site study, recruiting in the U.S. only at Nebraska Medicine in Omaha, Nebraska
Description of Study Intervention/Experimental Manipulation:	Participants are randomized to enhanced usual care or a 3 month coaching intervention.
Study Duration:	24 months
Participant Duration:	6 months

1.2 SCHEMA

This section should include a diagram or flowchart that provides a quick "snapshot" of the study and ideally is limited to 1 page. Below is an example schematic that shows the level of detail needed to convey an overview of the study design. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). The time point(s) indicated in the schematic should correspond to the time point(s) in ***Section 1.3, Schedule of Activities****, e.g., Visit 1, Day 1; Visit 2, Day 14 ± 7; etc. Although the convention is to call contacts with participants "Visit 1, Visit 2, etc.," participant contacts in which data will be collected remotely without an in-person visit should also be included in this schematic. One alternative is to use the term "Time 1, Time 2, etc.," to accommodate both in-person visits and assessments conducted remotely.*

Study Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Week 0	Visit 2 Week 12	Visit 3 – Final Week 24
EMR Review Eligibility	X			
Informed Consent		X		
Cardiopulmonary exercise test		X		
Demographics		X		
Clinical history		X	X	X
Height & Weight		X	X	X
Randomization		X		
Coaching Intervention*		*	*	*
Adverse Events Reporting		X	X	X
Feasibility Outcome Evaluations				
Recruitment and retention	X	X	X	X
Coach availability	X	X	X	X
Smart device availability	X	X	X	X
Connectivity issues	X	X	X	X
Patient Outcome Evaluation				
Intervention Acceptability				X
Pain Assessment (Brief Pain Inventory)		X	X	X
Quality of Life Questionnaire		X	X	X
Cognition		X	X	X
Health Status		X	X	X
Minutes of Exercise		X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Despite the worldwide acknowledgment of exercise as a beneficial, non-pharmacological therapy for patients with heart failure (HF), many patients, particularly those with heartfailure with preserved ejection fraction (HFpEF), do not engage in regular exercise and are unable to sustain exercise once started in a program. Patients with HFpEF report difficulties finding a routine place to exercise that includes support and accountability delivered near their home as barriers to continued exercise. These challenges are exacerbated by the ongoing COVID-19 pandemic. Therefore, we propose HEART Camp Connect that builds on the previously efficacious HEART Camp intervention. The primary objective of this study is to establish the feasibility and preliminary efficacy of the HEART Camp Connect intervention in patients with heart failure with preserved ejection fraction. We will accomplish this objective with two aims. Aim 1 examines the feasibility of administering HEART Camp Connect to patients with HFpEF. Our feasibility assessment will focus on process (e.g. recruitment rates, retention), resources (e.g. physical capacity, staff availability), management (e.g. data capture and management), and science (e.g. testing psychometrics of tools in the HFpEF population). Aim 2 tests the preliminary effects of HEART Camp Connect compared to enhanced usual care on adherence to exercise, physical activity, function, inflammation, patient-reported outcomes, and our theory-based interventional components. Impact: Exercise benefits patients with HFpEF by reducing morbidity and mortality and improving symptoms and quality of life. The proposed study uses a technology facilitated, theory-based intervention to help patients with HFpEF start and continue an exercise program over time. This feasibility, pilot study will give us data to refine the intervention and allow us to gather preliminary data for a competitive application to a federal funder.

2.2 BACKGROUND

Heart failure with preserved ejection fraction (HFpEF) is a growing public health concern. Over 13 million adults in the world, including 3 million in the U.S., live with severe activity intolerance and poor quality of life associated with HFpEF.1,2 HFpEF is difficult to manage, is quickly surpassing reduced ejection HF as one of the most common causes of hospitalization in the U.S., and is a significant driver of the $30.7 billion annual cost of HF.1 In the last decade, improvements have been made in the treatment of reduced ejection fraction HF and pharmacological therapies are standardized for these patients.3 However, these same therapies tested in HFpEF do not show significant benefits.4SGLT2 inhibitors, initially developed to treat diabetes, have shown promise in recently completed clinical trials, but remain off-label for adults with HFpEF.5,6 Non-pharmacological interventions, such as exercise, show promise in improving physiologic and patient-reported outcomes, but require adherence to behavioral change, which remains a barrier to achieving improved health outcomes.7-9 This study tests the feasibility, acceptability, and preliminary effects of an intervention designed to promote exercise adherence in adults with HFpEF.

Exercise is a promising, non-pharmacological strategy to improve outcomes in adults with HFpEF.10 Outcomes from exercise trials in HF are encouraging, with studies demonstrating exercise as safe and eliciting improved aerobic capacity (peak VO2) and quality of life.11-15However, key gaps in this evidence remain 1. Most studies to date have enrolled adults with HF (HFpEF and HFrEF), including our group's HEART Camp study,16 instead of focusing exclusively on HFpEF. 2. HFpEF trials have inconsistently defined

HFpEF with ejection fractions ranging from 40 to 50% and above. The validated H2FPEF algorithm17 is now available to identify HFpEF which we incorporate into our inclusion/exclusion criteria. 3. Prior exercise interventions tested in HF were not specifically designed to promote adherence using theory-based components. HEART Camp Connect is designed to promote adherence to exercise by supporting the adoption and maintenance of exercise behavior. 4. Adherence is inconsistently defined across studies and often not objectively measured. Several studies use session attendance as a measure of adherence, but this does not allow for examination of dose-response effects or comparison to other clinically meaningful outcomes.18-20

In this study, we monitor coaching session attendance and measure adherence objectively using minutes of moderate intensity exercise from a heart rate monitor. 5. No studies have tested interventional effects on inflammatory biomarkers, despite the known relationship between HFpEF and inflammation.21 This pilotincorporates examination of the impact of exercise on inflammatory biomarkers. 6. Cardiac rehabilitation is the predominate model for exercise in adults with HF, but the program is not specifically designed for adults with HFpEF and current Medicare guidelines do not reimburse attendance .22 Further, exercise is rarely sustained after program completion and programs are often inaccessible. This has resulted in notoriously low attendance at cardiac rehabilitation and subsequent poor long-term adherence to exercise.23-27 Our intervention is delivered virtually making exercise content accessible to participants at any time to improve sustainability.

Adherence is the Achilles heel of exercise in HF. The 2013 ACCF/AHA Guideline for the Management of Heart Failure recommends exercise as a non-pharmacological therapy that is safe and effective for individuals with HF (Class I - Level of Evidence A).10 Yet, studies indicate that as many as 91% of patients with HF do not participate in regular exercise.28-30 Therefore, promoting adherence to exercise in HF, particularly HFpEF, is a major priority for the National Heart Lung and Blood Institute (NHLBI) and the long-term goal of this proposal.31

HFpEF and exercise in HFpEF are assigned a high priority status by the NHLBI. The NHLBI convened two working groups, one addressed exercise as a non-pharmacological treatment for HF (2015)7 and the other (2019)31 identified knowledge gaps and set priorities for HFpEF research in the next 10 years. The HFpEF working group urged the development of effective HFpEF treatment strategies and referred to HFpEF as the greatest unmet need in cardiovascular medicine today. The panels set several priority targets for future study, including: 1. to examine optimal strategies and interventions to promote exercise initiation and adherence; 2. to identify behavioral mechanisms to improve adherence to exercise in HF; and 3. examine longitudinal changes in inflammatory biomarkers to better understand correlates to clinical status in HFpEF.7,31 This proposal addresses these high priority areas by evaluating the feasibility, acceptability and preliminary efficacy of HEART Camp Connect in promoting adherence to exercise, and physical activity and function, inflammatory markers, patient-reported outcomes, and theory-based components in HFpEF.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks associated with this study include those associated with cardiopulmonary exercise testing, venipuncture, exercise, emotional or psychological discomfort while answering questionnaires, and the risk of loss of confidentiality.

Cardiopulmonary exercise testing (CPET):
CPET has been shown to be safe in adults with high-risk cardiovascular diseases including heart failure. (Skalski 2012).However, participants may experience shortness of breath, angina, cardiac arrhythmias, or bronchospasm during CPET. All CPET will be completed in the pulmonary function lab at Nebraska Medicine - Durham Outpatient Center or Oakview Clinic under the supervision of a physician or advanced practice provider that has been trained in advanced cardiac life support (ACLS). Participants will walk on a treadmill or pedal a stationary bike for the test.

Blood draws:
Participants are at risk for pain, discomfort or infection at the venipuncture site.
Exercise: Exercise training may have an associated risk of cardiac arrhythmias, blood pressure disturbances, fatigue, muscle, and joint discomfort, and ultimately death. Exercise training in stable chronic HF patients has been shown to be safe in clinical trials and became part of the recommended Heart Failure Society of America guideline of evidence-based care in 2010.

Emotional/Psychological Discomfort:
Participants may experience fatigue, emotional or psychological discomfort when completing study questionnaires.

Loss of Confidentiality:
There is a risk of a loss of participant confidentiality. We have taken measures as outlined above to minimize this risk to the greatest extent possible. Although reasonable efforts have been taken, confidentiality cannot be guaranteed since research data will be transmitted electronically to REDCap.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may benefits from exercise although benefits are not guaranteed.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Minimization of Risk of CPET:
Risk of CPET is minimized with testing completed under the supervision of a physician or advanced practice provider trained to recognize adverse events and in initiating an ACLS protocol. Safeguards are in place to protect patients before and during testing. At both testing sites, prior to beginning the test, a technician will measure vital signs - including heart rate and blood pressure - to ensure normal pre-test values. Abnormal values will result in the test being rescheduled. During testing, the technician will stand within 2 feet of the patient at all times to "spot" them in case of an adverse event. All patients wear a gait belt during testing to support the patient if needed during an emergency. The treadmill is

equipped with an emergency stop button that can be pushed if needed during the test. A second stop button is attached to a wristband worn by the patient that would be pulled if the patient were to fall or stumble. The bike is powered by the patient so if the patient is in distress and stops pedaling, the bike stops. Patients are monitored throughout the testing with an EKG and frequent blood pressure readings. We will follow Nebraska Medicine policy in the event of an adverse event during testing. If the patient were to suffer a cardiac arrest during testing, the code cart is readily available and ACLS would be initiated by the supervising provider. Security would be notified and the hospital-based code team would be alerted to respond. If testing is completed at the Oakview clinic, security would notify the rapid response team who would respond.

Minimization of Risk of Blood Draws:
To mitigate the risk of infection or discomfort at the venipuncture site, we will attempt to coordinate study-related venipuncture with that needed for clinical care as much as possible. In addition, blood will be collected at an outpatient laboratory center at Nebraska Medicine by a certified phlebotomist.

Minimization of Risk of Psychological Discomfort:
We advise all participants that they are under no obligation to respond to our questions and may decline to answer or stop at any time. Should a participant experience fatigue, we will allow them to take a break and continue or schedule another time within the next 48 hours to complete remaining questionnaires. If a subject responds to the symptom questionnaires that they have often or always felt depressed and/or hopeless in the past 7 days the researchers will refer them to their Primary Care Provider and provide a list of mental health resources including the Boys Town Grief Hotline. If upon questioning as to whether they have any plans to hurt themselves, they respond with a "yes" they will be immediately escorted to the Emergency Department or 9-1-1 will be contacted on their behalf.

Minimization of Risk of Exercise:
All participants will have successfully completed a cardiopulmonary exercise test (CPET). The results from the CPET will be used to develop an individualized exercise prescription for each participant that will guide heart rate parameters during exercise. Participants will be taught to monitor the intensity of their exercise by using heart rate and the rating of perceived exertion from their participation in our study orientation. We reduce the risk of exercising at home by requiring that another adult be present during the exercise in the event a subject experiences an adverse event requiring medical attention. The other adult will be instructed to contact the provider if the participant experiences a non-emergent adverse event or initiate local EMS, in the event of an emergency. The other adult will be instructed to then follow the instructions of the dispatcher. A list of potential adverse events that would warrant a call to a provider or EMS was attached to the application and will be shared with all participants. It is important to note that 150 minutes of moderate-intensity exercise is recommended for these patients and HFpEF patients are not eligible for cardiac rehabilitation. If these patients were not participating in this study, they could be doing this exercise on their own without the guidance that results from participating in this study.

Minimization of Risk of Loss of Confidentiality:
To protect against possible risks to confidentiality, research data will be stored in a locked

cabinet in the research office of the PI. Subjects' names and other contact information (phone and emails if available) will be kept in a locked file accessible only by the PI. The contact information is needed in order to schedule study-related activities. All records will be coded with study identification numbers and kept in locked files in a locked research office. All downloaded files from the server will be kept on the hard drive of the principal investigator's computer, which is password-protected, and housed in PI's research office. All study personnel will be CITI trained. Study personnel will be involved in meetings and training sessions regarding data collection procedures in which procedures to ensure confidentiality will be covered.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assessment of Feasibility & Acceptability	Process, resources, procedures, data management, fidelity, acceptability	*Needed to refine intervention for future testing*
Secondary		
Preliminary effects on exercise	Minutes of exercise/week	*We are not statistically powered to test for an effect*
Tertiary/Exploratory		
Preliminary effects on symptoms & interventional strategies	Symptoms, quality of life, interventional mechanisms	Evaluate symptoms and intervention strategies

4 STUDY DESIGN

4.1 OVERALL DESIGN

Single-site feasibility randomized controlled trial/pilot study

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We need to test our planned strategies to support a larger trial.

4.3 JUSTIFICATION FOR INTERVENTION

Adults with heart failure are recommended exercise as part of their plan of care; however, few do and in large part because they do not know how to get started. Our study helps to initiate exercise and sustain it over time.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 24 week follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. *Diagnosis of heart failure with an ejection fraction greater than or equal to 50*
2. *Age greater than or equal to 19 years old*
3. *English-speaking*
4. *Echocardiogram in prior 24 months*
5. *Stable pharmacologic therapy in past 30 days*
6. *Score greater than or equal to 6 on the H2FPEF algorithm or hemodynamic evidence of HFpEF (i.e., elevated pulmonary wedge pressure)*

5.2 EXCLUSION CRITERIA

1. Life-limiting illness precluding study completion
2. Clinical evidence of decompensated heart failure
3. Unstable angina or marked shortness of breath on exertion at less than 2 metabolic equivalents
4. Myocardial infarction, coronary artery bypass graft, or biventricular pacemaker in prior 6 weeks
5. Orthopedic or neuromuscular disorders preventing aerobic exercise
6. Cardiopulmonary exercise test results that preclude safe exercise
7. Unwilling/unable to complete pre-randomization procedures
8. Pregnancy
9. Implantable cardioverter defibrillator

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Study personnel will coordinate all recruitment and enrollment from Nebraska Medicine (NM). Inclusion/exclusion criteria are listed above. Potential participants will be approached in our HFpEF Optimize Clinic or in the Home Instead Center for Successful Aging Gerontology clinics. As a secondary recruitment strategy, we will use the UNMC/NM Opt-in database. Informed consent will be completed using the UNMC RSS e-consent portal or in-person on paper depending on the participant's preference by study personnel. More detail about screening, recruitment, and consent is provided in subsequent sections.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.1.1 STUDY INTERVENTION

The HEART Camp Connect intervention is founded in social-cognitive theory46 and the future-oriented motivation and self-regulation model proposed by Miller and Brickman.47 HEART Camp Connect (n=25) includes weekly virtual coaching sessions with experienced coaches from Engage. For 3 weeks per month, coaches and participants meet 1-on-1 via videoconference to review heart rate data, exercise diaries from the prior week and initiate discussion related to behavioral change mechanisms. One week per month HEART Camp Connect participants will be assigned to a small group (1 coach:5 participants) exercise/observation session. During these sessions, coaches will demonstrate exercises and observe participants via videoconference for proper form and real-time encouragement in a group setting. Coaches will call any HEART Camp Connect participant that fails to

attend their scheduled weekly coaching session for 2 consecutive weeks. Participants achieving a minimum of 120 minutes of moderate-intensity exercise per week on average weeks 1-12 will be given the option to opt-out of coaching sessions for weeks 13-16. We recognize that this could potentially create variation in the dose of the coaching and therefore, will closely monitor the minutes of coaching per participant throughout the study. We will also closely monitor adherence during this time. Participants that relapse (become non-adherent for 2 consecutive weeks) for any reason (e.g., hospitalization, loss of motivation) will return to weekly coaching for the remainder of the intervention. Testing optional coaching is part of our feasibility assessment and increases the future scalability of this intervention. In the sustainability period (Weeks 17-24), weekly coaching stops, and HEART Camp Connect participants are expected to self-regulate exercise and maintain adherence.

6.1.2 ADMINISTRATION AND/OR DOSING

The intervention is delivered by trained exercise coaches.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will test coach and research personnel training as part of our feasibility objective.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants are randomized to intervention or usual care using a random number generator in a 1:1 intervention to control fashion. Due to funding restraints we are not using blinded date collectors for this pilot feasibility study.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Adherence to exercise is a secondary outcome.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

If patients are unable to safely complete the CPET or if their CPET results indicate they exceed our thresholds for cardiorespiratory fitness, they will be immediately withdrawn from the study. If the patient withdraws consent, the patient will be removed from the research study..

When a subject discontinues from HEART Camp Connect but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
-

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit <specify time frame>, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Data monitoring will occur on an ongoing basis, weekly at a minimum, and in the event of
Any adverse event the Data Safety monitor will be notified.

8.2 SAFETY ASSESSMENTS

Cardiopulmonary exercise testing is used a baseline safety evaluation.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

The study will be stopped if any adverse events result in the necessity for emergency care.
These events will be reported immediately to the IRB and closely investigated by study

personnel. If any death occurs as the result of exercise or within 3 hours of an exercise session, the study will be stopped.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to

concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in heart failure will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

[The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

<Insert role or name> will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The study will be stopped if any adverse events result in the necessity for emergency care. These events will be reported immediately to the IRB and closely investigated by study personnel. If any death occurs as the result of exercise or within 3 hours of an exercise session, the study will be stopped.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

There are no interventions that are likely to be of risk to a fetus. Pregnancy is unlikely in our patient population.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within <insert timeline in accordance with policy> of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within <insert timeline in accordance with policy> of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

We do not have a separate statistical plan for this pilot study.

- Primary Endpoint(s): Feasibility and acceptability

- Secondary Endpoint(s): Exercise, symptoms, quality of life

9.2 SAMPLE SIZE DETERMINATION

Sample size was determined on the basis of what we expect to recruit vs. a formal power calculation given the pilot nature of this study.

9.3 POPULATIONS FOR ANALYSES

We will not be completing inferential analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will report descriptive statistics including counts, proportions, and means only.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

- *We will describe feasibility and acceptability.*

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Descriptive statistics will be calculated as appropriate.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will compare groups on baseline statistics.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent will be documented in a private room or over the phone taking into account the participants' preferences.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided

by the suspending or terminating party to <study participants, investigator, funding agency, and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to

share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at REDCap. After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of Nebraska, for use by other researchers including those outside of the study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Windy Alonso, PhD, RN	*Bunny Pozehl, PhD, APRN*
UNMC College of Nursing	*UNMC College of Nursing*
985330 Nebraska Medical Center	*985330 Nebraska Medical Center*
402-559-8342	402-559-8413
Windy.alonso@unmc.edu	*bpozehl@unmc.edu*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB)/Safety Monitoring Committee (SMC) composed of individuals with the appropriate expertise.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

This is single site study

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Data will be collected and managed in REDCap.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the

formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.]

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within <specify number> working days of identification of the protocol deviation, or within <specify number> working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to <specify NIH Institute or Center (IC)> Program Official and <specify Data Coordinating Center or sponsor>. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of

the primary endpoint by contacting <specify person or awardee institution, or name of data repository>. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Great Plains IDeA CTR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption

IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
NA			

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE).

References

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: A report from the American Heart Association. Circulation. 2021;143(8):e254-e743. Accessed Apr 25, 2021. doi: 10.1161/CIR.0000000000000950.

2. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-1847. Accessed Oct 30, 2019. doi: 10.1093/eurheartj/ehs104.

3. Hsu JJ, Ziaeian B, Fonarow GC. Heart failure with mid-range (borderline) ejection fraction: Clinical implications and future directions. JACC. Heart failure. 2017;5(11):763-771. https://www.ncbi.nlm.nih.gov/pubmed/29032140. doi: 10.1016/j.jchf.2017.06.013.

4. Kjeldsen SE, von Lueder TG, Smiseth OA, et al. Medical therapies for heart failure with preserved ejection fraction. Hypertension. 2020;75(1):23-32. Accessed Apr 22, 2021. doi: 10.1161/HYPERTENSIONAHA.119.14057.

5. Williams DM, Evans M. Dapagliflozin for heart failure with preserved ejection fraction: Will the DELIVER study deliver? Diabetes Ther. 2020;11(10):2207-2219. Accessed Apr 22, 2021. doi: 10.1007/s13300-020-00911-0.

6. Anker SD, Butler J, Filippatos G, et al. Baseline characteristics of patients with heart

failure with preserved ejection fraction in the EMPEROR-preserved trial. Eur J Heart Fail. 2020;22(12):2383-2392. Accessed Apr 27, 2021. doi: 10.1002/ejhf.2064.

7. Fleg JL, Cooper LS, Borlaug BA, et al. Exercise training as therapy for heart failure: Current status and future directions. Circ Heart Fail. 2015;8(1):209-220. Accessed May 19, 2020. doi: 10.1161/CIRCHEARTFAILURE.113.001420.

8. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: A meta-analysis of randomized control trials. Circ Heart Fail. 2015;8(1):33-40. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4792111/. Accessed Apr 25, 2021. doi: 10.1161/CIRCHEARTFAILURE.114.001615.

9. Pandey A, Kitzman DW. Searching for the optimal exercise training regimen in heart failure with preserved ejection fraction. JAMA. 2021;325(6):537-539. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=148673493&login.asp%3fcustid%3ds5794986&site=ehost-live&scope=site&custid=s5794986. doi: 10.1001/jama.2020.26347.

10. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776-803. Accessed Dec 18, 2019. doi: 10.1016/j.jacc.2017.04.025.

11. Brubaker PH, Avis T, Rejeski WJ, Mihalko SE, Tucker WJ, Kitzman DW. Exercise training effects on the relationship of physical function and health-related quality of life among older heart failure patients with preserved ejection fraction. J Cardiopulm Rehabil Prev. 2020;40(6):427-433. Accessed Apr 25, 2021. doi: 10.1097/HCR.0000000000000507.

12. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart

failure with preserved ejection fraction: A randomized clinical trial. JAMA. 2016;315(1):36-46. Accessed Apr 25, 2021. doi: 10.1001/jama.2015.17346.

13. Maldonado-Martín S, Brubaker PH, Eggebeen J, Stewart KP, Kitzman DW. Association between 6-minute walk test distance and objective variables of functional capacity after exercise training in elderly heart failure patients with preserved ejection fraction: A randomized exercise trial. Arch Phys Med Rehabil. 2017;98(3):600-603. Accessed Apr 25, 2021. doi: 10.1016/j.apmr.2016.08.481.

14. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. Highintensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: A pilot study. J Appl Physiol (1985). 2015;119(6):753-758. Accessed Apr 25, 2021. doi: 10.1152/japplphysiol.00518.2014.

15. Edelmann F, Gelbrich G, Düngen H, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: Results of the ex-DHF (exercise training in diastolic heart failure) pilot study. J Am Coll Cardiol. 2011;58(17):1780-1791. Accessed Apr 25, 2021. doi: 10.1016/j.jacc.2011.06.054.

16. Pozehl BJ, McGuire R, Duncan K, et al. Effects of the HEART camp trial on adherence to exercise in patients with heart failure. J Card Fail. 2018;24(10):654-660. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197231/. Accessed May 19, 2020. doi: 10.1016/j.cardfail.2018.06.007.

17. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidencebased approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018;138(9):861-870. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202181/. Accessed Dec 9, 2020. doi: 10.1161/CIRCULATIONAHA.118.034646.

18. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients

hospitalized for heart failure. New England Journal of Medicine. 2021;0(0):null. https://doi.org/10.1056/NEJMoa2026141. Accessed Jul 8, 2021. doi: 10.1056/NEJMoa2026141.

19. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: A randomized clinical trial. JAMA. 2021;325(6):542-551. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=148673507&login.asp%3fcustid%3ds5794986&site=ehostlive&scope=site&custid=s5794986. doi: 10.1001/jama.2020.26812.

20. Mentz RJ, Whellan DJ, Reeves GR, et al. Rehabilitation intervention in older patients with acute Heart Failure with Preserved versus reduced Ejection Fraction. JACC Heart Fail. 2021. Accessed Jul 22, 2021. doi: 10.1016/j.jchf.2021.05.007.

21. Glezeva N, Baugh JA. Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target. Heart Fail Rev. 2014;19(5):681-694. Accessed Nov 17, 2021. doi: 10.1007/s10741-013-9405-8.

22. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602. Accessed Jan 2, 2020. doi: 10.1038/nrcardio.2017.65.

23. Park LG, Schopfer DW, Zhang N, Shen H, Whooley MA. Participation in cardiac rehabilitation among patients with heart failure. J Card Fail. 2017;23(5):427-431. Accessed May 19, 2020. doi: 10.1016/j.cardfail.2017.02.003.

24. Ritchey MD, Maresh S, McNeely J, et al. Tracking cardiac rehabilitation participation and completion among medicare beneficiaries to inform the efforts of a national initiative. Circ Cardiovasc Qual Outcomes. 2020;13(1):e005902. Accessed Apr 25, 2021. doi:

10.1161/CIRCOUTCOMES.119.005902.

25. Oosenbrug E, Marinho RP, Zhang J, et al. Sex differences in cardiac rehabilitation adherence: A meta-analysis. Can J Cardiol. 2016;32(11):1316-1324. Accessed May 19, 2020. doi: 10.1016/j.cjca.2016.01.036.

26. Conraads VM, Deaton C, Piotrowicz E, et al. Adherence of heart failure patients to exercise: Barriers and possible solutions. European Journal of Heart Failure. 2012;14(5):451-458. https://onlinelibrary.wiley.com/doi/abs/10.1093/eurjhf/hfs048. Accessed May 19, 2020. doi: 10.1093/eurjhf/hfs048.

27. Pandey A, Keshvani N, Zhong L, et al. Temporal trends and factors associated with cardiac rehabilitation participation among Medicare beneficiaries with Heart Failure. JACC Heart Fail. 2021. Accessed May 27, 2021. doi: 10.1016/j.jchf.2021.02.006.

28. van der Wal, Martje H. L., van Veldhuisen DJ, Veeger, Nic J. G. M., Rutten FH, Jaarsma T. Compliance with non-pharmacological recommendations and outcome in heart failure patients. Eur Heart J. 2010;31(12):1486-1493. Accessed Apr 25, 2021. doi: 10.1093/eurheartj/ehq091.

29. Evangelista L, Doering LV, Dracup K, Westlake C, Hamilton M, Fonarow GC. Compliance behaviors of elderly patients with advanced heart failure. J Cardiovasc Nurs. 2003;18(3):197-208. Accessed May 19, 2020. doi: 10.1097/00005082-200307000-00005.

30. Gary R. Exercise self-efficacy in older women with diastolic heart failure: Results of a walking program and education intervention. J Gerontol Nurs. 2006;32(7):31-41. Accessed Apr 25, 2021. doi: 10.3928/00989134-20060701-05.

31. Shah SJ, Borlaug BA, Kitzman DW, et al. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute working group summary. Circulation. 2020;141(12):1001-1026. Accessed Dec 7, 2020. doi:

10.1161/CIRCULATIONAHA.119.041886.

32. Warehime S, Dinkel D, Alonso W, Pozehl B. Long-term exercise adherence in patients with heart failure: A qualitative study. Heart Lung. 2020;49(6):696-701. Accessed Mar 17, 2021. doi: 10.1016/j.hrtlng.2020.08.016.

33. Norman JF, Kupzyk KA, Artinian NT, et al. The influence of the HEART camp intervention on physical function, health-related quality of life, depression, anxiety and fatigue in patients with heart failure. Eur J Cardiovasc Nurs. 2020;19(1):64-73. Accessed Mar 17, 2021. doi: 10.1177/1474515119867444.

34. Alonso WW, Kupzyk K, Norman J, et al. Negative attitudes, self-efficacy, and relapse management mediate long-term adherence to exercise in patients with heart failure. Ann Behav Med. 2021. Accessed Mar 17, 2021. doi: 10.1093/abm/kaab002.

35. Alonso WW, Kupzyk KA, Norman JF, et al. The HEART camp exercise intervention improves exercise adherence, physical function, and patient-reported outcomes in adults with preserved ejection fraction heart failure. J Card Fail. 2021. Accessed Oct 1, 2021. doi: 10.1016/j.cardfail.2021.09.003.

36. National Institutes of Health. Policy on good clinical practice training for NIH awardees involved in NIH-funded clinical trials. https://grants.nih.gov/grants/guide/notice-files/NOTOD-16-148.html. Updated 2016.

37. Sueta D, Yamamoto E, Nishihara T, et al. H2FPEF score as a prognostic value in HFpEF patients. Am J Hypertens. 2019;32(11):1082-1090. Accessed Dec 9, 2020. doi: 10.1093/ajh/hpz108.

38. Suzuki S, Kaikita K, Yamamoto E, et al. H2FPEF score for predicting future heart failure in stable outpatients with cardiovascular risk factors. ESC Heart Failure. 2020;7(1):65-74. https://onlinelibrary.wiley.com/doi/abs/10.1002/ehf2.12570. doi: 10.1002/ehf2.12570.

39. Pozehl BJ, Mcguire R, Duncan K, et al. Accelerometer-measured daily activity levels and related factors in patients with heart failure. J Cardiovasc Nurs. 2018;33(4):329-335.

Accessed Apr 25, 2021. doi: 10.1097/JCN.0000000000000464.

40. Thompson PD, Arena R, Riebe D, Pescatello LS, American College of Sports Medicine.

ACSM's new preparticipation health screening recommendations from ACSM's guidelines

for exercise testing and prescription, ninth edition. Curr Sports Med Rep.

2013;12(4):215-217. doi: 10.1249/JSR.0b013e31829a68cf [doi].

41. Keteyian SJ. Exercise training in congestive heart failure: Risks and benefits. Prog

Cardiovasc Dis. 2011;53(6):419-428. Accessed Apr 25, 2021. doi:

10.1016/j.pcad.2011.02.005.

42. Maldonado-Martín S, Brubaker PH, Ozemek C, Jayo-Montoya JA, Becton JT, Kitzman

DW. Impact of b-blockers on heart rate and oxygen uptake during exercise and recovery in

older patients with heart failure with preserved ejection fraction. J Cardiopulm Rehabil Prev.

2020;40(3):174-177. Accessed May 25, 2021. doi: 10.1097/HCR.0000000000000459.

43. Thompson LE, Bekelman DB, Allen LA, Peterson PN. Patient-reported outcomes in

heart failure: Existing measures and future uses. Curr Heart Fail Rep. 2015;12(3):236-246.

Accessed Dec 7, 2020. doi: 10.1007/s11897-015-0253-9.

44. McGuire R, Duncan K, Pozehl B. Incorporating intervention fidelity components into

randomized controlled trials promoting exercise adherence in heart failure patients. Res

Nurs Health. 2019;42(4):306-316. Accessed Apr 25, 2021. doi: 10.1002/nur.21949.

45. Borg G. Borg's perceived exertion and pain scales. Champaign, IL: Human Kinetics.;

1998.

46. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. Psychol Rev.

1977;84(2):191-215. Accessed Nov 21, 2017.

47. Miller RB, Brickman SJ. A model of future-oriented motivation and self-regulation. Educational Psychology Review. 2004;16(1):9-33. Accessed Apr 22, 2021. doi: 10.1023/B:EDPR.0000012343.96370.39.

48. Tromp J, Khan MAF, Klip IT, et al. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. J Am Heart Assoc. 2017;6(4). Accessed Dec 20, 2019. doi: 10.1161/JAHA.116.003989.

49. Tromp J, Westenbrink BD, Ouwerkerk W, et al. Identifying pathophysiological mechanisms in heart failure With Reduced versus preserved Ejection Fraction. J Am Coll Cardiol. 2018;72(10):1081-1090. Accessed Dec 9, 2019. doi: 10.1016/j.jacc.2018.06.050.

50. Sanders-van Wijk S, Tromp J, Beussink-Nelson L, et al. Proteomic evaluation of the comorbidity-inflammation paradigm in heart failure with preserved ejection fraction: Results from the PROMIS-HFpEF study. Circulation. 2020;142(21):2029-2044. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=147158347&login.asp%3fcustid%3ds5794986&site=ehost-live&scope=site&custid=s5794986. doi: 10.1161/CIRCULATIONAHA.120.045810.

51. Vijayaraghava A, K R. Alteration of interferon gamma (IFN-g) in human plasma with graded physical activity. Journal of clinical and diagnostic research. 2014;8(6):BC05-BC07. https://www.ncbi.nlm.nih.gov/pubmed/25120968. doi: 10.7860/JCDR/2014/9502.4440.

52. Zheng G, Qiu P, Xia R, et al. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: A systematic review and meta-analysis of randomized controlled trials. Frontiers in aging neuroscience. 2019;11:98. https://www.ncbi.nlm.nih.gov/pubmed/31080412. doi: 10.3389/fnagi.2019.00098.

53. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly

persons: MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci. 2000;55(12):709. Accessed May 25, 2021. doi: 10.1093/gerona/55.12.m709.

54. Cooper LB, Mentz RJ, Sun J, et al. Psychosocial factors, exercise adherence, and outcomes in heart failure patients: Insights from heart failure: A controlled trial investigating outcomes of exercise training (HF-ACTION). Circulation. Heart failure. 2015;8(6):1044. http://www.ncbi.nlm.nih.gov/pubmed/26578668.

55. Rosenberg-Hasson Y, Hansmann L, Liedtke M, Herschmann I, Maecker HT. Effects of serum and plasma matrices on multiplex immunoassays. Immunol Res. 2014;58(0):224-233. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332596/. Accessed May 25, 2021. doi: 10.1007/s12026-014-8491-6.

56. Tromp J, Westenbrink BD, Ouwerkerk W, et al. Identifying pathophysiological mechanisms in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. 2018;72(10):1081-1090. doi: S0735-1097(18)35407-X [pii].

57. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the american heart association. Circulation. 2010;122(2):191-225. Accessed Nov 17, 2021. doi: 10.1161/CIR.0b013e3181e52e69.

58. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Little, Brown, & Co.; 1994.

59. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-1255. Accessed May 15, 2019.

60. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: A comparison of methods. Am Heart J. 2005;150(4):707-715. Accessed Dec

12, 2019. doi: 10.1016/j.ahj.2004.12.010.

61. John A. Spertus, Philip G. Jones, John Kim, Denise Globe. Validity, reliability, and responsiveness of the kansas city cardiomyopathy questionnaire in anemic heart failure patients. Qual Life Res. 2008;17(2):291-298. http://www.jstor.org/stable/40212658. doi: 10.1007/s11136-007-9302-5.

62. Ruo B, Choi SW, Baker DW, Grady KL, Cella D. Development and validation of a computer adaptive test for Measuring dyspnea in heart failure. Journal of Cardiac Failure. 2010;16(8):659-668. http://www.sciencedirect.com/science/article/pii/S1071916410000953. Accessed Dec 11, 2020. doi: 10.1016/j.cardfail.2010.03.002.

63. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. J Clin Epidemiol. 2016;73:89-102. Accessed Nov 19, 2017. doi: 10.1016/j.jclinepi.2015.08.038.

64. Cella D, Riley W, Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-1194. Accessed Feb 8, 2018. doi: 10.1016/j.jclinepi.2010.04.011.

65. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. Health Qual Life Outcomes. 2006;4:89. Accessed Dec 12, 2019. doi: 10.1186/1477-7525-4-89.

66. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-1736. Accessed Dec 12, 2019. doi: 10.1007/s11136-011-9903-x.

67. Snipelisky D, Kelly J, Levine JA, et al. Accelerometer-measured daily activity in heart

failure with preserved ejection fraction: Clinical correlates and association with standard heart failure severity indices. Circ Heart Fail. 2017;10(6):e003878. Accessed Nov 17, 2021. doi: 10.1161/CIRCHEARTFAILURE.117.003878.

68. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-117. Accessed Apr 27, 2021. doi: 10.1164/ajrccm.166.1.at1102.

69. Chowdhury F, Williams A, Johnson P. Validation and comparison of two multiplex technologies, luminex® and mesoscale discovery, for human cytokine profiling. Journal of Immunological Methods. 2009;340(1):55-64. http://www.sciencedirect.com/science/article/pii/S0022175908003116. Accessed Jan 3, 2020. doi: 10.1016/j.jim.2008.10.002.

70. McAuley E. The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults. J Behav Med. 1992;15(1):65-88. Accessed Nov 17, 2021. doi: 10.1007/BF00848378.

71. Wójcicki TR, White SM, McAuley E. Assessing outcome expectations in older adults: The multidimensional outcome expectations for exercise scale. J Gerontol B Psychol Sci Soc Sci. 2009;64B(1):33-40. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2654993/. Accessed May 14, 2021. doi: 10.1093/geronb/gbn032.

72. Nelson TD, Benson ER, Jensen CD. Negative attitudes toward physical activity: Measurement and role in predicting physical activity levels among preadolescents. J Pediatr Psychol. 2010;35(1):89-98. Accessed Nov 17, 2021. doi: 10.1093/jpepsy/jsp040.

73. Umstattd MR, Motl R, Wilcox S, Saunders R, Watford M. Measuring physical activity selfregulation strategies in older adults. J Phys Act Health. 2009;6 Suppl 1:105. Accessed Nov 17, 2021. doi: 10.1123/jpah.6.s1.s105.

74. Pozehl BJ, Duncan K, Hertzog M, et al. Study of adherence to exercise in heart failure:

The HEART camp trial protocol. BMC Cardiovasc Disord. 2014;14:172. Accessed Jan 12, 2018. doi: 10.1186/1471-2261-14-172.