National Institute on Aging (NIA)

Guidelines for Developing a Single-Site Manual of Operations and Procedures (MOP)

Version 2.1 – March 2022

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ACRONYM GLOSSARY

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to capture all protocol-required information for a study.

Clinical Research or Study Coordinator (CRC) – An individual that handles the administrative and day-to-day responsibilities of a clinical trial. This person may collect or review data before it is entered in the study database.

Data and Safety Monitoring Committee (DSMC) – A group of individuals independent of the study investigators that is appointed to monitor participant safety, data quality and to assess clinical trial progress.

Electrocardiogram (ECG) – A record or display of a person's heartbeat produced by electrocardiography.

Good Clinical Practice (GCP) – A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – The first comprehensive Federal protection for the privacy of personal health information. The Privacy Rule regulates the way certain health care groups, organizations, or businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI).

ID – Identification

Informed Consent Form (ICF) – A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – An independent body constituted of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and material to be used to obtaining and documenting informed consent of the trial participant.

Manual of Procedures (MOP) – A "cook book" that translates the protocol into a set of operational procedures to guide study conduct. A MOP is developed to facilitate

consistency in protocol implementation and data collection across study participants and clinical sites.

NIA – National Institute of Aging

NIH – National Institutes of Health

Not Applicable (NA) – When recording data on a study form, if the information is not applicable, then the acronym NA should be used to fill out the field.

Not Available (NAV) – When recording data on a study form, if the information is not available, then the acronym NAV should be used to fill out the field.

Not Done (ND) – When recording data on a study form, if the evaluation required for a field is not done, then the acronym ND should be used to fill out the field

Office for Human Research Protection (OHRP) – A federal government agency within the Department of Health and Human Services (DHHS) charged with the protection of human subjects participating in government-supported research. The OHRP issues assurances to institutions reviewing human subjects research and oversees compliance of regulatory guidelines by research institutions.

Package Insert – A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

Principal Investigator (PI) – The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial and administrative policies and regulations associated with the award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the sponsored research award rests with the Principal Investigator.

Protected Health Information (PHI) – A subset of individually identifiable health information, oral or recorded, relating to a subject's past, present, or future physical or mental health or condition (e.g., medical or research record). The institutional review board (IRB) or Privacy Board may determine what is considered PHI; however, in general, PHI includes health information that is linked to identifiers of the individual or of relatives, employers, or household members of the individual. Some common identifiers of health information include names, social security numbers, addresses, and birth dates, among others.

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.)

Safety Officer (SO) – The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single site clinical studies. The Safety Officer advises NIA Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Serious Adverse Event (SAE) – Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

INTRODUCTION

The purpose of this document is to provide a Manual of Operating Procedures (MOP) template for Principal Investigators of single-site clinical trials. NIA defines a single-site study as a trial that is conducted by a single funded institution implementing a trial. The role of the MOP is to facilitate consistency in study implementation and data collection across study visits and participants. Use of the MOP increases the likelihood that the results of the study will be scientifically credible, that participant safety will be protected, and scientific integrity will be closely monitored.

In preparing the MOP, the Principal Investigator must be aware of the terms of award with respect to required reporting, data and safety monitoring, and Institutional Review Board (IRB) approval (see *NIA Guidance on Clinical Trials*). All staff members participating in the conduct of this study at participating institutions should have ready access to the MOP and be trained on contents.

The protocol, case report forms (CRFs), informed consent documents, and administrative forms (e.g., screening and enrollment log, protocol deviation log, etc.) should be finalized before the development of the MOP. Additionally, the MOP should be drafted prior to study commencement.

Overview

A MOP serves as a reference and handbook that details a study's conduct and operations. Its purpose is to provide the operational detail to ensure that study procedures are carried out consistently. The MOP is intended to serve as a study "cookbook" that facilitates adherence to study procedures to promote high quality research and to help clinical investigators comply with federal regulations and procedures, and good clinical practice (GCP).

The study team (investigators, coordinators, statisticians, etc.) develops the MOP before the study can commence and keeps it updated throughout the study to record and implement amendments to the protocol and to document refinement of procedures.

MOP development requires complete versions of a final protocol, study forms (often called case report forms (CRFs), Package Insert or Device Manual, if applicable, and Informed Consent Form (ICF).

During a study's planning phase, the Principal Investigator and study staff draft the protocol. The protocol must be approved by the Institutional Review Board (IRB) of record for the study, and by the Data and Safety Monitoring Board (DSMB) or Safety Officer (SO). Prior to developing the MOP, the final protocol, CRFs, informed consent forms, and administrative forms (e.g., screening and enrollment log, protocol deviation log, etc.) should be finalized. Additionally, if the study is to be submitted to the Food and Drug Administration (FDA) under an Investigational New Drug Application (IND), an Investigator's Brochure (for investigational products) or Package Insert (for marketed drugs) must be included. The timeline for the development of study materials must be planned for and typically takes approximately six months.

Development of the MOP requires the involvement of the Principal Investigator and study staff to ensure that the MOP accurately describes how the study procedures will be performed. In multi-site clinical studies, a Steering Committee comprised of the study site and coordinating center investigators often finalizes the protocol and develops or oversees the development of the MOP.

The MOP is a dynamic document that will be updated throughout the conduct of a study to reflect any protocol or consent amendments as well as the refinement of the CRFs and study procedures. The MOP should be maintained in a format that allows it to be easily updated and is typically filed in a three-hole binder or kept electronically as a PDF with bookmarks for navigation between sections. For ease of organization, it is recommended that the MOP be subdivided into various sections separated by dividers or sheets of color paper between each section. Each page of a paper copy of the MOP should have the version number and date; electronic versions of the MOP should have consistent naming nomenclature that includes version dates. As pages are revised, an updated version number and associated date will replace the original page(s) in the MOP. All previous versions of the paper and/or electronic versions must be archived. Once approval to begin the study is received, any changes to the MOP, including the new version number and date, should be submitted to the NIA with track changes for easy reference for review and approval before implementation of any modifications.

MOP Contents and Organization

1.0 Introduction

Regular exercise and lifestyle physical activity (PA) are critical for quality of life and longevity among a growing aging population. Aging produces changes to the structure and function of the heart, which increases vulnerability to cardiovascular disease (e.g., coronary heart disease, heart failure, and stroke), frailty and falls, dementia, and Alzheimer disease. Exercise helps to slow the progression of aging-associated changes to the heart by promoting adaptations to the cardiovascular and pulmonary system, however exercise initiation and maintenance can be difficult in aging adults due to deconditioning, pain, frailty, and disability. Cardiac rehabilitation (CR) provides a valuable window-of-opportunity to promote exercise and lifestyle PA, and is an ideal way to initiate a new exercise routine, particularly in aging adults who would benefit from an individually-tailored exercise prescription and supervised exercise to ensure safe uptake and maintenance of PA. However, low adherence to CR is common, and lifestyle PA declines with advancing age. We have identified exercise anxiety as a novel mechanism related to non-adherence to exercise and lifestyle PA, that is driven by cognitive, behavioral, and physiological underpinnings. Our preliminary work indicates that exercise anxiety is common among 40-50% of patients attending outpatient CR and is linked exercise non-engagement. Exercise anxiety is particularly elevated in individuals with cardiovascular disease given that the physical sensations of exercise often feel like the sensations experienced or attributed to cardiovascular disease (e.g., shortness of breath, chest tightness, dizziness, fatigue, pain). We developed a mechanism-driven cognitive-behavioral intervention to target exercise anxiety, called Behavioral Exposure For Interoceptive Tolerance (BE-FIT). This study aims to conduct a Stage II randomized-controlled trial of a novel behavioral intervention, titled Behavioral Exposure for Interoceptive Tolerance (BE-FIT), to evaluate (1) its efficacy in improving exercise adherence in cardiac rehabilitation (CR) and (2) its mechanisms of change.

The objectives of this study include:

Objective 1. Compare physical activity outcomes (e.g., lifestyle physical activity levels, CR adherence) between participants randomized to receive Behavioral Exposure for Interoceptive Tolerance (BE-FIT) intervention or a health education control (HEC).

Objective 2. Compare exercise anxiety levels between BE-FIT vs. HEC

Objective 3. Examine the mechanisms by which BE-FIT affects physical activity outcomes

2.0 Study Overview

Title: A tailored exposure intervention targeting exercise anxiety and avoidance in cardiac rehabilitation (CR)

This study is a Stage II randomized-controlled trial of a novel behavioral intervention, titled BE-FIT, to evaluate (1) its efficacy in improving exercise adherence in CR and (2) its mechanisms of change in individuals 40 years of age and older. One hundred and forty-six patients enrolled in Robert Wood Johnson University Hospital (RWJ) CR program who have elevated exercise anxiety, as indicated by endorsement of much to very much concern about at least 3 items on the Exercise Sensitivity Questionnaire (ESQ; Farris et al., 2020) and meet other eligibility criteria will be randomly assigned to either receive BE-FIT, a tailored intervention specifically for CR patients with high levels of exercise anxiety (n=73), or HEC (n=73), which are matched for contact time. Eligible participants will be stratified based on their risk profile (determined by their EHR), age, sex, and ESQ score. These stratification variables were selected because they are associated with anxiety and fitness levels which could impact PA outcomes. Both conditions will be administered by trained doctoral-level students enrolled at Rutgers University and will be supervised throughout the course of the study by Dr. Farris and other listed co-investigators.

The BE-FIT intervention is a cognitive-behavioral intervention and is designed to target exercise anxiety. The three main components of BE-FIT include: 1) exposure to feared bodily sensations and exercise, 2) prevention of safety behavior use before/during/after exercise, and 3) use of a wrist-worn activity monitor (Fitbit) for PA feedback and activity goal setting. HEC is a time-matched control intervention that will be delivered on the same delivery schedule as BE-FIT. The doctoral-level clinicians who will be delivering HEC will be exclusively trained in order to avoid contamination with the BE-FIT intervention. In this control arm, participants will be provided educational information about health topics relevant to healthy aging delivered through PowerPoint lectures and handouts and use a Fitbit for PA monitoring. The HEC protocol has been used in prior studies conducted by Dr. Abrantes (co-investigator).

The overall duration of the study is 24 weeks, or approximately 6 months. Subjects will be involved in 6 individual sessions delivered twice weekly during the initial weeks of outpatient CR. Sessions occur for 45 minutes either immediately before or after regularly scheduled CR sessions. Five independent assessments are conducted at baseline, EOT, and three follow-ups (Weeks 12, 18, 24). Data collection will occur at each visit, with baseline data collected at the initial visit.

The primary outcome is objectively measured exercised (MVPA mins/day). Secondary outcomes are percentage of prescribed CR sessions attended and objectively measured lifestyle PA (steps/day). Direct tests of the target mechanisms, exercise anxiety and its components (cognitions, safety behaviors, cardiac vagal control), will be evaluated to examine target engagement outcomes.

3.0 Study Organization and Responsibilities

This section aims to provide a roster of the core study staff and a brief description of their roles as well as an organization chart of the full team. An organizational chart is provided below for a full scope of the study personnel and the study's organizational scheme.

On the next page, Table 1 describes and provides a roster of the core investigators and primary coordinators of the study team. For each member, a mailing address, phone number, email address, and study role are provided.

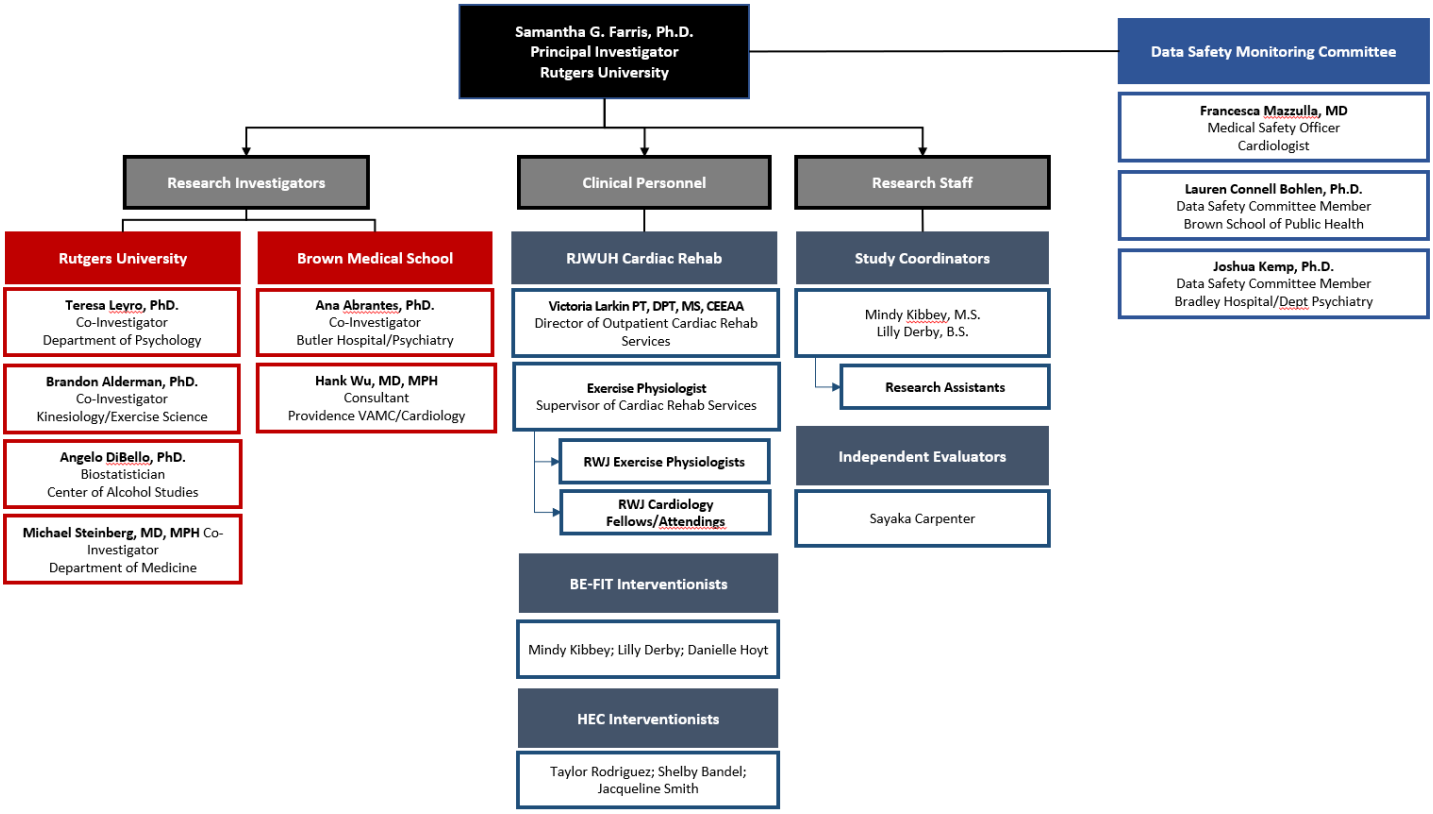


Table 1: Staff Roster

Name	Address	Phone	Email	Role	Responsibilities
Samantha Farris	*1 Spring Street New Brunswick, NJ 08901*	*Telephone: (848)445-8843* *Fax: (732) 445-0036*	*samantha.farris@rutgers.edu*	*Principal investigator*	• *Scientific director responsible for maintaining scientific and procedural integrity* • *Primary management of fiscal and administrative items* • *Development and maintenance of all study materials (e.g., files/records)* • *Reporting and monitoring of adverse events* • *Compliance with and accountability of study intervention administration* • *Submitting documents to regulatory bodies (i.e., IRB, NIA)* • *Quality control procedures* • *Ensuring compliance with human subjects regulations and policies and protecting participants* • *Clinical supervisor and expert in cognitive-behavioral and exposure-based interventions for anxiety disorders* • *Working in conjunction with Dr. DiBello on the development of the randomization scheme and procedures* • *Training interventionists on active intervention arm*
Teresa Leyro	*1 Spring Street New Brunswick, NJ 08901*	*Telephone: (848) 445-2090* *Fax: (732) 445-0036*	*teresa.leyro@rutgers.edu*	*Co-Investigator*	• *Clinical psychologist and anxiety and psychophysiology expert* • *Overseeing psychophysiological assessments* • *Leading coordination of data scoring/cleaning of psychophysiology data with statistician* • *Developing and overseeing data management procedures including the data flow and procedures for data entry, error identification and correction for all psychophysiology data* • *Training interventionists and conducting clinical supervision*
Brandon Alderman	*607 Allison Road, Room 109 Piscataway, NJ 08854*	*Office: (848) 445-9336* *Fax: (732) 932-9151*	*alderman@rutgers.edu*	*Co-Investigator*	• *Exercise physiologist and cardiac physiology expert* • *Providing guidance during clinical supervision meetings on tailoring of exercise and physical activity prescription* • *Providing input in investigator meetings on physiological assessment methods*

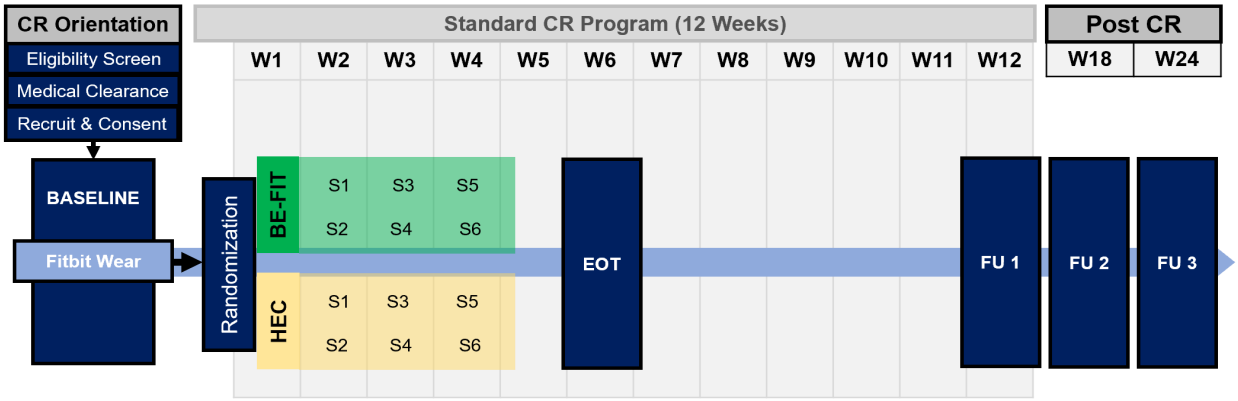
Name	Address	Phone	Email	Role	Responsibilities
					• *Coordinating data scoring/cleaning of psychophysiology data in close conjunction with statistician (Dr. DiBello) to conduct analyses in the later stages of the project*
Angelo DiBello	*607 Allison Road, Room 213 Piscataway, NJ 08854*	*Office: 848-445-2190* *Fax: 732-445-3500*	*angelo.dibello@rutgers.edu*	*Co-Investigator*	• *Study statistician* • *Providing advice on the execution of the study, design considerations, randomization, and conduct primary and secondary data analysis and interpretation of findings* • *Developing and implementing data management procedures including the data flow and procedures for data entry, error identification and correction* • *Enrollment tracking*
Ana Abrantes	*Butler Hospital 345 Blackstone Blvd. Providence, RI 02906*	*Office: 401-455-6440*	*ana_abrantes@brown.edu*	*Investigator*	• *Developing control arm materials* • *Training interventionists and conducting clinical supervision* • *Overall support to study design and implementation* • *Providing guidance on Fibit usage and monitoring data*
Mindy Kibbey	*1 Spring Street New Brunswick, NJ 08901*	*Office: 732-289-5036*	*mmk192@psych.rutgers.edu*	*Interventionist/Study Coordinator*	• *Obtaining informed consent from each participant* • *Recruitment, screening, and enrollment of participants* • *Collecting study data and following participants through study completion* • *Overall support to study design and implementation* • *Maintenance of study binders and materials* • *Reports - enrollment, participant status (e.g., withdrawals), adverse events, independent safety monitoring body reports* • *Study interventionist*
Lilly Derby	*1 Spring Street New Brunswick, NJ 08901*	*Office: 732-289-5036*	*ld681@psych.rutgers.edu*	*Interventionist/Study Coordinator*	• *Obtaining informed consent from each participant* • *Recruitment, screening, and enrollment of participants* • *Collecting study data and following participants through study completion* • *Overall support to study design and implementation* • *Maintenance of study binders and materials* • *Reports - enrollment, participant status (e.g., withdrawals), adverse events, independent safety monitoring body reports* • *Study interventionist*

Name	Address	Phone	Email	Role	Responsibilities
Sayaka Carpenter	*1 Spring Street New Brunswick, NJ 08901*	*Office: 732-289-5036*	*sc1937@psych.rutgers.edu*	*Study Coordinator*	• *Obtaining informed consent from each participant* • *Recruitment, screening, and enrollment of participants* • *Collecting study data and following participants through study completion* • *Overall support to study design and implementation* • *Maintenance of study binders and materials* • *Reports - enrollment, participant status (e.g., withdrawals), adverse events, independent safety monitoring body reports*

4.0 Study Flow

An overview of the study processes is presented in Figure 1 and provides the timing of each of the study's major steps.

Figure 1: Timing of Intervention and Assessment Components



5.0 Informed Consent

This section of the MOP describes the specific instructions for obtaining informed consent.

- Prior to the eligibility screen, patients that are scheduled to attend the RWJ CR Program in New Brunswick (and East Brunswick), NJ will be asked if they are interested in participating in a research study following a written script by RWJ CR staff. At this time, patients who express interest in participation will verbally agree to have their medical records reviewed by study staff in consultation with the nursing team.
- Medical records for these patients will be screened by study staff to assess potential eligibility prior to their in-person orientation visit date.
- At CR orientation, participants who are potentially eligible based on preliminary review of medical history will be administered additional screening assessments (ESQ, EVS, MoCA). Those who meet all eligibility criteria based on medical history and screening assessments will be approached by study staff (independent assessor) at their CR orientation visit to introduce themselves to the patient and provide detailed information about the study, as well as answer any questions.
- If these patients express interest in participation, study staff will walk through the consent details.
- Study Coordinator (independent assessor) explains risks and benefits, reminding patient participation is voluntary, and may discontinue at any time (and procedure for termination).
- Coordinator provides contact information in case of medical emergency due to study participation, or for questions about subject rights.
- Coordinator explains who has access to patient's protected health information, and how confidentiality is maintained.
- Coordinator explains any costs participation may incur.
- Coordinator explains how participant may learn outcome of study and be provided with a copy of publication of any article published.
- After discussing the components of the consent form the potential participant can ask any remaining questions and then sign the form. When needed, the interested participant can take some additional time to look over the consent form while at the CR space prior to signing.
- Copies of signed informed consent form (ICF) will be provided to participant and placed in their file.
- Signed ICF will be stored in a secure locked file box in a locked office.

5.1 HIPAA Authorization

In the pre-orientation semi-scripted phone call, the RWJ CR staff member will ask the potentially-eligible participant for verbal permission to allow the study team to access their protected health information (PHI) prior to or at the beginning of CR orientation. Participant information for those who provide verbal assent will only be accessed as needed to determine initial eligibility based on their electronic health records and collect study-relevant data. This information may include the participant's name, age, qualifying

medical condition, and relevant comorbidities for inclusion into the research study. Patients found to be eligible through pre-screen procedures will meet with the study coordinator at their CR orientation appointment. The study coordinator (independent assessor) will thoroughly present the ICF and explain to the participant that, if they choose to enroll in the research study, the study coordinator will collect additional PHI for research use in this study and any future uses the participant has agreed to, as specified in the consent form.

6.0 Recruitment and Retention

6.1 Participant Recruitment

Potential participants will be recruited at RWJ CR and will be identified through the CR program's record system via consultation with RWJ CR staff. RWJ CR personnel will briefly describe the study to patients and interested individuals will consent to study staff conducting an eligibility review of their medical records in advance of and/or during the CR orientation appointment. Upon orientation at RWJ CR, patients that are potentially eligible based on screening assessments will be approached by a member of the study team who will introduce themselves to the patient and provide initial information about the study. Patients will also receive a study brochure that will include more details about the study. If the participant is eligible and interested, the study coordinator will review the brochure content and consent form with the potential participant and obtain a written signature on the form for patients who consent to study procedures.

6.2 Participant Retention

Every effort will be made by the PI and study team to ensure participants complete each study visit and the study overall. We will use the following strategies to help to maximize retention and minimize loss to follow-up:

- Following a proactive plan for retention, including calling participants to see how they are doing and to ensure that they can maintain the study protocol.
- Providing a printed timeline/visual aid to remind patient of study appointments and calling/texting participants before each session.
- Scheduling sessions to coincide with the CR visits
- Building participant relations and participant satisfaction, with the study coordinator taking a central role on this effort e.g., the study coordinator to talk with the participants during their established visit schedule to check how they are doing and determine if they are satisfied etc.
- Giving participants and their families the opportunity to ask questions and express concerns pertaining to their condition throughout the study.
- Obtaining contact information of family/supports to aid in communication and coordination of study visits.
- Enhancing participant's understanding of the study's objectives and the protocol by reminding the participant of the study aim during study visits or having question and answer sessions after each visit, if needed.
- Assessing each participant's drop-out potential.
- Participants will also receive compensation for their participation.

In the event that a participant does not return for study visits, the PI and/or study coordinator will make several contacts using all of the contact information provided by the participant.

7.0 Screening and Eligibility Criteria

7.1 Screening

The Study Coordinator will utilize the following steps to screen participants for the study:

I. Pre-Screening Phase
   a. Potential participant will be called by a trained RWJ CR staff member to schedule their orientation session.
   b. CR staff will explain the study and describe how this involvement is an optional adjunct to their normally scheduled CR. If participant is interested, the staff member will walk through the consent information to the pre-screen procedures (chart review, screening measures).
   c. Verbal agreement to pre-screen procedure will be given during the phone conversation by patients who wish to be pre-screened for eligibility.

II. Screening Phase
   a. All screening evaluation to determine eligibility (outlined in Section 7.3) will be completed prior to and/or on the day of orientation (review of medical history, ESQ, EVS, and MoCA).
   b. Study coordinator will meet with eligible potential participant to explain the study.
   c. Study coordinator will probe for participant's ability to complete the duration of the study:
      i. Is the participant planning to move during the duration of the study?
   d. Study coordinator will invite the participant to sign an ICF and provide a copy to participant while placing originals in a secure file.
   e. Study coordinator will collect contact information, including contact information for two personal contacts.

7.2 Screening Log

During the CR orientation screening, a thorough review of medical history, paper questionnaires (ESQ, exercise vital sign (EVS)) and Montreal Cognitive Assessment (MoCA) will be completed by the nursing staff at RWJ CR in consultation with the study research coordinator. The person entering data from screening will be that same study research coordinator/independent assessor. All data entry will take place electronically using Qualtrics.

Everyone screened who is eligible will have all their deidentified screening information logged in the main Qualtrics survey. Their name, screening date, and screening ID number will be entered in a password protected excel file that is kept separate from deidentified data. Pertinent information will also be entered in the secure Screening and Eligibility Log.

Those who are screened and deemed ineligible will have their information logged in a separate, but parallel Qualtrics survey which includes only screening assessments: EVS, ESQ, MoCA, medical history review for eligibility criteria. These ineligible patients will have name, screening date, screening ID, primary reason(s) for exclusion kept in a separate password-protected excel file. Pertinent information will also be entered in the secure Screening and Eligibility Log.

The PI will regularly review the excel log of ineligible patients with exclusionary information. Based on this, if any changes to screening procedures and/or exclusionary criteria are deemed necessary, the paper forms and Qualtrics survey will be modified by study staff to reflect those changes, with PI approval. These procedural changes will also be reflected in all study documents (e.g., MOP).

A secure Screening and Eligibility Log documents all individuals evaluated for study eligibility. It generally contains the individual's initials, identification number (screening number), age, gender, race, ethnicity, screening date, and eligibility status. (e.g., eligible for study participation and date enrolled; ineligible for study participation and reason; refused consent and reason). It may also contain the randomization number if different from the screening number.

7.3 Eligibility Criteria

Individuals who are attending CR at RWJ in New Brunswick and East Brunswick who provide verbal assent will be screened for study eligibility. Study eligibility is determined by the following inclusion/exclusion criteria:

Inclusion Criteria

1. ≥ 40 years of age
2. Elevated exercise anxiety (total score ≥30 or score ≥3 on at least 3 items on ESQ)
3. Low active (< 90 min self-reported moderate-to-vigorous intensity physical activity/day in past three months)
4. Medically approved for cardiac rehabilitation
5. English proficiency

Exclusion Criteria

1. Evidence of cognitive impairment (< 23 on Montreal Cognitive Assessment; MoCA)
2. Severe disabling chronic medical and/or psychiatric comorbidities determined on a case-by-case basis that prevents safe or adequate participation
3. Expectation that patient will not live through study periods

If the participant does not meet all the above criteria, he/she will not be eligible for study participation.

8.0 Study Intervention

BE-FIT is a brief, manualized, individual-based intervention specifically designed to target exercise anxiety that involves 6 sessions (twice/week) that are ~45 min delivered during the first three weeks of outpatient CR, as a supplement to CR. Each session will be delivered by a doctoral-level clinician who is exclusively trained to deliver BE-FIT. The interventionists will work in tandem with the study exercise physiologist and cardiac-technician to coordinate tailoring of BE-FIT content to the patient. BE-FIT content includes: (1) Psychoeducation about anxiety/avoidance and values clarification and committed action for exercise and lifestyle PA; (2) Graded, repeated exposure to bodily sensations and exercise to foster tolerance of discomfort; (3) Fading safety behaviors and elimination of exercise avoidance behaviors to build tolerance to uncertainty and reduce catastrophizing; and (4) Use of the Fitbit activity tracker to facilitate PA monitoring, and to facilitate PA feedback and goal setting. Patients will be given a structured workbook that will be used with the interventionist at each session to facilitate learning objectives, PA goal setting, and practice. The workbook corresponds to session content as follows: Session 1- Psychoeducation & Setting PA Goals; Session 2- Rationale for Exposure/Fading Safety Behaviors & Developing Exposure Hierarchy; Sessions 3, 4, 5- Exposure Practice, Mindful Observing, and Fading Safety Behaviors; Session 6- Goal Setting and Planning for Maintenance of Physical Activity. (PA monitoring/feedback occurs each session).

The **Health Education Control** is a time-matched control intervention that will be delivered on the same "delivery schedule". HEC will be delivered by doctoral-level clinicians who are trained to exclusively deliver HEC (i.e., these interventionists will be different from those delivering BE-FIT to avoid contamination). HEC intervention content includes: (1) educational information about health topics relevant to healthy aging, and (2) Use of the Fitbit activity watch for PA monitoring. Health information will be conveyed through one-on-one interactive lectures and a structured workbook with handouts. The following 6 topics will be presented: nutrition, sleep hygiene, how to be a smart patient, brain health, emotional health as you age, and living with chronic health conditions. The goal of each session will be to provide education, particularly as it relates to healthy aging. Patients will be given the same Fitbit as in the BE-FIT but will not be given PA goals. Interventionists will routinely address questions related to the Fitbit such as syncing issues, charging the battery, and any other technical problems that may arise.

All study assessments will be conducted in-person at RWJUH CR. Assessments will be completed by an independent evaluator, who will be blinded to aspects of CR treatment and study randomization. Patients will be informed to not discuss the nature of their treatment with the evaluator to minimize chance of bias and contamination across arms.

9.0 Randomization

After completing 7-days of physical activity monitoring, patients will be randomized to either BE-FIT or HEC. The statistician, Dr. DiBello will be responsible for generating randomization codes using the following information as blocking variables: 1) age (older or equal to 65 years old/younger than 65); 2) sex (female/male); 3) ESQ score (above/below 30); 4) risk profile (moderate-high risk/low risk).

Method:

1. The statistician will be notified of a new eligible participant by the study coordinator 1/independent assessor.
2. The statistician will use an automated computerized log that is separate from the study data which will identify the next available code. The statistician will notify the other coordinator 2 that the code is available.
3. Coordinator 2 will transfer this code to the screening and enrollment log and notify the interventionist that the randomized code is available using a newly assigned study ID number for the participant.

The statistician will maintain the master randomization list, assign randomization codes, notify appropriate study staff regarding randomization, and securely store randomization files. The study coordinator (not the independent assessor) will initiate randomization procedure and must know who to contact once a participant is deemed eligible for the study, including which forms to complete prior to randomization.

10.0 Blinding and Unblinding (Masking and Unmasking)

All study assessments prior to enrollment, at baseline, and those administered at end-of-treatment (EOT) and Weeks 12, 18, and 24 will be completed by an independent evaluator who will be blinded to aspects of CR treatment and study randomization. Patients will be informed to not discuss the nature of their treatment with the evaluator to minimize chance of bias.

The study statistician and the interventionists will not be blinded to the randomization or the delivered intervention. However, interventionists will either be trained to deliver BE-FIT or HEC, to limit contamination across interventions.

Unblinding is a serious action and should be limited to reduce potential bias and maintain the integrity of the data. In the event that unblinding occurs, the following should be recorded:

- The ID of the unblinded participant,
- The reason for unblinding,
- The study staff person responsible for unblinding
- A list of person(s) who have been unblinded.

11.0 Study Measurements and Procedures

All assessments will be conducted in-person at RWJ CR. Data will be collected via participant self-reports and Fitbit Charge 5 activity tracker that will be worn by enrolled participants, as well as Biopac MP150 System for psychophysiological data collection. All study data will be coded with a de-identified study ID number. An independent evaluator will collect self-report assessments and psychophysiological data. Graduate-level research assistants will administer treatment sessions (BE-FIT or HEC) to participants. Dr. Farris will be responsible for overseeing the data collection process.

Demographics. General demographic information including age, sex, race/ethnicity, income level and level of education will be collected from medical records and/or at the baseline assessment.

Health and Exercise History. Psychological and health history will be evaluated at baseline. Medical records will be referenced at baseline to determine eligibility based on cardiac diagnosis, medical conditions and medications, and score on Exercise Sensitivity Questionnaire (ESQ; see preliminary data). Cognitive ability will be assessed using the Montreal Cognitive Assessment (MoCA). The 2-item Exercise Vital Sign will be utilized to measure patients' self-reported exercise levels. Medical records will be accessed again at 18-Week follow-up to collect data regarding the percentage of subscribed CR sessions that were attended.

Exercise Anxiety. The Exercise Sensitivity Questionnaire (ESQ) will be used to measure exercise anxiety.

Psychological Functioning. Validated measures commonly used in medical settings to screen for common psychiatric conditions (PHQ-9, GAD-7), and a measure of values-consistent living validated for use in CVD populations (Valuing Questionnaire; VQ), and a general index of anxiety sensitivity (Anxiety Sensitivity Index; ASI-3) will be administered.

Anxious Cognitions. Validated report assessment of anxious cognitions will be used to tap catastrophizing (Cardiac Anxiety Questionnaire; CAQ and Threat Perceptions), intolerance of uncertainty (Intolerance of Uncertainty Scale-Short; IUS-12), discomfort intolerance (Discomfort Intolerance Scale; DIS), interoceptive awareness and appraisal (Body Vigilance Scale; BVS and Multidimensional Assessment of Interoceptive Awareness; MAIA), and fear of falling (Falls Efficacy Scale-International (Short FES-I).

Avoidance/Safety Behaviors. Avoidance behaviors will be assessed via the Safety Behaviors Assessment Form (SBAF), Fear of Activity in Coronary Artery Disease (Fact-CAD), and The Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q).

Physical Activity. A Fitbit Charge 5 activity tracker will be used to assess how much physical activity participants partake in per day and objective exertion of exercise. A number of options exist for goal setting, and we will customize each participant's account to display the following: daily steps, very active minutes, and activity during each hour of the

day. While the vast majority of lifestyle PA will consist of walking, Fitbit trackers are waterproof and can be worn while swimming. Also, we will provide exchangeable clips to allow for trackers to be attached to a sneaker when cycling. In doing so, we likely capture all types of lifestyle activities.

For BE-FIT Intervention ONLY: During Session One, the interventionist will review baseline PA from the baseline assessment, including daily steps and MVPA. The interventionist will use these data to tailor two possible PA prescriptions (goals) – (1) Increasing steps/day: If baseline steps/day reflect sedentary/low activity (accumulate avg<4,000 steps/day), patients will be given the goal of achieving 4,500 steps/day and increasing each session by 500 steps/day (about 1/4 mile increase), as recommended by the recent update to PA guidelines. At this rate, patients will reach ~7,500 steps/day by EOT, which is an empirically-derived minimum for daily PA in older adults for longevity; and/or (2) Increasing PA intensity: If baseline active min/day reflect low MVPA (accumulated avg < 30 active mins/day), patients will be given the goal of working gradually towards achieving and maintaining 30 very active minutes/day. This gradual approach is consistent with implementation of exposure therapy and will ensure that patients are not engaging in anxiety-driven avoidance of higher intensity-PA.

Physiological Parameters. To assess cardiac vagal control as a physiological parameter of exercise anxiety and a putative BE-FIT target, respiratory sinus arrhythmia (RSA), an index of cardiac vagal control will be indexed at baseline, end-of-treatment, and week 12 follow-ups. At each time point, we will specifically assess cardiac vagal control during a 5-minute resting period (i.e., tonic) and cardiac vagal reactivity during a 5-minute attentional demand (i.e., phasic changes in RSA), which has previously been used to assess acute changes in cardiac vagal control as an index of psychological flexibility and vulnerability. We will also assess heart rate deceleration (event-related potential) in response to a 5-min Stroop task. Continuous measures of electrocardiograph (ECG), impedance cardiograph (IC), and blood pressure (BP) will be acquired at 1000 Hz using a Biopac MP150 and an integrated CNAP blood pressure monitor. Signals will be scored and offline in 1-minute bins in accordance with recommendations of the Society for Psychophysiological Research using MindWare's integrated system (BioNex 8SLT Biolab Acquisition Application, MindWare Technologies, Gahanna OH). RSA will be specified as the integral power within typical adult respiration frequency (.12 to .4 Hz), and respiration rate will be derived from IC. Reactivity will be computed by subtracting baseline scores from the attentional demand scores; because RSA decreases during attentional demand, lower numbers for vagal reactivity represent greater reactivity. Cardiac output will be calculated with the Kubicek formula to provide an estimate of the amount of blood processed by the heart in 1 min. The pre-ejection period will be measured as the time in ms from the onset of ventricular depolarization to the aortic valve opening. Continuous assessment of BP will allow scoring of the baroreceptor reflex, defined as changes in the interbeat interval per unit change in BP (ms/mmHG), a supplemental index of vagal control. Use of beta blockers will be used as a covariate when interpreting parameters given its physiological effects.

11.1 Timeline and assessment schedule

Study visit schedule with assessments table below:

Assessment	Screen/ BL	Treatment Visit: Week 1	Treatment Visit Week 2	Treatment Visit Week 3	Treatment Visit Week 4	EOT Week 6	Follow-up Week 12	Follow-up Week 18	Follow-up Week 24
Exercise Vital Sign	X								
Cardiac/Medical History	X								
ESQ	X					X	X	X	X
MoCA	X								
Eligibility/Randomization	X								
Informed Consent Form	X								
MVPA minutes/day; steps/day	X	X	X	X	X	X	X	X	X
# CR attendance								X	
CAQ	X					X	X	X	X
IUS-12	X					X	X	X	X
ASI-3	X					X	X	X	X
DIS-R	X					X	X	X	X
SBAF	X					X	X	X	X
Fact-CAD	X					X	X	X	X
PRETIE-Q	X					X	X	X	X
Threat Perceptions	X					X	X	X	X
VQ	X					X	X	X	X
FES-I	X					X	X	X	X
BVS	X					X	X	X	X
MAIA	X					X	X	X	X
GAD-7	X					X	X	X	X
PHQ-9	X					X	X	X	X
Vagal Flexibility and tone	X					X	X		
Respiration Rate, HR, Baroreceptor Reflex	X					X	X		
Adverse Events		X	X	X	X	X	X	X	X

11.2 Visit Procedures

Enrollment. The enrollment date is day the individual has met all the screening criteria and signs the informed consent form (CR orientation day).

Baseline. During CR orientation, patients will be provided with the Fitbit, shown how to wear, charge, and sync it. Patients will be required to wear the Fitbit for at least 7 consecutive days for 10+hrs/day to establish baseline PA activity prior to randomization. For participants who have successfully been screened for eligibility and are enrolled into the study, paper-copy baseline self-report questionnaires and psychophysiological assessments are administered by the study coordinator. After completing the assessments, the coordinator will remind the participant of their next scheduled visit, and re-check the participant's contact information for accuracy. All self-report data collected during this session will be reported on Qualtrics. Psychophysiological data (heart rate and blood pressure) will be recorded via Biopac AcqKnowledge. After this session has ended, participant is free to leave.

Sessions 1-6. Each intervention session will occur either before or after CR and will last for 45-minutes. Depending on the sequence of when the session will take place (either before or after CR), interventionists will greet the participant in the waiting area of the CR space. Together they will walk to a semi-private location to begin the session. Once the session has been completed, the interventionist will ask if the participant has any questions and remind them of their next appointment and homework. Once discussion has been completed, the interventionist will walk the participant out to the door or to their CR class.

End-of-Treatment. This visit will similarly take place either before or after the participant's CR appointment. However, no intervention will be delivered during this meeting. During this session, participants will complete self-report measures and physiological assessments conducted by the independent assessor. Once all assessments have been completed, the independent assessor will ask if the participant has any questions and remind of their next appointment at week 12 (final day of CR). The participant and the assessor will conclude the session and walk the participant out to the door or to their CR class.

11.3 Follow-up

Participants will be followed through all study visits through the study completion. Follow-up appointments will take place at weeks 12 (final CR session), 18, and 24. Similar to the end-of-treatment session, the independent assessor will meet with the participant at RWJ CR to complete self-report and physiological assessments (only week 12). Week 12 follow-up (follow-up 1) will last for 1 hour. The subsequent two follow-ups should take around 20-30 minutes.

We will use the following strategies when meeting with and following the participants:

- Regular phone calls and/or to ensure Fitbit compliance
- Answer any questions or concerns the participant may have

11.4 Final Study/Early Discontinuation Evaluations

In the event a participant discontinues study treatment before study completion, every effort will be made by the study team to have the participant continue to complete all other study

procedures until end-of-treatment/follow-up. However, if the participant is not willing to continue study participation, the study team will attempt to collect the final visit data.

Extenuating circumstances due to unexpected illness/injury, insurance difficulties, travel, etc. may also result in intervention discontinuation or temporary delay. Modifications to the schedule and the duration of continued follow-up will be determined on a case-by-case basis for the completion of the study procedures. If applicable, outcomes may continue to be followed.

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. Participants should continue to be followed, with their permission, even if the study intervention is discontinued. If participants discontinue early, a new participant will be enrolled into the study to complete the protocol.

The intervention may be discontinued at any time by the IRB, the NIA, or other government agencies as part of their duties to ensure that research participants are protected.

12.0 Concomitant Medications

The following includes all the medications that are prohibited during the course of the study:

- None

**Note: all treatment as usual as prescribed by medical professionals is allowed throughout the study duration*

13.0 Safety Reporting

Adverse Event (AE) and Serious Adverse Event (SAE) definitions:

- ***Adverse Event*** – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom (e.g. dizziness or shortness of breath), or disease (CVD event), temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.
- ***Serious Adverse Event*** – A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

13.1 Adverse Event Reporting

All AEs and SAEs will be collected and documented starting once the participant has consented to participating in the study through the end of the study. At each visit, study staff will specifically query participants for adverse events. Upon notification of an Adverse Event (AE), the study coordinator will notify all appropriate parties as described in the protocol:

1. The study coordinator and/or interventionist will complete the AE form as it exists in **Appendix F.**

2. The study coordinator and/or interventionist will immediately notify the PI and medical monitor at CR.
    a. The event will be reviewed by the PI upon notification and determine the severity of the event.
3. All reports will detail whether the event was expected or unexpected, a rating of severity of the event, a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, and whether informed consent should be changed because of the event.
4. The PI will advise the Study Team regarding screening, enrollment, and ongoing participation.
5. Upon advisement by the IRB, the PI will determine the study's status, and notify the Study Team.
6. Adverse events will be followed until resolution, stabilization, or until it is determined that the study participation is not the cause.
7. All events will be tracked and reported throughout the study.

13.2 Unanticipated Problems

In addition to regular monitoring and reporting of adverse events, study staff will be fully trained in the OHRP definitions of adverse events that are also unanticipated problems; serious adverse events; or unanticipated problems that are not adverse events. In the case of any of those events, study staff are required to report that information to the PI immediately both verbally and in writing. When necessary, a report of a serious adverse event will result in the PI contacting the participant to further assess the event. In all cases, Dr. Farris will determine if a follow-up to an experienced SAE/AE or unanticipated problem is necessary. When deemed so, Dr. Farris will be in contact with the research participant and/or their treating providers to facilitate information transfer (with the participant's consent) and coordinate care as needed.

Upon notification of an Unanticipated Problem, the study coordinator will notify all appropriate parties as described in the protocol:

1. The study coordinator and/or interventionist will notify the Principal Investigator and Medical Monitor at CR immediately.
2. The PI will review the details of the event
3. When necessary, the coordinator will draft a notification email to the SO (and IRB, if needed). The coordinator will review and submit the draft notification to the PI.
4. The PI will advise the Study Team regarding screening, enrollment, and ongoing participation.
5. Upon advisement by the SO and/or the IRB, the Principal Investigator will determine the study's status and notify the Study Team.

13.3 Serious Adverse Event Reporting

Consistent with NIH guidelines and OHRP policy, serious adverse events (SAEs) are adverse events that meet any of the following criteria: fatal or life-threatening, result in significant or persistent disability, require or prolong hospitalization, result in a congenital

anomaly/birth defect, or are important medical events that investigators judge to represent significant hazards or harm to research subjects. Any adverse event that meets any of these criteria (e.g. results in hospitalization) will be documented and reported as a SAE.

Upon notification of a Serious Adverse Event (SAE), the study coordinator will notify all appropriate parties as described in the protocol:

1. The SAE form (**Appendix G**) will be completed by study investigators with the help of the participant who can provide information about the event.
2. The study coordinator will immediately notify the PI and Medical Monitor at CR.
3. A written letter detailing the nature of the event will be drafted by the study coordinator and/or interventionist and be sent to the PI.
4. SAEs that are unexpected (e.g., serious medical event during intervention session or prescribed activities, suicide attempt within study period) are unlikely but will be reported to the NIA PO (Dr. Lisa Onken) and the SO (Dr. Mazzulla) via written report within 48 hours of becoming aware of the SAE, and to the IRB per their reporting requirements. All deaths of patients actively enrolled in the study will be reported within 24 hours of study's knowledge of death to the NIA PO, Dr. Mazzulla, and the IRB.
5. A summary of all other SAEs (i.e., expected) will be reported to the NIA PO and Dr. Mazzulla in regular quarterly reports. Given the age and medical comorbidities of patients enrolled in this study, non-study-related medical events and hospitalizations may be expected to occur during the period of study enrollment and follow-up assessment. These events, when deemed unrelated to study participation (i.e., not a direct result of intervention activities or study assessment procedures) will be included in adverse event documentation and reporting at regular quarterly intervals.
6. All SAEs will be reviewed by the full committee of the Rutgers University IRB.
7. The PI will advise the Study Team regarding screening, enrollment, and ongoing participation.
8. Upon advisement by the IRB, the Principal Investigator will determine the study's status, and notify the Study Team.

14.0 Study Compliance

All other deviations will be reported routinely to the independent safety monitoring body. The study coordinator will maintain a log of all protocol deviations.

Protocol deviations/violations, include, but are not limited to, the following:

- Enrollment or randomization of an ineligible participant
- Failure to obtain Informed Consent
- Visits or procedures conducted outside of the protocol specified window
- Failure to keep IRB approval up-to-date
- Wrong treatment administered to participant
- Follow-up visit at a time point different from that specified in the protocol

The study site will maintain a log of all protocol deviations/violations and should report them as specified in the DSMP to the safety monitoring committee. A log is presented in **Appendix B**. Please note, only protocol deviations that impact participant safety should be reported within 24 hours of occurrence if possible, or as soon as they are discovered.

15.0 Data Collection and Study Forms

The following documents are used in this study for initial screening and data collection. See **Appendix E.**

All incomplete forms are saved on a shared drive that can be accessed by study personnel. Prior versions will be stored in an "archive" folder. Any updates needed for study forms and assessments will be completed by the study team and approved by the PI. All study questionnaires will be delivered to the patient as a paper copy (organized in preparation for study visit by study personnel) and will then be entered into Qualtrics by a study coordinator.

1. **Medical History & CR Attendance**
    a. Medical Data Extraction Form. Relevant medical history collected at screening; CR attendance collected at F2.
2. **Exercise Questionnaires**
    a. Exercise Vital Signs (EVS). Assessed at screening
    b. Exercise Sensations Questionnaire (ESQ). Assessed at screening, EOT, F1, F2, F3.
    c. Fear of Activity in Patients with Coronary Artery Disease (Fact-CAD). Assessed at BL, EOT, F1, F2, F3.
    d. Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q). Assessed at BL, EOT, F1, F2, F3.
3. **Psychological Factors**
    a. Montreal Cognitive Assessment (MOCA). Delivered at screening.
    b. Cardiac Anxiety Questionnaire (CAQ). Assessed at BL, EOT, F1, F2, F3.
    c. Safety Behaviors Assessment Form (SBAF). Assessed at BL, EOT, F1, F2, F3.
    d. Threat Perceptions. Assessed at BL, EOT, F1, F2, F3.
    e. Valuing Questionnaire (VQ). Assessed at BL, EOT, F1, F2, F3.
    f. Intolerance of Uncertainty Scale Short Form (IUS-12). Assessed at BL, EOT, F1, F2, F3.
    g. Falls Efficacy Scale-International (Short FES-I). Assessed at BL, EOT, F1, F2, F3.
    h. Discomfort Intolerance Scale (DIS-R). Assessed at BL, EOT, F1, F2, F3.
    i. Body Vigilance Scale (BVS). Assessed at BL, EOT, F1, F2, F3.
    j. Multidimensional Assessment of Interoceptive Awareness (MAIA). Assessed at BL, EOT, F1, F2, F3.
    k. Anxiety Sensitivity Index (ASI-3). Assessed at BL, EOT, F1, F2, F3.
    l. General Anxiety Disorder 7-Item Scale (GAD-7). Assessed at BL, EOT, F1, F2, F3.
    m. Patient Health Questionnaire-9 (PHQ-9). Assessed at BL, EOT, F1, F2, F3.

In addition, Fitbit data will be downloaded from the participant devices using appropriate software. Fitbit data is identified only with a randomly generated study ID. Fitbits will be worn throughout the study duration.

Physiological data will be collected at BL, EOT, and F1 to assess: 5-min average RSA, 5-min attentional demand, and 5-min Stroop task. Respiration rate, heart rate, and baroceptor reflex will also be measured. For data collection, participants will be hooked up to Biopac's integrated psychophysiological system (MP150) and an integrated CNAP

blood pressure monitor to obtain continuous non-invasive measures of blood pressure, electrocardiograph (ECG), and impedance cardiograph (IC), which allows for the extraction of respiration data. This will require placing three passive spot electrodes to the chest area to index electrocardiogram, and four passive spot electrodes to the neck and chest region to measure cardiac impedance and respiration. In addition, participants will be attached to arm and finger cuffs to index blood pressure. Four five-minute segments will be scored using MindWare.

15.1 Source Documentation

The source documentation used in this study will include the medical data obtained prior to enrollment to determine eligibility for participation. All medical data will be reviewed along with a medical staff member at RWJ CR.

In addition, all signed consent forms with identifying information from the participants will be filed in a locked study file, separate from any de-identified information pertaining to the participant (e.g., paper versions of administered assessments).

At conclusion of the study, all forms will be kept with the study records based on the requirements of the IRB guidelines.

15.2 General Instructions for Completing Forms

Print using black or blue ink when completing study forms. Note, participants must not be identified by name on any study document submitted with the forms. Replace the participant's name with the participant identification (ID) number.

- Header: Complete the header information on EVERY page, including pages for which no study data are recorded.
- Participant ID: The participant ID must be recorded on EVERY page, including pages for which no study data are recorded.
- Dates: All dates must be recorded on the date of form completion.
- Study timeline must also be recorded on the form.
- Extraneous Writing: Comments written extraneously on forms cannot be captured in the database; thus, write only in the spaces indicated.
- Correcting errors: If an error has been made on the study forms, place a <u>single</u> line through the erroneous entry and record the date and your initials. Indicate the correct response.
- Skipping items: Do not skip any items. Some items may carry "Unknown" or "Not Applicable" response choices which should be checked when necessary.
- Incomplete data: Data may not be available to complete the form for various reasons. Circle the item for which data is not available and indicate the reason near the appropriate field:
    - If an evaluation was <u>not done</u>, write <u>ND</u> and provide a reason.
    - If the information is <u>not available</u>, but the evaluation was done, write <u>NAV</u>.

      Note: Only in rare circumstances, as in the case of lost documentation, should NAV be recorded on the form. Every effort should be made to obtain the information requested.

- If an evaluation is not applicable, write NA.
- Incomplete or Illegible forms: Incomplete forms that do not have adequate explanation (as described above) compromise the integrity of the entire study.

15.3 Data Flow

Data will be collected via participant self-reports, Biopac psychophysiological data acquisition, and Fitbit Charge 5 activity trackers that will be worn by enrolled participants. All collected data will be de-identified throughout the study. An independent evaluator will collect self-report and psychophysiological assessments. Graduate-level research assistants will administer the treatment sessions (BE-FIT or HEC) to participants. Dr. Farris will be responsible for overseeing the data collection process.

All forms will be completed with the participants to ensure that all information is complete, intact, and transmitted into Qualtrics. All data uploaded onto Qualtrics will be monitored weekly by the study statistician and study personnel.

Any errors identified during this data check will be documented and an attempt to correct any errors will be made.

15.4 Administrative Forms

Administrative forms provide documentation of study processes and assist with study operations (e.g., screening log). In this section of the MOP, listed below are the study forms that will be used.

- ***Screening and Enrollment Log -*** Used to list participants screened; includes those who fail screening and those who are enrolled.
- ***Participant Identification Code List***
- ***Interventionist Manual***
- ***Study Administration Checklist***

15.5 Retention of Study Documentation

After the study ends, study staff shall maintain participant forms in a secure location at Rutgers University in New Brunswick, NJ, USA for 6 years, as indicated by the protocol and IRB guidance.

16.0 Data Management

All study-generated self-report measures are compiled in standardized formats and reviewed for ease of reading to minimize missing data. Data will first be data entered into Qualtrics by a coordinator and then checked by a senior research assistant in a blind verification of the original entry. A program will run to flag discrepancies. Discrepancies will be reconciled directly with original assessment by the PI and Dr. DiBello, who will make final decisions about data coding. Data will be downloaded and backed-up on the Rutgers University secure network weekly. RWJ CR will support data management from their medical records and will coordinate data extraction from screening as needed. We will implement regular cleaning routines that will be used on hand-entered data in order to

identify miscoded or duplicate variables, mismatched admission/discharges dates, and out of range values. Documents containing identifying and personal information of study patients are kept entirely separate from their coded data.

All data collected by the research team are considered part of the subject's confidential record. There are several sources of data. In most cases, data from assessments will be first written on paper and then entered into the research database.

Physiological data will be collected at BL, EOT, and F1. Data will be collected via Biopac's integrated psychophysiological system (MP150) to obtain continuous non-invasive measures of blood pressure, electrocardiograph (ECG) and impedance cardiograph (IC), which allows for the extraction of respiration data. This will require placing three passive spot electrodes to the chest area to index electrocardiogram, and four passive spot electrodes to the neck and chest region to measure cardiac impedance and respiration. In addition, participants will be attached to arm and finger cuffs to continuously index blood pressure. Four five-minute segments will be scored using Mindware. Dr. Leyro will oversee data scoring.

Fitbit data will be downloaded from the devices using appropriate software. Fitbit data is identified only with a randomly generated study ID.

Audio recordings of intervention sessions will be uploaded and stored on a secure server in a digital format. A study ID will be used to identify the recordings. Otherwise, they are not connected with the primary study database in any way. In addition, all patients in the study will be provided with a Google Gmail account to activate their Fitbit. A standardized account name and password without identifying information (e.g., absent of name, initials, date of birth, exc.) will be established for each patient by a member of the research team. The account log and password list will be linked with the patient research identification number but will not contain PHI information. The Gmail account will be shared by the research interventionist, who will be able to access the patient' Fitbit activity data for purposes of the proposed intervention. Google services and data centers protect data with multiple layers of security, including leading encryption technology like HTTPS. The study Gmail accounts will be used to establish and sync Fitbit accounts only and not for study-related or any other communication purposes.

16.1 Quality Control Procedures

At the outset of the study, Dr. Farris and Dr. DiBello (biostatistician) will review the incoming data to assess adequacy for analytic purposes (not to evaluate study outcomes). As the study progresses, Dr. DiBello will continue to monitor the data. These practices ensure data quality so that the primary aims of the study will be met. Given that the independent evaluators will be blinded to outcomes during data collection and will not share results with any study staff who may interact with participants, the risk of these procedures incurring experimenter bias is low.

16.1.1 Standard Operating Procedures

Data are monitored on an ongoing basis to produce a number of standard reports that are made available to the study PI automatically as data tables are populated. Additional

reports can be created as requested. Most reports display data such as recruitment reports comparing goal versus actual recruitment; participant retention reports indicating the number of participants attending each assessment visit, etc. Monitoring reports will also be presented to the DSMC along with outcomes and safety data.

16.1.2 Data and Form Checks

Data and form checks will occur weekly/bi-weekly by the study statistician, PI, Dr. Leyro, and study personnel. Additionally, computer programming will run to flag any discrepancies. Data quality control checks may identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

16.1.3 Site Monitoring

Site monitoring may take place through periodic site visits conducted during the study. The frequency of visits may depend upon the site's performance and the number of participants enrolled.

The purposes of monitoring visits are to:

- Ensure the rights and safety of participants
- Confirm that the study is conducted in accordance with GCP guidelines
- Ensure maintenance of required documents
- Verify adherence to the protocol
- Monitor the quality of data collected
- Ensure accurate reporting and documentation of all AEs and unanticipated problems

During monitoring visits, the recorded data are reviewed and verified against source documents to ensure:

- Informed consent has been obtained and documented in accordance with IRB regulations
- The information recorded on the forms is complete and accurate
- There are no omissions in the reports of specific data elements
- Missing examinations are indicated on the forms
- Participant disposition when exiting the study is accurately recorded

In preparation for monitoring, the monitor has access to all study documents, including informed consent forms, intervention records, and assessments as provided by the PI.

Once the site visit is complete, a site monitoring report is drafted to provide feedback regarding any problems or issues that may have been uncovered during the visit. The report should state the problems uncovered during the visit and describe recommendations to correct them. A timeline will be agreed upon and included in the report to ensure that the

follow-up of the issues is completed and implemented into the study's procedures.

17.0 Data and Safety Monitoring Activities

The data safety monitoring plan (DSMP) for this study focuses primarily on monitoring of study progress by the principal investigator in conjunction with the local data/safety committee, led by the medical SO. Note: This is a single-site, low risk study, thus we are NOT proposing to use a Data and Safety Monitoring Board. Study procedures for monitoring recruitment, data collection, data quality and data management/confidentiality have been outlined below. All reports will be compiled by Dr. Farris and will be circulated to the IRB and the sponsor. Measures to maintain participant privacy and security will be implemented.

Data and Safety Monitoring Committee

Oversight of the participants' safety and quality of data will be conducted by the PI, Dr. Farris, along with our monitoring committee composed of external faculty outside of the Rutgers University IRB. Committee members:

Francesca Mazzulla, MD (Chair/Safety Officer), Cardiologist at Columbia St. Mary's Cardiovascular Specialists

Joshua Kemp, PhD (Member), Clinical Psychologist at Bradley Hospital/Brown Medical School

Lauren Connell Bohlen, PhD (Member), Behavioral Scientist at Brown School of Public Health

The committee will review rates of adverse events to determine any changes in participant risk, recruitment and retention, participant drop out, and will make appropriate recommendations for changes in protocol. Any changes in the protocol will be submitted to the Rutgers University IRB for review.

17.1 Reports

Every six months, study personnel and PI will submit tables indicating progress with recruitment, retention at assessment sessions, and reasons for dropouts to the committee for review. IRB compliance will be reviewed annually by the committee. They will meet twice annually, either in-person or by teleconference, to consider whether corrective action, or a change to protocol is required and if so, report that in writing to the PI, the Rutgers IRB responsible for oversight of this trial, and the NIH sponsor. At any point during the trial, the committee can recommend that a meeting be held to discuss any issues with the progress or safety of the trial. The committee members will also be available to meet outside of the biannual meetings, if necessary, to discuss concerns regarding a particular participant or research problem.

The SO, Dr. Mazzulla, will receive quarterly reports of expected SAEs and will be informed of unexpected SAEs and deaths of actively enrolled participants within 48 and 24 hours, respectively. These reports will be synthesized together with all other adverse events into biannual reports including a detailed analysis of study progress, data and safety issues, which will be submitted for review by Dr. Mazzulla and Safety Monitoring Committee members and also reported to the IRB according to their procedures.

17.2 Study Completion and Close-Out Procedures

Study close-out activities will be performed to confirm that the site investigator's study obligations have been met and post-study obligations are understood.

Close-out activities include, but are not limited to, the following:

- Verification that study procedures have been completed, data have been collected, and study intervention(s) and supplies are returned to the responsible party or prepared for destruction.
- Assurance that all data queries have been completed.
- Assurance that correspondence and study files are accessible for external audits.
- Assurance that the study records are maintained and any relevant study information reported to the NIA.
- Assurance that the investigator will notify the IRB of the study's completion and store a copy of the notification.
- Preparation of a report summarizing the study's conduct.
- Participant notification of the study completion.

Additional close-out activities can be found in **Appendix H**.

17.2.1 Participant Notification

The PI and study staff will notify participants that the study is over at their 3rd follow-up visit (week 24). Participants will be asked whether they would like to be informed of the results and then will thank them for their participation.

17.2.2 Confidentiality Procedures

All data will be collected for research purposes only and all records will be stored in locked files (physical or on computer) in locked rooms accessible only to research staff. Data gathered from people who are screened but who do not meet inclusion criteria or decide not to participate will be stripped of personal identifiers or links and only demographic characteristics and the reason for study exclusion will be kept. Paper forms with personal identifiers (such as consent forms or contact information) will be stored in a locked file that does not contain subject code numbers. All other data will be stored in files locked in a separate location with only code numbers identifying subjects, no personal identifiers. A cross-index of code numbers and participant names will be kept in a separate, password-protected computer file that is available only to research staff (for collecting follow-ups), the PI, and mandated auditing agencies during audits. All de-identified research data will be entered into Qualtrics, a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks) and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Network transmissions (data entry, survey submission, web browsing, etc.) in Qualtrics are protected via Secure Sockets Layer (SSL) encryption. Access to Qualtrics databases can be restricted to specific study personnel. Exported data from Qualtrics will be stored on the Rutgers University secure password-protected server. Multiple redundant backup systems

are in place to ensure security of data storage. In addition, we ensure local confidentiality by requiring rotating password access to client machines and password protected access to database clients. Only the participants' study identification number will appear on any of the final paper data collection instruments. Once data have been entered and passed audit verification, paper copies of data will be housed at a facility that specializes in the storage of medical/research information. Only the subject's study identification number will be present on the forms. Any indication of the subject's name will be removed from the questionnaires prior to its archiving. The destruction date of these paper files will be at least 7 years from the termination of the study and will be authorized by the PI of the research study.

The following is a list of study participant confidentiality safeguards:

- ***Electronic files*** – Data identifying participants that are stored electronically should be maintained in an encrypted form or in a separate file.
- ***Forms*** – Forms or pages containing personal identifying information should be separated from other pages of the data forms and retained in a secure location.
- ***Data listings*** – Participant name, name code, hospital chart, record number, Social Security Number, or other unique identifiers should not be included in any published data listing.
- ***Data distribution*** – Data listings that contain participant name, name code, or other identifiers easily associated with a specific participant should not be distributed.
- ***Data disposal*** – Computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
- ***Access*** – Participant records should not be accessible to persons outside the site without the express written consent of the participant.
- ***Storage*** – Study forms and related documents retained both during and after study completion should be stored in a secure location
- ***Passwords*** – Passwords provide limitations on general access to computer systems and to the functions that individuals can use. Passwords should be changed on a regular basis.
- ***User Training*** – Study staff with access to clinical computer systems should be trained in their use and in related security measures. Training should include explanations of how to access the system and a discussion of the need for, and importance of, system security.
- ***System Testing*** – Prior to the use of a new computer system, and after any modifications, the system should be tested to verify that it performs as expected. Testing should verify that the password-activated access system performs as intended.
- ***System Backups*** – Backup copies of electronic data should be made at specified intervals. Backups should be stored in file cabinets or secure areas with limited access. Storage areas should have controlled temperature (i.e., approximately 68°F (20°C)) and relative humidity (i.e., 50%) so that backup tapes are not damaged.

17.2.3 Publications

Rutgers University is committed to the open and timely dissemination of outcomes and useful information that stems from the proposed research. Similarly, Dr. Farris recognizes that the innovative treatment methods used in this project may have potential for future widespread clinical utility and agree to comply with the requirements, guidelines, and principles described by NIH in NOT-OD-16-149 "NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" for and "NIH Sharing Policies and Related Guidance on NIH-funded Research Resources." Dr. Farris will ensure compliance with the requirements. She will register the study on ClinicalTrials.gov no later than the beginning of month 6 of Project Year 1 or one month before the first study participant is enrolled. The record will include all required content including study description details, recruitment status, location and contact information, and administrative data. The informed consent documents for the study will include a statement that information about the study will be available on clinicaltrials.gov. Study results will be added to the clinicaltrials.gov study record no later than the end of the project period (anticipated to occur at Year 5, month 12). Rutgers University has an internal policy in place via the Office of Sponsored Research to ensure that the clinical trials registration and results reporting occur in compliance with NIH policy requirements. Data generated by this study will be presented at national and international conferences. Results pertaining to study aims will be published no later than 1 year after the end of the project period. All final peer-reviewed manuscripts will be submitted to the digital archive PubMed Central. Also, whenever possible, data will be deposited to appropriate public repositories. Personnel effort, equipment, and other resources necessary to achieve full compliance with requirements for dissemination are included in the study budget.

18.0 MOP Maintenance

The MOP will be continuously reviewed by the study staff to ensure that the operating procedures described are accurate. If any procedures have been changed or modified, the MOP should be updated, and the revised document distributed, with instructions, for replacement in the MOP. See **Appendix D**.

Appendix A - Protocol

INTERVENTIONAL RESEARCH PROTOCOL TEMPLATE

(HRP-503a)

STUDY INFORMATION

- **Title of Project:** A Tailored Exposure Intervention for Exercise Anxiety and Avoidance in Cardiac Rehabilitation
- **Principal Investigator Name:** Samantha Farris, PhD
- **Principal Investigator Div. & Dept.:** Department of Psychology, SAS
- **Principal Investigator Contact Info:**
  Email: samantha.farris@rutgers.edu
  Work Address: 1 Spring Street, New Brunswick, NJ 08901
  Work Phone Number: (845) 445-2174
- **Protocol Version and Date:** 1.2 03/04/2022

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1.0 Research Design

1.1 Purpose/Specific Aims

This study aims to conduct a Stage II randomized-controlled trial of a novel behavioral intervention, titled Behavioral Exposure for Interoceptive Tolerance (BE-FIT), to evaluate (1) its efficacy in improving exercise adherence in cardiac rehabilitation (CR) and (2) its mechanisms of change.

A. Objectives

Objective 1. Compare physical activity outcomes (e.g., lifestyle physical activity levels, CR adherence) between participants randomized to receive BE-FIT or a health education control (HEC).
Objective 2. Compare exercise anxiety levels between BE-FIT vs. HEC.
Objective 3. Examine the mechanisms by which BE-FIT affects physical activity outcomes.

B. Hypotheses / Research Question(s)

Objective 1. We hypothesize that BE-FIT, compared to HEC, will result in higher levels of objectively measured, moderate-to-vigorous intensity physical activity at end-of-treatment and follow-up sessions. We also predict that BE-FIT vs. HEC control will produce a higher lifestyle physical activity (steps/day) on CR and non-CR days and higher rates of CR adherence (% of prescribed CR sessions attended).
Objective 2. We hypothesize that, compared to a health education control, BE-FIT will generate greater reductions in exercise anxiety at end-of-treatment and Week 12. Specifically, we expect BE-FIT vs. HEC to produce **(a)** greater decreases in anxious cognitions (e.g., catastrophizing, uncertainty, intolerance); **(b)** greater decreases in safety behaviors; and **(c)** greater increases in cardiac vagal control, at end-of-treatment and Week 12.
Objective 3. We hypothesize that reductions in exercise anxiety and related components (e.g., reduced cognitive bias, safety behaviors, increased vagal control) at end-of-treatment and Week 12 will mediate the effect of BE-FIT on physical activity outcomes at Weeks 18 and 24.

1.2 Research Significance

Regular exercise and lifestyle PA are critical for quality of life and longevity among a growing aging population and are particularly important for a healthy heart. [1–3] Aging particularly produces changes to the structure and function of the heart [4–6], which explains the increase in risk of cardiovascular disease (CVD) related to advancing age. [7–11] Out of approximately 80 million Americans with CVD, adults aged 60 years or older account for nearly 50% of cases and older adults account for more than 80% of CVD deaths. [11,12] Exercise can promote adaptations to the cardiovascular and pulmonary system and reverse cardiac aging phenotypes, which can help diminish the progression of age-related changes to the heart. [13,14] Despite these benefits, increasing age is related to decreased PA and exercise engagement. [15,16] Cardiac rehabilitation (CR), a multi-component secondary intervention used to speed recovery from acute cardiac events, provides a valuable window-of-opportunity to promote exercise and lifestyle PA [17,18], especially in aging adults who would benefit from individually tailored exercise prescriptions and supervision to guarantee safe uptake and maintenance of PA. [17]

However, adherence to CR is typically low, and exercise adherence in CR is expected to further decrease due to the advanced age of CR patients. [19–23] Therefore, there is a need to determine and target the obstacles for adherence to (a) exercise in CR and (b) lifestyle PA. One mechanism that is relevant to exercise and CR is fear of physical activity, or "exercise anxiety," a construct with cognitive, behavioral, and physiological underpinnings. [24] For CR patients, exercise may be particularly alarming because the exercise sensations may be viewed as intolerable or indistinguishable from sensations typically associated with CVD (e.g., shortness of breath, dizziness, pain). [25–29] Indeed, our preliminary work found that exercise anxiety is common among 40-50% of patients attending outpatient PR and is related to exercise non-adherence. [30,31]

We developed a mechanism-informed behavioral intervention to target exercise anxiety called

Behavioral Exposure for Interoceptive Tolerance (BE-FIT). The three primary components of BE-FIT include: (1) exposure to feared bodily sensations and exercise; (2) prevention of safety behavior use before/during/after exercise, and (3) use of a wrist-worn activity monitor for PA feedback and activity goal setting. Evidence from our Stage I trial indicated that BE-FIT is feasible, acceptable, and safe and produced reductions in exercise anxiety and exercise outcomes (short-term moderate-to-vigorous intensity physical activity and steps/day). Our present aim is to conduct a Stage II randomized-controlled trial to further evaluate the efficacy of BE-FIT in decreasing exercise anxiety in CR patients and examine whether changes in this target yield successive changes in exercise adherence outcomes.

1.3 Research Design and Methods

A. Research Procedures

This study will be a prospective Stage II randomized-controlled trial with patients enrolled in cardiac rehabilitation at Robert Wood Johnson (RWJ) University Hospital Cardiac Rehabilitation Program. One hundred and forty-six patients in cardiac rehabilitation who have elevated exercise anxiety, as indicated by endorsement of *much* to *very much* concern about at least 3 items on the Exercise Sensitivity Questionnaire (ESQ; Farris et al., 2020), and who meet other eligibility criteria will be randomly assigned to either receive BE-FIT, an intervention tailored specifically for CR patients with high levels of exercise anxiety, or a health education control (HEC).

B. Data Points

Patients attending CR orientation at RWJ Cardiac Rehabilitation Program will be screened for study eligibility. Aside from screening, five independent assessments will be performed at baseline, end-of-treatment (EOT), and three follow-ups at Weeks 12, 18, and 24 (See *Table 1* in Section 1.9 below.). All assessments will be performed at RWJ Cardiac Rehabilitation Program.

1. **Screening:** Patients who are scheduled for CR orientation and have provided verbal agreement for study screening procedures (see telephone script) will have their medical records reviewed by study staff to assess for any potential inclusion/exclusion criteria (Medical Data Extraction Form). During orientation, patients will complete a measure of exercise anxiety (Exercise Sensitivity Questionnaire; ESQ) and exercise levels via the 2-item Exercise Vital Sign (EVS). Next, all patients will meet with the medical team during orientation, during which the physician and assistant review physical exams and cardiac history, administer the MoCA, and determine clearance for CR and study participation. Those appearing to meet eligibility criteria will be briefed by the research team about the opportunity to participate in a brief lifestyle program as an adjunct to CR, consented, and enrolled if interested.

2. **Baseline Assessment:** Fully consented and enrolled patients will complete the following baseline assessment questionnaires (20-25 minutes):

   Self-Report Assessments:

   - Cardiac Anxiety Questionnaire (CAQ)[32]
   - Fear of Activity in Coronary Artery Disease (Fact-CAD)[33]
   - Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q)
   - Safety Behaviors Assessment Form (SBAF)[34]
   - Threat Perceptions[35]
   - Valuing Questionnaire (VQ)[36]
   - Intolerance of Uncertainty Scale Short Form (IUS-12)[37]
   - Falls Efficacy Scale-International (Short FES-I)
   - Discomfort Intolerance Scale-Revised (DIS-R)[38]
   - Body Vigilance Scale (BVS)[39]
   - Multidimensional Assessment of Interoceptive Awareness (MAIA)
   - Anxiety Sensitivity Index-3 (ASI-3)[40]
   - General Anxiety Disorder 7-Item Scale (GAD-7)[41]
   - Patient Health Questionnaire-9 (PHQ-9)[42]

These assessments, and those administered at end-of-treatment (EOT) and Weeks 12, 18, and 24 will be completed by an independent evaluator who will be blinded to aspects of CR treatment and study randomization. Patients will be informed to not discuss the nature of their treatment with the evaluator to minimize chance of bias.

Physiological Assessment: Fully consented patients will also complete the following physiological assessments: a 5-min average resting respiratory sinus arrythmia (RSA), 5-minute attentional demand, and 5-minute Stroop task. Respiration rate, heart rate, and baroceptor reflex will also be assessed at baseline. Participants will also be asked to wear a Fitbit activity tracker on their wrist during waking hours for at least 7 consecutive days for 10+ hours/day to establish baseline physical activity prior to randomization. Patients will be given instructions on using the Fitbit and the study tasks requested of them.

Randomization: After completion of at least 7-days of PA monitoring, patients will be randomized to either BE-FIT or HEC using randomization procedures with age (older or equal to 65 years old/younger than 65) and sex (male vs. female) as blocking variables. Age and sex were selected as stratification variables because they are associated with anxiety and fitness levels which could impact PA outcomes. Intervention sessions will coincide with scheduled CR sessions, but the study content (BE-FIT or HEC) is supplemental to CR. Research staff will schedule BE-FIT/HEC sessions in the medical record system in consultation with the CR coordinator to ensure that study sessions and CR appointments coincide, and patients receive reminder calls about the longer appointment times on visit days.

3. **Baseline-Week 24:** Physical activity adherence will be measured continuously through Week 24 via the Fitbit activity trackers.

   End-of-Treatment (EOT) & Weeks 12, 18, 24: Participants will complete the following self-report measures (20-25 minutes)ESQ
   CAQ
   Fact-CAD
   PRETIE-Q
   SBAF
   Threat
   VQ
   IUS-12
   FES-I
   DIS-R
   BVS
   MAIA
   ASI-3
   GAD-7
   PHQ-9

4. **End-of-Treatment (EOT) & Week 12:** Participants will complete the following physiological assessments: 5-min average RSA, 5-min attentional demand, and 5-min Stroop task, and 5-min recovery. Respiration rate, heart rate, and baroceptor reflex will also be measured.

5. At **Week 18**, the number of CR sessions attended by the participant will be assessed.

C. Study Duration

The overall duration of the study is 24 weeks, or approximately 6 months. Subjects will be involved in 6 individual sessions delivered twice weekly during the initial weeks of outpatient CR. Sessions occur for 45 minutes either immediately before or after regularly scheduled CR sessions.

1.4 Preliminary Data

Prior research has found that anxiety sensitivity and fear of exercise are elevated in patients attending cardiac rehabilitation [43], and that 43.5% of patients enrolled in CR had scores at or above the cutoff for moderate fear of bodily sensations and that fear of bodily sensations was not significantly associated with what week in treatment patients were in. This suggests a lack of improvement in fear of bodily sensations over the course of standard CR treatment. Additionally, 18.3% of variance in fears and exercise avoidance was significantly associated with fear of bodily sensations after adjusting for age, sex, week of CR, CVD risk status, and anxiety and depressive symptoms.

In a follow-up study with this same sample, we found that a sizable percent of patients in CR reported specific catastrophic exercise cognitions, including: not being able to breathe during exercise (51.3%), having a cardiac event during exercise (41.9%), and that something terrible physically might happen suddenly during exercise (40.2%); in addition, exercise safety behaviors were common, including stopping/slowing during exercise when experiencing sensations (72.6%) and avoiding exercise when alone because of heart health (32.5%). [30] We also found that practitioners (*n*=16; exercise physiologists in CR) used significantly fewer cognitive-behavioral strategies compared to safety-behaviors (e.g., providing reassurance about HR) in response to a hypothetical exercise anxiety scenario. Thus, both patients and CR practitioners may perform safety behaviors that can unintentionally maintain anxiety. The majority of patients (73%) and practitioners (100%) said it would be beneficial to address exercise anxiety in CR, suggesting wide interest in targeted intervention.

We developed and validated the first measure of exercise anxiety called the *Exercise Sensitivity Questionnaire* (ESQ) for use in CR. [44] The ESQ is an 18-item self-report measure that conceptualizes exercise anxiety as worry and fear about the physical sensations of exercise. The ESQ has two dimensions: (1) anxiety about cardiopulmonary sensations during exercise (i.e., blurry vision, chest pain/tightness, difficulty breathing) and (2) anxiety about pain/weakness sensations during exercise (i.e., joint/back/body pain, aches, soreness). Among older adults enrolled in outpatient CR (*n* = 50): ESQ-Total (Mean=29.4, SD=18.0, Median=31.0, Observed Range = 0-66), ESQ-Total and subscales demonstrated high internal consistency (alpha's = .90 to .93), and good convergent validity (with cardiac anxiety, discomfort intolerance). We also evaluated predictive validity in two samples. In the first sample (*n* = 252 adults with CVD risk, 23.4% with a CR qualifying condition), we found that adults with high exercise anxiety had a 67% lower likelihood of any past 7-day moderate-to-vigorous intensity physical activity (MVPA) participation (OR=.33, CI95%=0.13-0.81, *p*=.016) compared to those with minimal/no exercise anxiety. In a second sample of older adults in outpatient CR, exercise anxiety was correlated with lower objectively measured MVPA during a 7-day period (*r* = -.35).

We evaluated BE-FIT in an open trial of patients (n=12) who were attending outpatient CR at the Cardio Metabolic Institute (CMI). The pilot study of BE-FIT involved an orientation session, six 30-minute individual sessions with a study interventionist delivered 2x weekly during the initial weeks of CR, and an exit interview to assess intervention acceptability. Assessments were conducted at baseline, mid-treatment (session 3), and end-of-treatment (1-week post-treatment). At baseline and end-of-treatment, a 7-day PA monitoring period was completed. PA was monitored via wrist-worn activity monitor with heart rate sensor, which was provided to patients at orientation. We enrolled 12 patients (M_{age}*=72±8.37yrs, range = 53-84yrs, 75% ≥ 65yrs; 25% female*). Findings indicated that BE-FIT was highly feasible (100% session attendance, 97.5% watch compliance [wear ≥ 10hr/day]), acceptable, and safe (no adverse events reported). BE-FIT produced large, significant reductions in exercise anxiety and produced significant medium-sized increases in exercise (MVPA mins/day, steps/day), which was evidenced on CR and non-CR days.

1.5 Sample Size Justification

Power analyses focuses on estimating a sample size large enough to detect "true" effects, avoiding

Type II errors. Sample size estimates were obtained for intervention contrasts, and mediation effects via sample size and power equations using the G*Power software program. Based on pilot data (see 1.4; Preliminary Data), we anticipate intervention effects of BE-FIT vs HEC to be in the medium to large range (d = 0.50-0.60). Based on the proposed sample size of 146, given 5 assessment points, we anticipate the ability to detect effects of intervention contrasts in the medium to large range (Aim 1 and 2) and mediation in the small to medium range (Aim 3). Considering maximum anticipated attrition rates of 15% (N = 124) we will have .80, .85, .90, and .95 power to detect effects sizes of delta = .30, .45, .50, and .60, respectively.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

The independent variable will be the type of intervention received: BE-FIT vs. a health education control (HEC).

BE-FIT: BE-FIT will consist of a 6-session one-on one program with a clinician that are approximately 45 minutes delivered, over the course of 3 weeks (twice/week). Sessions will coincide with scheduled cardiac rehabilitation sessions at RWJ Cardiac Rehabilitation Program. The elements of BE-FIT are (1) psychoeducation about avoidance/anxiety and values clarification and committed action for exercise and lifestyle PA; (2) graded, repeated exposure to bodily sensations and exercise to build tolerance of discomfort; (3) fading safety behaviors and elimination of exercise avoidance behaviors to promote tolerance of uncertainty and reduce catastrophizing; and (4) use of Fitbit activity tracker to facilitate physical activity monitoring and provide physical activity feedback and goal-setting.

Session content is as follows*:

- Session 1: Psychoeducation & Setting PA Goals

  In Session One, patients will be provided with a rationale for the BE-FIT via targeted psychoeducation about the relationship between bodily sensations, anxiety, and related exercise avoidance, and it will be explained that they can improve both their physical and mental health by actively participating in this program. The interventionist will review the patient's anxiety about exercise, the specific feared sensations endorsed on the ESQ and their relationship to the patient's cardiac events/procedures (e.g., surgery).

  Interventionists review the cognitive-behavioral model of anxiety, discuss normal (healthy) vs. feared exercise sensations, and the role of avoidance in maintaining anxiety and suffering. The interventionist will also review the role of exercise and lifestyle PA for healthy aging, and discuss how daily accumulation of short bouts (≥10 minutes) of both planned and unplanned activities as part of day life can aid in manageable and sustainable changes to lifestyle PA. Interventionists will help patients to identify values for exercise and PA change to aid in motivational enhancement for lifestyle change throughout the intervention.

- Session 2: Rationale for Exposure/Fading Safety Behaviors & Developing Exposure Hierarchy

  Within the manualized intervention, therapists will follow a procedure to identify and target each participant's feared exercise sensations. It is anticipated that patients will present with a variety of qualifying and co-morbid medical conditions, as well as a varied array of feared sensations which contribute to avoidance of PA. Any exercise sensations whether cardiopulmonary in nature or related to other sensitivities (e.g., pain, weakness, instability) are relevant to older adults with a variety of cardiovascular and other health issues, thus are targeted in BE-FIT. Patients will be provided the rationale and participate in guided practice of exposure – regular and systematic practice of avoided activities and activities that intentionally elicit feared bodily sensations. The goal of exposure is to

facilitate interoceptive tolerance and learning that sensations can be experienced without avoidance.[45] Exposures will be planned by the interventionist in collaboration with the patient, exercise physiologist and cardiac technician, and tailored to each patients' needs based on the nature of their anxiety and avoidance behaviors. Exposures will increase in difficulty during treatment to maximize tolerability and acceptance of bodily sensations. Patients will be reminded that sensations are normal reactions and that while they are uncomfortable, experiencing them during exposure will help them build tolerance and help to facilitate exercise and PA in the long term. Exposures will be practiced in session with the guidance of the interventionists: for example -- short bouts (1-2 min. intervals) of aerobic or resistance training to elicit certain body sensations, or other activities that elicit sensations like breathing through a straw (shortness of breath) or standing on one foot (wobbly balance).[46,47] In addition, patients will be assigned exposure practice to be completed at home during lifestyle PA in order to facilitate generalizability of learning.

- Sessions 3, 4, 5: Exposure Practice & Fading Safety Behaviors

  The interventionist will help patients to recognize and increase awareness of anxiety-motivated behaviors and aid in identifying any patterns or persistent themes of avoidance. Interventionist will discuss how anxiety's effect on avoidance can be overt (choosing not to engage in exercise when unsupervised, skipping CR because of anxiety) and subtle (i.e., less obvious ways). For example: ending bouts of walking earlier than planned, walking at a slower pace (lower intensity), or relying on safety ("just in case") behaviors (e.g., calling someone to seek reassurance about bodily sensations). Because excessive HR checking is a common safety behavior in CR, thus will be proactively targeted as a 'teachable moment'.

  Patients will be taught how checking HR during exercise (e.g., via Fitbit) provides safety reassurance in the moment but can reinforce false beliefs that exercise is only safe because of HR feedback (e.g., "It's only ok for me to be active because I've checked to be sure my heart rate is in the safe zone), thus while safety checking behaviors temporarily alleviating distress, they ultimately narrow the range of tolerated conditions for exercise. Fading and eventual elimination of safety behaviors will be encouraged during exercise to aid in reduction of anxiety, including shifts in cognitions about exercise (e.g., increase tolerance for uncertainty; reduce catastrophizing).

- Session 6: Goal Setting and Planning for Maintenance of Physical Activity

BE-FIT will be administered by doctoral-level clinicians who are trained exclusively to deliver BE-FIT. The interventionist will work with the study exercise physiologist to coordinate tailoring of BE-FIT content to the patient.

*Note: Physical activity monitoring and feedback occur at each session.

Health Education Control (HEC): HEC is a time-matched control intervention that will be administered on the same "delivery schedule" as BE-FIT. The intervention content includes: (1) educational information about health topics relevant to healthy aging, and (2) Use of the Fitbit activity watch for PA monitoring. The 6 topics introduced in the HEC include: nutrition, sleep, brain health, emotional health, living with chronic conditions, how to be a smart patient. The health information will be conveyed through lectures and handouts. The goal of sessions will be to provide education, particularly as it relates to healthy aging. Patients will be given the same Fitbit as in the BE-FIT but will not be given PA goals.

The HEC will be delivered by two doctoral-level clinicians who will be trained to exclusively deliver HEC and will differ from the interventionists administering BE-FIT to avoid contamination. Interventionists will routinely address questions related to the Fitbit such as syncing issues, charging the battery, and any other technical problems that may arise.

B. Dependent Variables or Outcome Measures

The primary outcome is objectively measured exercise (moderate-to-vigorous intensity physical activity mins/day) on both CR and non-CR days. The secondary outcomes are (1) % of prescribed CR sessions attended and (2) objectively measured lifestyle PA (steps/day). Target mechanisms are exercise anxiety and its components (cognitions, safety behaviors, and cardiac vagal control).

1.7 Drugs/Devices/Biologics

N/A

1.8 Specimen Collection

N/A

1.9 Data Collection

A. Primary Data Collection

- **Location**: All data collection will occur at RWJ Cardiac Rehabilitation Program locations in New Brunswick and East Brunswick.
- **Process of Data Collection**: Data will be collected via participant self-reports and Fitbit Charge 5 activity trackers that will be worn by enrolled participants. An independent evaluator will collect self-report assessments. Graduate-level research assistants will administer the physiological assessments and treatment sessions (BE-FIT or HEC) to participants. Dr. Farris will be responsible for overseeing the data collection process.
- **Timing and Frequency**: All participant study visits will occur during their regularly scheduled CR appointments at RWJ Cardiac Rehabilitation Program. The screening visit will occur during the patient's orientation. The treatment sessions will occur for 45 minutes biweekly for a period of 3 weeks either immediately before or after their regularly scheduled CR sessions. EOT and 12-week Follow-Ups will coincide with patients' CR appointments. Week 18 and 24 Follow-Up appointments will be scheduled at participants' convenience, coinciding with medical appointments when possible.
- **Procedures for Audio/Visual Recording**: Drs. Farris and Leyro will monitor adherence through weekly supervision and audiotape-review of sessions (separate supervision groups for BE-FIT and HEC interventionist). Additional details regarding audio recordings will be included in the consent document given to patients. All audiotapes will be erased upon completion of data analysis. Audio-recorded data will be stored in a locked filing cabinet and the tapes will be destroyed after the data is analyzed.

- **Study Instruments**:

Table 1. Study Measures	Time Point	Method
Eligibility Assessment		
Exercise Sensitivity Questionnaire (ESQ)	Screen, EOT, W12, W18, W24	Self-Report
Exercise Vital Sign (EVS)	Screen	Self-Report
Montreal Cognitive Assessment (MoCA)	Screen	Interview
Cardiac/medical history and treatments	Screen	Medical Record
Physical Activity Adherence		
MVPA minutes/day; Steps/day	Continuous (BL-W24)	FitBit Tracker
# CR sessions attended	EOT, W18	Medical Record
Psychological Functioning		
Patient Health Questionnaire (PHQ-9)	BL, EOT, W12, W18, W24	Self-Report
General Anxiety Disorder 7-Item Scale (GAD-7)	BL, EOT, W12, W18, W24	Self-Report
Valuing Questionnaire (VQ)	BL, EOT, W12, W18, W24	Self-Report
Anxiety Sensitivity Index (ASI-3)	BL, EOT, W12, W18, W24	Self-Report
Target Mechanisms		
Cognitions		
Cardiac Anxiety Questionnaire (CAQ)[158]	BL, EOT, W12, W18, W24	Self-Report
Threat Perceptions	BL, EOT, W12, W18, W24	Self-Report
Intolerance of Uncertainty Scale Short Form (IUS-12)[160]	BL, EOT, W12, W18, W24	Self-Report
Falls Efficacy Scale-International (Short FES-I)	BL, EOT, W12, W18, W24	Self-Report
Discomfort Intolerance Scale (DIS-R)[161]	BL, EOT, W12, W18, W24	Self-Report
Body Vigilance Scale (BVS)	BL, EOT, W12, W18, W24	Self-Report
Multidimensional Assessment of Interoceptive Awareness (MAIA)	BL, EOT, W12, W18, W24	Self-Report
Avoidance/Safety Behaviors		
Safety Behaviors Assessment Form (SBAF)[162]	BL, EOT, W12, W18, W24	Self-Report
Fear of Activity in Coronary Artery Disease (Fact-CAD)	BL, EOT, W12, W18, W24	Self-Report
Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q)	BL, EOT, W12, W18, W24	Self-Report
Physiological parameters		
Vagal tone: 5 min avg resting Respiratory Sinus Arrhythmia (RSA)	BL, EOT, W12	Physiological
Vagal flexibility: change in RSA from resting to demand	BL, EOT, W12	Physiological
Heart rate deceleration: Stroop task event-related potential	BL, EOT, W12	Physiological
Respiration Rate (RR), Heart Rate (HR), Baroreceptor Reflex	BL, EOT, W12	Physiological

Demographics. General demographic information including age, sex, race/ethnicity, income level and level of education will be collected from medical records and/or at the baseline assessment.

Health and Exercise History. Psychological and health history will be evaluated at baseline. Medical records will be referenced at baseline to determine eligibility based on cardiac diagnosis, medical conditions and medications, and score on Exercise Sensitivity Questionnaire (ESQ; see preliminary data). Cognitive ability will be assessed using the Montreal Cognitive Assessment (MoCA). [48] The 2-item Exercise Vital Sign will be utilized to measure patients' self-reported exercise levels. [49]

Exercise Anxiety. The Exercise Sensitivity Questionnaire (ESQ) will be used to measure exercise anxiety. [31] Please see the preliminary data section for more information related to the measure's reliability and validity.

Psychological Functioning. Validated measures commonly used in medical settings to screen for common psychiatric conditions (PHQ-9[42], GAD-7[41]),a measure of values-consistent living validated for use in CVD populations (Valuing Questionnaire[36,50]; VQ), and a general index of anxiety sensitivity (Anxiety Sensitivity Index; ASI-3)will be administered**.**

Anxious Cognitions. Validated report assessment of anxious cognitions will be used to tap catastrophizing (Cardiac Anxiety Questionnaire; CAQ[40] and Threat Perceptions), intolerance of uncertainty (Intolerance of Uncertainty Scale-Short; IUS-12)[51], discomfort intolerance (Discomfort Intolerance Scale; DIS)[52], interoceptive awareness and appraisal (Body Vigilance Scale; BVS and Multidimensional Assessment of Interoceptive Awareness; MAIA), and fear of falling (Falls Efficacy Scale-International (Short FES-I).

Avoidance/Safety Behaviors. Avoidance behaviors will be assessed via the Safety Behaviors Assessment Form (SBAF)[14] and Fear of Activity in Coronary Artery Disease (Fact-CAD), and The Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q).

Physical Activity. A Fitbit activity tracker will be used to assess how much physical activity participants partake in per day and objective exertion of exercise. A number of options exist for goal-setting and we will customize each participant's account to display the following: daily steps, very active minutes, and activity during each hour of the day. While the vast majority of lifestyle PA will consist of walking, Fitbit trackers are waterproof and can be worn while swimming. Also, we will provide exchangeable clips to allow for trackers to be attached to a sneaker when cycling. In doing so, we likely capture all types of lifestyle activities.

During Session One, the interventionist will review baseline PA from the baseline assessment, including daily steps and MVPA. The interventionist will use these data to tailor two possible PA prescriptions (goals) – (1) Increasing steps/day: If baseline steps/day reflect sedentary/low activity (accumulate avg<4,000 steps/day),[54] patients will be given the goal of achieving 4,500 steps/day and increasing each session by 500 steps/day (about 1/4 mile increase), as recommended by the recent update to PA guidelines.[55] At this rate, patients will reach ~7,500 steps/day by EOT, which is an empirically-derived minimum for daily PA in older adults for longevity;[56] and/or (2) Increasing PA intensity: If baseline active min/day reflect low MVPA (accumulated avg < 30 active mins/day), patients will be given the goal of working gradually towards achieving and maintaining 30 very active minutes/day. This gradual approach is consistent with implementation of exposure therapy[46] and will ensure that patients are not engaging in anxiety-driven avoidance of higher intensity-PA.

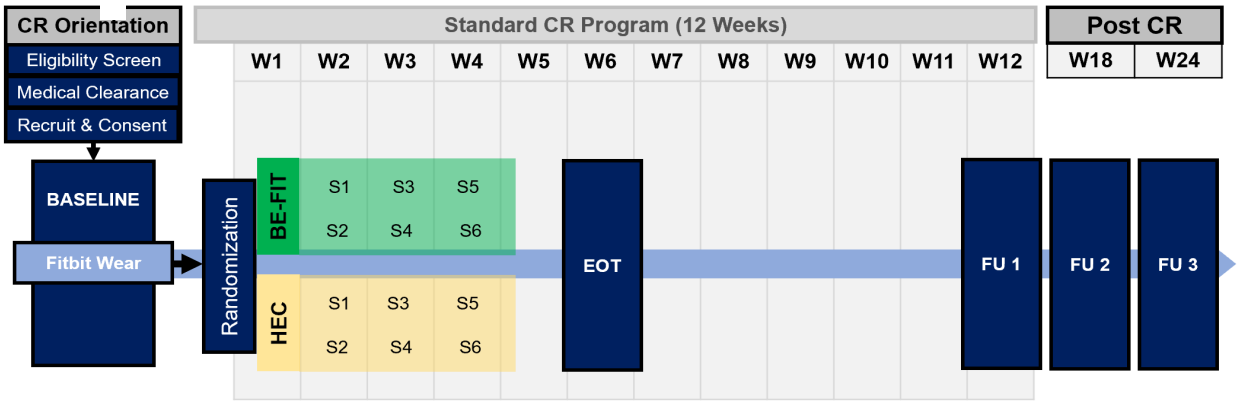
Physiological Parameters. To assess cardiac vagal control as a physiological parameter of exercise anxiety and a putative BE-FIT target, respiratory sinus arrhythmia (RSA), an index of cardiac vagal control will be indexed at baseline, end-of-treatment, and 12-Week follow-up. At each time point, we will specifically assess cardiac vagal control during a 5-minute resting period (i.e., tonic) and cardiac vagal reactivity during a 5-minute attentional demand (i.e., phasic changes in RSA), which has previously been used to assess acute changes in cardiac vagal control as an index of psychological flexibility and vulnerability.[57] We will also assess heart rate deceleration (event-related potential) in response to a 5-min Stroop task. Continuous measures of electrocardiograph (ECG), impedance cardiograph (IC), and blood pressure (BP) will be acquired at 1000 Hz using a Biopac MP150 and an integrated CNAP blood pressure monitor. Signals will be scored and offline in 1-minute bins in accordance with recommendations of the Society for Psychophysiological Research[58–60] using MindWare's integrated system (BioNex 8SLT Biolab Acquisition Application, MindWare Technologies, Gahanna OH).

RSA will be specified as the integral power within typical adult respiration frequency (.12 to .4 Hz), and respiration rate will be derived from IC. Reactivity will be computed by subtracting baseline scores from the attentional demand scores; because RSA decreases during attentional demand, lower numbers for vagal reactivity represent greater reactivity. Cardiac output will be calculated with the Kubicek formula to provide an estimate of the amount of blood processed by the heart in 1 min. The pre-ejection period will be measured as the time in ms from the onset of ventricular depolarization to the aortic valve opening. Continuous assessment of BP will allow scoring of the baroreceptor reflex, defined as changes in the interbeat interval per unit change in BP (ms/mmHG), a supplemental index of vagal control. Use of beta blockers will be used as a covariate when interpreting parameters given its physiological effects.

- **Subject Identifiers**: All study data will be coded with a de-identified study ID number.

1.10 Timetable/Schedule of Events

Figure 2. **Timing of Intervention and Assessment Components**



CR Orientation: Prior to the eligibility screen, patients will already be scheduled for their CR orientation at RWJ Cardiac Rehabilitation Program in New Brunswick, NJ. Medical records for these patients will be screened by study staff to assess potential eligibility.

Eligibility Screen/Medical Clearance: In addition to reviewing patient medical records, patients will complete an assessment of exercise anxiety (ESQ) and exercise levels via the 2-item Exercise Vital Sign (EVS) during CR orientation. Next, all patients meet with the medical team during orientation, during which the physician and assistant will review physical exams and cardiac history, administer the MoCA, and determine clearance for CR and study participation. Potentially eligible subjects will be approached by study staff at their CR orientation visit to see if they're interested in the study.

Recruit & Consent: Those appearing to meet eligibility criteria will then be fully briefed by the research team about the opportunity to participate in a brief lifestyle program as an adjunct to CR. After receiving this thorough introduction, they will complete informed consent for study enrollment, if interested.

Baseline: Baseline appointments will be scheduled with interested and potentially eligible patient on the same day as orientation or on a subsequent day, based on patient preference. Enrolled patients will complete the baseline assessments, be provided with the Fitbit, and be shown how to wear and charge it. Patients will be required to wear the Fitbit for at least 7 consecutive days for 10+hrs/day to establish baseline PA activity prior to randomization. The following self-reports will be administered at baseline:

- Fact-CAD
- PRETIE-Q
- PHQ-9
- GAD-7
- VQ
- CAQ
- IUS-12
- FES-I
- DIS-R
- BVS
- SBAF
- Threat Perceptions
- MAIA
- ASI-3

The following physiological assessments will be completed:

- Vagal tone
- Vagal flexibility
- Respiration rate, heart rate, and baroceptor reflex

Randomization to BE-FIT/HEC: After completion of at least 7-days of PA monitoring, patients will be randomized to either BE-FIT or HEC. Intervention sessions will coincide with scheduled CR sessions, but study content will be supplemental to the CR. The sessions are scheduled in this way to minimize risk of treatment contamination. Research staff will schedule BE-FIT/HEC sessions in the medical record system in consultation with the CR coordinator to ensure that study sessions and CR appointments coincide, and patients receive reminders about longer CR visits on study days. BE-FIT or HEC will be delivered biweekly for 3 weeks before or after a patient's scheduled CR sessions (please see Independent Variables, Interventions, or Predictor Variables for more details on these treatment types).

End-of-Treatment (EOT) and Follow-up Assessments (Week 12, 18, and 24): At EOT and weeks 12, 18, and 24, patients will complete assessments that involve multimethod approaches including a medical record review, interview with independent evaluator, self-report questionnaires, and objective physical activity monitoring.

- The following self-report assessments will be administered at EOT and Weeks 12, 18 & 24: ESQ
- Fact-CAD
- PRETIE-Q
- PHQ-9
- GAD-7
- VQ
- CAQ
- IUS-12
- FES-I
- DIS-R
- BVS
- SBAF
- Threat Perceptions
- MAIA

ASI-3Physiological assessments via ECG/Impedance Cardiography using Biopac MP150 will be administered at EOT and Week 12:

- Vagal tone
- Vagal flexibility
- Respiration rate, heart rate, and baroceptor reflex

Physical activity adherence will be assessed throughout the study (Baseline to Week 24) via the Fitbit activity trackers.

2.0 Project Management

2.1 Research Staff and Qualifications

Samantha G. Farris, Ph.D., (Principal Investigator, Director of REHAB Lab). Dr. Farris is an Assistant Professor in the Department of Psychology at Rutgers University and is a licensed clinical psychologist. Dr. Farris has published over 80 peer-reviewed publications, with a primary focus on fear of bodily sensations and somatization and its role in the maintenance of problem health behaviors, including physical inactivity. Dr. Farris' training and research has been supported by NIH for the past 6 years (R25-CA057730; T32-HL076134; F31 DA035564; PI Farris) and has served as a project director on 8 NIH-funded intervention trials. Dr. Farris completed a two-year fellowship in Cardiovascular Behavioral Medicine at the Brown Medical School (Providence, Rhode Island), during which she conducted research and clinical work in Outpatient Cardiac Rehabilitation. Dr. Farris has expertise in cognitive-behavioral and exposure-based interventions for anxiety disorders, including

fear of bodily sensations, and has trained and supervised research therapists on the delivery of interoceptive exposure to target somatization. On the present study, Dr. Farris will be the overall scientific director of the proposed work and will be responsible for maintaining the scientific and procedural integrity of the project. She will work closely with the co-investigators to provide training and ongoing weekly supervision to research staff involved in assessment procedures and to therapists in the provision of the treatment. Additionally, Dr. Farris will oversee the data management and analysis and will assume primary responsibility for the preparation of scientific reports and the dissemination of the results of the study.

Teresa Leyro, Ph.D. (Co-Principal Investigator, Director of ABUSA Lab). Dr. Leyro is a licensed clinical psychologist experienced in research on anxiety, including adults with panic disorder (F31DA024919) and adults with mixed anxiety/depression (R34DA043751; R03DA041556). She also has experience in the measurement of physiological parameters (R34DA043751; R03DA041556). She completed a Ph.D. in Clinical Psychology at the University of Vermont where she served as a member of the Vermont Tobacco Evaluation and Review Board. Dr. Leyro completed post-doctoral training in substance abuse treatment and services research at the University of California, San Francisco. She will be aiding in referrals and recruitment of participants through a shared universal phone screen. Dr. Leyro will work closely with Dr. Farris to provide training and ongoing weekly supervision to research staff involved in assessment procedures and to therapists in the provision of the treatment. She will also oversee the data management and analysis with Dr. Farris.

Brandon Alderman, Ph.D., Co-Investigator. Dr. Alderman is an Associate Professor and Vice Chair in the Department of Kinesiology and Health at Rutgers University, and is the Director of the Rutgers Exercise Psychophysiology Lab. Dr. Alderman has established a patient-oriented research program to study how exercise and other behavioral interventions can be used to enhance physiological, neurocognitive and psychological resilience. His work utilizes the use of advanced psychophysiological techniques including impedance cardiography and electroencephalography to better inform intervention development. Dr. Alderman will provide input on all aspects of the project. Additionally, Dr. Alderman will assist with biofeedback and exercise monitoring to maximize efficacy of the intervention protocol. During the later stages of the project, Dr. Alderman will assist with data management protocols for exercise data and will participate in the preparation of scientific reports and dissemination of study results.

Angelo DiBello, Ph.D., Co-Investigator. Dr. DiBello is an Associate Professor in the Center for Alcohol & Substance Use Studies at Rutgers University. Dr. DiBello has expertise in advanced data analyses and experience in conducting longitudinal analyses specific to behavior change interventions. He has specific training and proficiency in areas consistent with this research application and is well-prepared to serve as a Co-Investigator and lead analyst for the study being proposed in this application. Over the past 7 years he has contributed to the execution of 5 RCTs, and he has relevant experience running large scale NIH-funded projects. Dr. DiBello will serve as the primary data analyst and conduct primary and secondary analyses with a specific focus on modeling non-normal exercise related outcomes.

Michael Steinberg, MD, MPH (Collaborator, RWJ Cardiac Rehabilitation Program). Dr. Steinberg Professor and Chief in the Division of General Internal Medicine as well as Vice-Chair of Research for the Department of Medicine at Rutgers Robert Wood Johnson (RWJ) Medical School. He is involved in connecting researchers with primary care clinics within the RWJ University Hospital network where they can evaluate their treatments. He will facilitate recruitment efforts and providing additional support, if needed, to recruit subjects at other clinics in order to meet study enrollment goals.

Anagha Babu, B.S. (Lab Manager). Ms. Babu is the laboratory manager of the Rutgers Emotion Health and Behavior Laboratory (REHAB Lab), which Dr. Farris serves as the director of. Ms. Babu completed her B.A. in Applied Mathematics & Statistics at Johns Hopkins University. Ms. Babu will assist in the preparation of all assessment materials, subject recruitment, screening, and scheduling participants, and will assist with conducting baseline and follow-up visits. She will also be responsible for the coding, entry, and verification of study data and oversee all research assistants.

Sonali Singal, (Lab Manager): Ms. Singal is the laboratory coordinator of the Affective and Biological Underpinnings of Substance Abuse Laboratory (ABUSA Lab) under the direction of Dr. Teresa Leyro (Co-I). Ms. Singal has completed her B.S. in Psychology from Northeastern University and has multiple years of experience conducting research in psychology, as well as working with clinical populations. Ms. Singal oversees study protocol for Dr. Leyro's various projects, which include

data management, subject assessments, conducting intervention, baseline, and follow-up protocols, and overseeing undergraduate research assistants.

Sayaka Carpenter, (Study Coordinator): Ms. Carpenter is a study coordinator in the Rutgers Emotion Health and Behavior Laboratory (REHAB Lab), directed by Dr. Samantha Farris. Ms. Carpenter completed her B.S. in Exercise Science at Rutgers University during which time she conducted research in Dr. Brandon Alderman's (Co-I) Exercise Psychophysiology Laboratory. Ms. Carpenter will be assisting in the preparation of BE-FIT study materials and overseeing undergraduate research assistants. She will also serve as the primary Independent Assessor during study start-up, collecting physiological and self-report data at baseline and follow-up visits,

Graduate Student Interventionists and Independent Assessors.

- Mindy Kibbey, M.S
- Erick Fedorenko, M.S
- Jacqueline Smith, M.S.
- Hannah Brinkman, M.S
- Danielle Hoyt, M.A.
- Andrew Ude,, M.S.
- Lilly Derby, B.S.
- Shelby Bandel, M.S.
- Taylor Rodriguez, M.

Ms. Kibbey, Mr. Fedorenko, Ms. Smith, Ms. Brinkman, Ms. Hoyt, Ms. Derby, Ms. Bandel, and Ms. Rodriguez are all current graduate students in the Clinical Psychology Ph.D. program at Rutgers University. They will serve as either (1) interventionists at RWJ Cardiac Rehabilitation Program, meeting with patients in order to deliver their treatment sessions in either the BE-FIT or HEC condition, or (2) independent assessors administering study measurement tools and psychophysiological monitoring protocols. Mr. Ude is a current graduate student in the Department of Kinesiology under the supervision of Dr. Brandon Alderman (Co-I) and has experience in psychophysiological assessment and exercise science. He will serve as an independent assessor. Under the oversight of PI Dr. Farris, all graduate student evaluators will be trained in intervention protocol in order to ensure optimal practice of patient interactions and informed delivery of patient care. All graduate student research assistants have prior research and clinical experience and are familiar with standard research procedure including confidentiality and ethical practice.

- **Undergraduate and Post-bacc Research Assistants**Aastha Parikh
- Aisha Ghauri
- Asher Hong
- Dana Steinberg
- Dipabali Jana
- Eric Quartey
- Sarah Farhan
- Huong Le
- Jason Marum
- Kathleen Kildosher
- Kunj Patel
- Melissa Kao
- Muhammad Razi Hussain
- Samantha Stucchi
- Sarah Farhan
- Sathya Gopinath

Yuthikaa RajUndergraduate and Post-bacc research assistants may assist in entering, cleaning, and scoring participant data at the REHAB Lab.

2.2 Research Staff Training

Study staff will complete CITI training for working with human subjects and will be trained using Fitabase software and Fitbit physical activity watches. BE-FIT training will be conducted by Drs. Farris and Leyro,

who will provide overviews of the conceptual and theoretical bases of the approaches, as well as providing practical recommendations for protocol delivery and opportunities to practice the implementation of the protocols. We will employ a previously developed treatment fidelity assessment tool [61] based on NIH's Behavior Change Consortium (BCC) framework that includes the 5 domains: treatment design, training providers, delivery of treatment, receipt of treatment, and enactment of treatment skills. This framework has been employed in the context of PA interventions [62]. We also developed an adherence manual for BE-FIT. The fidelity rater will indicate whether a specific treatment component was discussed in the session. If interventionist-drift is detected, interventionists will be given feedback and the problem will be corrected through supervision.

2.3 Other Resources

The primary research setting will be RWJ University Hospital Cardiac Rehabilitation Program in New Brunswick and East Brunswick, NJ. See Letter of Support from Dr. Steinberg. The RWJ Cardiac Rehabilitation Program is an American Association of Cardiovascular and Pulmonary Rehabilitation nationally certified program that provides supervised exercise regimens and health education for CR patients. RWJ Cardiac Rehabilitation Program has electronic medical database and paper charts with patient records that clinicians and therapists will use to inform the study in terms of patient eligibility and scheduling. The RWJ Fitness and Wellness Centers contain state-of-the-art exercise facilities including exercise bike ergometers, treadmills, step machines, exercise arm ergometers, and elliptical machines which will be utilized by participants in the study. There are also private rooms used to conduct individual assessments and interventions. These rooms include computers that can be used to assess medical records. Participants will be patients at RWJ Cardiac Rehabilitation Program, and all assessments will take place the same day as their sessions there.

The REHAB Lab will be utilized for data analysis. The lab includes a 7-room suite (approximately 1,200 square feet) and a research exercise facility (600 square feet), all dedicated for Dr. Farris' research. Each of the offices used by the REHAB Lab contains at least one or more networked computers (Dell PC computer). These machines are used for data entry, data analysis, and centralized communications among Dr. Farris and research staff. All workstations are equipped with computers that operate on Windows XP platforms and are linked to a local secure network with email, a dedicated server and remote access to Rutgers University libraries and catalogs. The REHAB Lab is equipped with a high-capacity Hewlett Packard LaserJet printer, an additional HP color printer, a high-capacity copy machine, a fax machine, and a color scanner. All computers are equipped with a variety of licensed research related software packages including Microsoft Office, SPSS (v. 25), and Stata (v. 10). The Psychology Department provides full IT and application support by a full-time dedicated employee.

2.4 Research Sites

The research will be conducted in partnership Robert Wood Johnson (RWJ) University Hospital Cardiac Rehabilitation Program. Research activities will take place at the program's New Brunswick location at 100 Kirkpatrick St, #201, New Brunswick, NJ 08901 and at the East Brunswick location at 593 Cranbury Road, East Brunswick, NJ 08816.

3.0 Multi-Center Research

All research will be conducted in collaboration with RWJ University Hospital Cardiac Rehabilitation Program.

Data will be accessed by IRB-approved personnel for analysis at the Rutgers Emotion, Health and Behavior (REHAB) Laboratory overseen by Dr. Farris in the Department of Psychology at Rutgers University, 1 Spring St., New Brunswick, NJ, 08901.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects and Recruitment Details

Subjects will be recruited at RWJ Cardiac Rehabilitation Program. Potential subjects will be identified via the RWJ Cardiac Rehabilitation Program medical records system which will include both electronic records and paper charts. Patients scheduled for CR orientation who verbally agree to screening procedures will have their medical record pre-reviewed by study staff prior to their orientation visit to assess potential inclusion and exclusion criteria.

Patients who are identified as eligible by study staff and have been cleared by staff at RWJ Cardiac Rehabilitation program will be approached by a member of the study team who will use a recruitment script to introduce themselves to the patient and provide initial information about the study. Patients will also receive a study brochure that will include more details about the study.

B. Subject Screening

Individuals who are attending CR orientation at RWJ Cardiac Rehabilitation Program in New Brunswick and East Brunswick will be screened for study eligibility.

- **Inclusion Criteria:**
  1. ≥ 40 years of age
  2. Elevated exercise anxiety (score of ≥ 30 on ESQ-18)
  3. Low active (< 90 min self-reported moderate-to-vigorous intensity physical activity/day in past three months)
  4. Medically approved cardiac rehabilitation
  5. English proficiency
- **Exclusion Criteria:**
  1. Evidence of cognitive impairment (< 23 on Montreal Cognitive Assessment; MoCA)
  2. Severe disabling chronic medical and/or psychiatric comorbidities determined on a case-by-case basis that prevents safe or adequate participation
  3. Expectation that patient will not live through study periods

C. Privacy Protections

Subject identifiers will be coded with a de-identified study ID number. There will be one physical copy of names with corresponding study ID numbers that will be kept under lock and key at the REHAB Lab suite in Spring Street. There will also be a password-protected digital copy of the participant database that can be accessed by 1-2 members of the research staff (study coordinator and Dr. Farris). Patient health records can only be accessed via the RWJ Cardiac Rehabilitation Program electronic records system or paper charts and will only be accessed by trained study staff at the site according to RWJ Cardiac Rehabilitation policy.

4.2 Obtaining Identifiable Information About Non-Subjects

We may potentially collect the name and phone number of caretakers or family members who help manage the scheduling and/or transportation for patients at RWJ Cardiac Rehabilitation Program. This information will be collected to advise the caretaker of the patient's appointment schedule. We will first ask patients to provide contact information for their family member/caretaker and then obtain verbal consent from the caretaker to contact them and to have their contact information saved in a secure file. These non-subjects will also be briefed on the study protocol.

4.3 Number of Subjects

A. Total Number of Subjects

We will recruit 146 subjects enrolled in CR with elevated exercise anxiety across both locations of RWJ Cardiac Rehabilitation Program. This is the total number of subjects needed to complete the research procedures.

B. Feasibility

In our Phase I pilot study, we screened a total of 79 patients over the course of 9 months (~8.5 /month). Of those screened, roughly 50% were eligible, of which ~50% enrolled (2.5/month). Notably though, this pilot was operating with a lean research staff which limited our capacity to

fully screen all patients scheduled for CR orientations, in addition to our inability to enroll eligible patients (n=7 not enrolled due to staffing limitations). Given the planned, slower pace of recruitment for our pilot study, our original recruitment rates do not fully reflect our capabilities. With increased effort and resources devoted to recruitment, we expect to enroll a greater proportion of eligible patients and eliminate instances where enrollment/recruitment is otherwise limited by staffing availability.

Given the proposed staffing and resources from our grant, we will be positioned to allow all eligible and interested patients into the RCT. With our expanded capacity, we expect to be able to enroll all eligible and interested patients, which based on the pilot numbers would be ~60% of eligible patients (and 33% of screened patients). Given that RWJ Cardiac Rehabilitation Program treats ~150 pts/year in CR, we expect that approximately 75 patients/year would be eligible, of which ~45 patients would enroll per year (~3-4 pts/month). At this rate, we would be able to meet our planned recruitment of 146 over ~40 months.

In the event that further assistance is needed to support recruitment for the proposed study, we will work with Co-I Dr. Steinberg to facilitate the necessary recruitment efforts within additional outpatient cardiac rehabilitation clinics at RWJ University Hospital.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Informed consent will be obtained at RWJ Cardiac Rehabilitation Program, an outpatient cardiac rehabilitation program in New Brunswick, NJ.
- **Individual Roles for Researchers Involved in Consent**
  REHAB laboratory staff, including project coordinators, graduate students, and research assistants will all be appropriately trained to obtain verbal and written consent from potential participants.
- **Consent Discussion Duration**
  The consent discussion will take approximately 15-20 minutes. At this time, patients will have the study pitched to them, be told of the potential benefits and risks of participation and have the chance to ask questions about procedures/participation. If subject is still interest after the consent discussion, they will be asked to sign and date the consent form.
- **Coercion or Undue Influence**
  Interested and eligible patients will be told that their decision to participate is completely voluntary. Study staff will emphasize to patients that they will still complete their regular CR at RWJ Cardiac Rehabilitation Program if they choose not to participate, that there is no penalty to them if they choose not to participate, and they will not lose any benefits that are entitled to as a patient at RWJ Cardiac Rehabilitation Program.
- **Subject Understanding**
  Potential participants will be approached by a trained member of REHAB laboratory staff who will explain all aspects of the study, including potential risks and benefits and the expected duration and time commitment. If a patient verbally consents, they will be a given a written consent form detailing the nature of the study, as well as the opportunity to ask any questions. Subjects will be informed that they may discontinue their participation at any time. The consent form will also include authorization of use of protected health information (PHI) from patients' medical records and the participant will also be made aware they are signing over access to that information.
- **Protecting Privacy**
  There will be a designated space at RWJ Cardiac Rehabilitation Program for communication between study staff and patients where they will be able to privately sign consent and ask any questions regarding participation. This designated space will also have the same safeguards in place as the spaces dedicated to regularly scheduled appointments at RWJ Cardiac Rehabilitation Program.

B. Waiver or Alteration of Consent Process

We are not requesting Waiver of Documentation of Consent, Waiver or Alteration of Consent Process, Destruction of Identifiers, or Use of Deception/Concealment.

C. Documentation of Consent

- **Documenting Consent**

  Trained REHAB laboratory staff will obtain verbal consent from potential participants prior to giving them a written consent form at RWJ Cardiac Rehabilitation clinics. Written informed consent will only be from patients medically cleared for the study by their attending cardiologist who are scheduled to start CR. Individuals will be asked to sign the consent document in front of a trained member of the REHAB laboratory.

4.5 Special Consent Populations

N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

Patients will partake in the study at RWJ Cardiac Rehabilitation Clinics on the same day as their scheduled cardiac rehabilitation sessions. They are not expected to unduly undertake additional expenses as all equipment will be provided to them.

B. Compensation/Incentives

Patients will be compensated up to $705.00 for participation via cash:

- $100 for the baseline assessment
- $100 for end-of-therapy follow-up at week 6
- $100 for 12-week follow-up
- $50 for 18-week follow-up
- $50 for 24-week follow-up
- $100 bonus for completing all assessment visits
- $10 per week for every week of 5 or more days of valid wear time (i.e., 10 hours/day; 25 weeks = max $250)

C. Compensation Documentation

Compensation will be recorded and tracked via a password-protected subject payment database within Excel that can only be accessed by research staff. The Excel file can be accessed via the Dell PC computers within the REHAB laboratory suite in 1 Spring Street that are connected to a local secure network. Participants will also sign and date two receipts to confirm that they were compensated. Participants will keep one copy, and the other will be stored in the respective participant's folder that will be housed in one of our filing cabinets in 1 Spring Street under lock and key.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

Injury or medical complications during physical activity

Risks. There are minimal risks associated with participation in moderate-intensity bouts of physical activity.

Minimization. The most common injuries include muscle strains, joint sprains, and bone injuries. To minimize the risk of injury, participants will be instructed in appropriate warm-up and cool-down exercises. During brisk walking, heart rate and blood pressure may

increase. Under extreme conditions, this can lead to a serious cardiac event. Only patients deemed medically appropriate by their cardiologist will be enrolled in the study. Home-based moderate-intensity physical activity is consistent with exercise goals in cardiac rehabilitation. Patients will be instructed to engage in moderate-intensity physical activity (64-76% age-predicted heart rate max) and will be given biofeedback during treatment to ensure that exercise is occurring at the appropriate intensity. Study staff will be able to monitor activity and heart rate levels in real-time. Attending cardiologist will be consulted for any patients who have a heart rate that exceeds 85% of age predicted maximum heart rate during at-home exercise. Patients will be encouraged to continue compliance with home-medications (e.g., beta blockers). It is important to emphasize that moderate-intensity home-based physical activity is recommended for patients with cardiovascular disease. In the unlikely event of any suspected or actual imminent cardiac event, patients will be instructed to call 911 for immediate medical care. Any medically related incidents will be reported immediately to patients' attending cardiologist at the RWJ University Hospital Cardiac Rehabilitation Program.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**

  Panic attacks/increased somatic sensations from exercise sensitivity treatment

  Risks. In this type of patient population, the risk of panic attacks or subjective somatic distress is present, which may be exacerbated from interoceptive exposures (i.e., moderate-intensity walking).
  Minimization. Patients will be provided with information about common bodily sensations that accompany panic attacks: e.g., increased heart rate, sharp/stabbing chest pain that is temporary (last 5-10 seconds), localized pain to one small area, pain relieved/worsened when changing body position. Patients will be provided with psychoeducation about what sensations are potentially indicative of a true cardiac emergency: e.g., escalating crushing pain in chest reaching maximum severity for several minutes; constant pain, pressure, fullness or aching in chest; radiating pain from chest to other areas (arms, abdomen, back, shoulders, neck, throat, or jaw). Patient's specific feared bodily sensations will be reviewed prior to treatment initiation to assist the therapist and patient with appropriate planning for addressing symptoms if they arise. Patients will be fully informed about the nature and intention of exposure treatment (to intentionally elicit feared yet benign uncomfortable bodily sensations) and will be given the opportunity to ask questions. Patients will likely experience a range of sensations during brisk walking (muscle tightness, increased heart rate, shortness of breath). These symptoms are temporary, not harmful (although may be fearful). It is worth noting that the experience of a panic attack is not harmful or dangerous, and symptoms peak/dissipate typically within 20-30 minutes. While there is risk for experiencing these sensations, engagement in exposure techniques and physical activity is the treatment for anxiety and walking is also critical for heart health. Thus, while intervention techniques can initially elicit anxiety/somatic sensations, repeated practice and engagement will serve to decrease anxiety and likelihood of fearful responses to bodily symptoms. Dr. Farris has extensive experience in conducting interoceptive exposure interventions, including use of more intensive forms of interoceptive exposure than proposed in this study. Exposures are safe, typically well-tolerated by patients, and no significant adverse events have resulted from Dr. Farris' prior use of these interventions. Patients will be informed that they can stop exposures at any time. Continuing participation of the patients will remain voluntary, and patients will remain free to terminate participation at any time.

- **Other Foreseeable Risks of Harm**

  Breach of Confidentiality

  Risks. The risk of loss of privacy is judged to be minimal.

Minimization. Breach of confidentiality is highly unlikely because all data are identified only by numeric code and are stored in locked file cabinets. A master list of names and numbers is kept in a separate location and is used to facilitate the collection of follow-up data. Only senior grant staff will have access to the master list linking names and code numbers. Clinically important assessment data (e.g., suicidal ideation) will be made available to clinical staff to coordinate services more effectively. All staff will be fully trained in relevant ethical principles and procedures, particularly around confidentiality. All assessment and treatment procedures will be closely supervised by the project's professional staff. All audiotapes will be erased upon completion of data analysis. No personal participant information will be presented in any publication or presentations resulting from this research.

B. Assessment of Social Behavior Considerations

Depression or suicidal ideation

Risks. The risk of depression or suicidal ideation may be present in this patient population.
Minimization. All research staff who have direct involvement with patients will be fully trained by the principal investigator in procedures for assessment and intervention in cases where significant depression or suicidal ideation is expressed. In such cases, research staff will also immediately contact the principal investigator (Dr. Farris) who will always be on-call. Appropriate clinical action will be taken in such circumstances, which may include hospitalization and/or referral to another level of clinical care. These are standard procedures, and these services are readily available at Rutgers Behavioral Health Care in Piscataway, NJ.

C. Minimizing Risks of Harm

- **Certificate of Confidentiality**
  This study is an NIH-funded study for which a Certificate of Confidentiality is automatically issued to protect the data obtained.
- **Provisions to Protect the Privacy Interests of Subjects**
  All data from questionnaires and the Fitbit Inspire 2 data will be stored confidentially, using a secure web server with a 128-bit encryption. Participants will be identified with a unique patient identification number not utilized outside research purposes. Consent forms containing identifying information will be locked securely and filed separately from the actual data. Information linking participant IDs to their name will be kept in a password protected computer file only accessible by senior research staff. When applicable, hard-copy data will also be locked away and will not have any personal identifiers. Audio-recorded data will be stored in a locked filing cabinet and the tapes will be destroyed after the data is analyzed. Data will be aggregated through qualitative analysis. Data from medical records kept securely at the Cardio Metabolic Institute is only accessed by trained clinicians working at the site.

D. Potential Direct Benefits to Subjects

The risks to patients in the HEC are expected to be minimal given that they will be receiving their typically prescribed exercise regimen during CR sessions and will not assigned any additional physical activity goals by study staff. Additionally, the risks to patients randomized to BE-FIT are judged to be acceptable relative to the anticipated benefits. By participating in this clinical research project, patients may benefit from the additional intervention that they will receive. In addition, all patients will receive a Fitbit Inspire 2 sports watch for exercise tracking, which can also help to increase activity levels. The risks of significant psychiatric symptoms (panic attacks, exacerbated anxiety/fear, depression, suicidal ideation) are inherent in this patient population. However, exacerbated short-term anxiety and panic attacks are the only side effects we anticipate due to this intervention. These symptoms are short-lived, leave no long-term effects on physical or mental health, and the risk of experiencing them is no more acute than that of standard cardiac rehabilitation. Our intervention program will provide potential opportunities to identify and respond to symptoms of exercise sensitivity that might remain undetected if patients

were not in this study. The risks associated with participation in brisk at-home walking are minimal. Given this level of risk(s) to the patients and the likelihood that many will benefit from the additional treatment (or from the additional assessment contacts) and the even greater possibility of benefits to the larger population of patients in cardiac rehabilitation, the risk/benefits ratio seems favorable.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

N/A

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A

6.0 Data Management Plan

6.1 Data Analysis

Aims 1 and 2 will be evaluated using generalized linear mixed models and structural equation modeling (SEM), an extension of general linear models allowing for multi-level data with non-normal distributions. [63,64] With respect to evaluating main effects of experimental conditions on exercise adherence, each participant will provide up to five assessments (baseline, EOT, Wk 12, Wk 18, Wk 24 follow-up data). Hypotheses will be tested using specific contrast vectors, using a general linear hypothesis framework. [65] Aim 3 will utilize an alternative approach which has arisen out of the structural equation modeling (SEM) tradition. [66,67] Linear and non-linear growth curve models and growth mixture models can accommodate non-normal distributions, count outcomes, zero-inflation, and two-part hurdle models. These approaches model individual trajectories and offer relatively straightforward means of addressing missing data with state-of-the-art strategies including maximum likelihood (i.e., FIML) or multiple imputation. The SEM approach can accommodate models simultaneously assessing multiple distinct mediation pathways and can readily address the limitations inherent in regression-based conditional process models.[68]

Aim 1. The primary outcome of interest in Aim 1, overall minutes of exercise, will be evaluated as a function of a dummy coded variable representing BE-FIT and HEC with HEC as the reference group. Time X BE-FIT will provide a direct test of differences in change between BE-FIT and HEC groups in overall minutes of exercise. Secondary outcomes of interest, changes in overall steps/day and CR adherence, will be modeled using the same framework with CR (vs. non-CR) days examined as an effect modifier. We will utilize a Bonferroni correction with Šídák adjustment for correlated outcomes to reduce alpha inflation associated with multiple outcomes (i.e., number of CR sessions attended, exercise on CR days and lifestyle PA (exercise on non-CR days)). For these analyses, each participant will provide up to 5 repeated measures, yielding up to 730 Level 1 cases (repeated-measures across 146 Level 2 cases). Assuming outcomes follow a negative binomial distribution with a natural log link, the following model will be the basis for evaluating intervention effects as specified in Aim 1 hypotheses:

Level 1: $\log(E[DV]_{ti}) = \pi_{0i} + \pi_{1i}(Time)_{ti} + \varepsilon_{ti}$ $\quad \varepsilon_{ti} \sim N((0, I\sigma^2_{\varepsilon}) I\sigma^2_{\varepsilon})$

Level 2: $\pi_{0i} = \beta_{00} + \beta_{01}(BE\text{-}FIT)_i + \beta + r_{00i}$

$\pi_{1i} = \beta_{10} + \beta_{11}(BE\text{-}FIT)_i + r_{10i}$

where *t* indexes repeated-measures and *i* indexes participants. BE-FIT reflects difference between conditions. DV_{ti} represents the outcome for each individual at each time point. $Time_{ti}$ measures weeks since baseline.

Aim 2 will be evaluated examining target engagement outcomes (i.e., exercise anxiety, anxiety cognitions, avoidance and safety behavior use, vagal tone and flexibility) as a function of a dummy coded variable representing BE-FIT and HEC with HEC reference group. Time X BE-FIT outcomes will provide direct tests of differences in change between BE-FIT and HEC groups. We will again utilize a Bonferroni correction with Šídák adjustment for correlated outcomes to reduce alpha inflation associated with multiple outcomes (i.e., exercise anxiety, anxiety cognitions, avoidance and safety behavior use, vagal tone, and flexibility).

Aim 3 will evaluate mediators of intervention effects. We will use SEM to test the hypothesis that decreases in exercise anxiety and its associated components (reduced cognitive bias, safety behaviors; increased cardiac vagal control), at EOT and Wk 12 will mediate the association between BE-FIT (vs. HEC) and PA outcomes at later follow-ups (i.e., Wks 18 and 24). Following the recommendations of Fritz and MacKinnon, we will use the bias-corrected bootstrap confidence interval estimates to test the mediation hypotheses. We will use MPlus statistical software to estimate the structural equation models. Power to test mediation depends on the effect of treatment on the mediator (path a) and the effect of the mediator on the outcome (path b). Fritz and MacKinnon describe a standardized effect of .14 as a small effect, and .39 as a medium effect. Our power estimate is generally consistent with the sample size requirements suggested by Fritz and MacKinnon in their simulation.

6.2 Data Security

All data will be completed confidentially, using a secure web server with a 128-bit encryption. Participants will be identified with a unique patient identification number not utilized outside research purposes. Consent forms containing identifying information will be locked securely and filed separately from the actual data. Information linking participant IDs to their name will be kept in a password protected computer file. When applicable, hard-copy data will also be locked away and will not have any personal identifiers. Once audio recordings of exit interviews are analyzed by research staff, they will be destroyed. Until that point, they will be under lock and key.

6.3 Data and Safety Monitoring

N/A

6.4 Reporting Results

A. Individual Subjects' Results

Full study results will only be shared with study participants if they contact Dr. Farris and express their desire to receive these results at the end of the study. Results from Fitbit activity monitoring will be shared with participants.

B. Professional Reporting

Results from this study, negative or positive, will be shared with the greater scientific community via manuscripts published in peer-reviewed journals, as well as through posters and presentations at relevant scientific conferences.

6.5 Secondary Use of the Data

After data have been collected and study results published, de-identified data will be made available to other qualified researchers upon request, on a CD or other electronic means compatible with our systems. The request will be evaluated by the PIs to ensure that it meets reasonable standards of scientific integrity. We may also choose to share de-identified data with colleagues/collaborators at other institutions. We will work on the data dictionary throughout the study. We will submit primary results for publication by the end of the project period and will have final de-identified datasets and data dictionaries available by the end of the project period.

7.0 Research Repositories – Specimens and/or Data

As previously described, de-identified data, apart from audio interview recordings, will be kept electronically by the study PI to be analyzed for future manuscripts and presentations. Recorded interviews will be destroyed.

8.0 Approvals/Authorizations

N/A

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Appendix B - Protocol Deviation/Violation Log

Protocol Title: _____ Protocol Number: _____

Site: _____ Principal Investigator: _____

Protocol Deviation/ Violation Code:	Participant Initials	Participant ID#	Date Deviation / Violation Occurred:	Date Protocol Deviation / Violation Form	Contact Person

SAMPLE PROTOCOL DEVIATION / VIOLATION CODES

Consent Form:

1. Missing or not obtained
2. Not signed and dated by participant
3. Does not contain all required signatures
4. Outdated, current IRB-approved version not used
5. Not protocol specific.
6. Does not include updates or information required by the IRB

Randomization:

7. Ineligible participant enrolled and/or randomized
8. Participant is randomized prior to determining whether eligible for study
9. Occurs outside protocol window

IRB:

10. Not reporting a serious complication within 24 hours
11. Approvals not kept up to date
12. Enrollment and/or treatment occurs prior to IRB approval or during period when "on hold"
13. Reportable serious adverse events not reported to IRB

Participant:

14. Receives wrong treatment
15. Visits occur outside expected follow-up window
16. Entered into another study

Study Data and/or Forms:

17. Missing data and/or forms
18. Missing radiology and/or operative reports
19. Forms or data not sent from clinical site to coordinating center

Appendix C - Consent Forms

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Behavioral **F**actors **I**nfluencing **T**reatment Outcomes in Cardiac Rehabilitation (BE-FIT)

Principal Investigator: Samantha G. Farris, Ph.D.

Co-Investigator: Teresa Leyro, Ph.D., Brandon Alderman, Ph.D, Michael Steinberg, M.D.

STUDY SUMMARY: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not.

The **purpose of the research** is to examine how different supplemental treatments enhance cardiac rehabilitation outcomes. You will be randomly assigned to 1 of 2 supplemental treatments. If you take part in the research, you will be asked to participate in an interventional research treatment, in which you will meet with a behavior coach for 6 sessions. You will also complete baseline and follow-up questionnaires, undergo measurement of heart rate and blood pressure activity, and wear a physical activity tracker (Fitbit). Your time in the study will take around 24 weeks, or 6 months.

Possible harms or burdens of taking part in the study may be distress during the assessments as we will ask you about your thoughts and emotional symptoms, discomfort during physiological tasks, skin irritation from wearing the sports watch, bodily discomfort during physical activity. Possible benefits of taking part may be improvement in mental and physical health through education in how to maintain and engage in exercise behavior. Your feedback may also provide researchers with new information to improve our intervention to treat people in cardiac rehabilitation more effectively. However, there may be no direct benefit to you for participating.

Your **alternative** to taking part in the research study is not to take part in it. You will complete the regular cardiac rehabilitation at the RWJ Cardiac Rehabilitation Program if you choose not to participate. There will be no penalty to you if you choose not to participate in this study and you will not lose any benefits you are entitled to as a patient at the RWJ Cardiac Rehabilitation Program.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and

should expect to be given answers you completely understand. After your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?

Dr. Farris is the Principal Investigator of this research study from the Department of Psychology at Rutgers University. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team. Dr. Farris is collaborating with co-investigator Teresa Leyro from the Rutgers Department of Psychology. We are doing this work in conjunction with your treatment team at the Robert Wood Johnson University Hospital Cardiac Rehabilitation Program. Dr. Farris or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Dr. Farris can be contacted at:

1 Spring Street, Suite 200
Department of Psychology,
Rutgers University,
New Brunswick, NJ 08901
Email: samantha.farris@rutgers.edu

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Sponsor of the Study: This study is being sponsored by the National Institutes of Health, National Institute on Aging.

Why is this study being done?

The purpose of this study is to promote healthy aging. We aim to discover whether there are any differences in outcomes between patients who receive two different types of interventions.

Who may take part in this study and who may not?

Your cardiologist at RWJ Cardiac Rehabilitation Program has already cleared you as physically capable of participation in this study. You must also have had a recent (within the past 3 months) diagnosis of myocardial infarction, percutaneous coronary intervention (stent or revascularization), chronic angina, or valve surgery (in other words, a recent heart attack or some medical procedure to improve the function of your heart or arteries). There are also baseline mental health criteria that must be met in order to participate in the study based on measures you completed during orientation with the cardiac rehabilitation nurse.People not attending outpatient RWJ are not able to participate in this study.

Why have I been asked to take part in this study?

You have been asked to participate in this study because you are a patient in cardiac rehabilitation at the RWJ Cardiac Rehabilitation Program and your cardiologist has assessed that you are physically capable of participating based on your medical records.

How long will the study take and how many subjects will take part?

A total of 146 patients attending cardiac rehabilitation will take part in our treatment study. The study will take place over the course of 24 weeks or approximately 6 months. The first week will be a 7-day baseline assessment of physical activity with no treatment sessions or time commitment outside of your normal daily routine. During the following three weeks, you will be asked to attend 6 treatment sessions (2x weekly). Each session is approximately 45 minutes long. You will also be asked to wear a FitBit throughout the course of the study to monitor your physical activity levels. After you complete all treatment sessions, you will be asked to return for 4 follow-up visits.

What will I be asked to do if I take part in this study?

If you consent to this study and are eligible based on a questionnaire, you will complete a few brief baseline questionnaires (~20-25 minutes) and we will obtain additional information from your medical record at RWJ Cardiac Rehabilitation Program on your medical history, cardiac diagnosis, and medication treatment.

We will also ask you to complete an electrocardiogram (ECG) and impedance cardiography (ICG), which are both non-invasive procedures used to record the electrical and mechanical activity of the heart (~30-45 minutes). Electrodes (sensors

with sticky gel) will be placed on your chest and limbs, and these electrodes will send information about your heart activity to a computer monitor to be recorded and measured. The risks associated with this procedure are minimal, but in very rare cases skin irritation may occur on electrode sites. You will also complete an exercise test, during which we will ask you how you feel. This exercise test is a required component of your orientation for rehab at the RWJ Cardiac Rehabilitation Center. Then we will ask you to wear a Fitbit activity tracker on your wrist that measures your movement throughout the day. This Fitbit will give us information about your daily physical activity levels. There will be one week after the baseline assessment where you wear the Fitbit to measure your standard amount of physical activity.

After seven days, you will be randomly assigned to receive one of two interventions at the RWJ Cardiac Rehabilitation Program. In other words, you will be assigned to one of two treatments based on a flip of a coin. Both treatments are intended to help you live a heart-healthy lifestyle, and this study aims to find out which treatment is most helpful. Your treatment sessions will take place on the same day as your cardiac rehabilitation sessions at the RWJ Cardiac Rehabilitation Program. The intervention will occur in 6 one-to-one sessions with a clinician. Sessions will be audio recorded. Sessions will focus on information about health and strategies to increase positive health behaviors. You will also be asked to wear the Fitbit on your wrist daily to capture your physical activity levels throughout the study, and study staff will have access to the data recorded by the FitBit for research purposes.

At the end of your treatment, you will be asked to complete an end-of-treatment assessment, during which you will complete questionnaires and the same physiological assessments from your baseline visit (ECG/ICG). You will also be asked to return for three follow-up visits at Weeks 12, 18, and 24 of your study enrollment. During the 12-Week visit, you willbe asked to complete the questionnaires and ECG/ICG again. During visits for Weeks 18 and 24, we will ask you to complete the questionnaires only.

What are the risks of harm or discomforts I might experience if I take part in this study?

The risks of participating in this study are minimal.

- Distress during assessments: During the assessments we will ask you about your thoughts, feelings, behaviors, and emotional symptoms. It is possible that talking about this information may increase distress or discomfort. You may choose not to answer questions if you find them upsetting.
- Irritation from the physiological assessments: The electrocardiogram and/or impedance cardiography) may cause skin irritation at the site where electrodes were placed. The irritation will not result in any permanent sensations or harm to your skin.
- Irritation from activity tracker: The Fitbit may cause irritation to the skin, and you should discontinue use and notify study staff if this happens to you. The irritation will not cause any permanent sensations or harm to your skin.

- Bodily discomfort during physical activity: Physical activity is healthy and recommended by the RWJ Cardiac rehab program, however you may experience some discomfort. During intervention sessions, you may be asked to engage in various types of physical activities. Physical activities can produce sensations like heart rate speeding up, feeling out of breath, or sweating. In addition to wearing the FitBit, your counselor and cardiac rehab team will work together and tailor your exercise plan. This discomfort won't be any higher than that experienced with other physical activities assigned to patients in cardiac rehabilitation and is associated with behavior that promotes overall health.

Are there any benefits to me if I choose to take part in this study?

You may benefit from this study in terms of improvement in mental and physical health through education informing you how to maintain and engage in positive health behaviors. Additionally, your feedback will provide researchers with tools to modify our intervention procedures to treat people more effectively in cardiac rehabilitation and therefore result in better treatment outcomes. However, there may be no direct benefit to you for participating.

What are my alternatives if I do not want to take part in this study?

There are no alternative treatments available. Your alternative is not to take part in this study and complete the standard cardiac rehabilitation at the RWJ Cardiac Rehabilitation Program if you choose not to participate. There will be no penalty to you if you choose not to participate in this study and you will not lose any benefits you are entitled to as a patient at the RWJ Cardiac Rehabilitation Program.

How will I know if new information is learned that may affect whether I am willing to stay in the study?

During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will there be any cost to me to take Part in this study?

There will be no cost to you to take part in the study.

Will I be paid to take part in this study?

You will be paid up to $750.00 for taking part in this study.

- $100.00 for your baseline assessment (questionnaires + ECG/ICG)
- $100.00 for end-of-treatment at Week 6 (questionnaires + ECG/ICG)
- $100.00 for Follow-up visit at Week 12 (questionnaires + ECG/ICG)
- $ 50 for follow-up visit at Week 18 (questionnaires only)

- $ 50 for follow-up visit at Week 24 (questionnaires only)
- $100.00 bonus for completing all assessment visits
- $10.00 per week for every week of 6 or more days of valid wear time (i.e., 10 hours/day for up to 25 weeks)

How will information about me be kept private or confidential?

All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Data will be de-identified and coded with an arbitrary ID number. A single, locked document will link participant names and ID numbers. Data with identifying information (i.e. consent forms, contact information) will be kept separate from coded de-identified data. Any collected data will be saved on a private, password protected computer accessible only by the study team. Any paper data will be stored in a locked filing cabinet. Audio recordings will not include your name and will be kept in a locked filing cabinet. Once data is analyzed from these recordings, they will be destroyed. Activity watch data will be downloaded to a secure software program and identified with your participant ID only. Any data accessed from your medical records will be identified with your participant ID only. Your actual medical records will remain at the clinic in their secure database.

The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University investigators involved in this study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- The National Institutes of Health
- Fitbit (https://www.fitbit.com/global/us/legal/privacy-summary#info-we-collect)
- Academic journals that require de-identified data be submitted along with the manuscript submitted for consideration for publication in that journal.

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

This study is protected by a Certificate of Confidentiality (CoC) from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state, or local laws require, such as laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

What will happen to my information—data, recordings and/or images—collected for this research after the study is over?

After information that could identify you has been removed, de-identified information collected for this research may be used for other research we conduct without obtaining additional informed consent from you.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?

It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time. If you do not want to enter the study or decide to stop taking part, your relationship with the study staff or the RWJ Cardiac Rehabilitation Program will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled

You may also withdraw your consent for the use of data already collected about you. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the study director and tell her of your decision:

Samantha Farris, Ph.D.
Rutgers Emotion, Health and Behavior Laboratory
Department of Psychology
Rutgers, the State University of New Jersey
1 Spring Street, Suite 200 New Brunswick, NJ 08901

Who can I contact if I have questions?

If you have questions, concerns, or complaints about the research, wish more

information or if you feel you may have suffered a research related injury, you can contact the Principal Investigator:

Samantha Farris, Ph.D.
Telephone: 848-445-2174
Email samantha.farris@rutgers.edu

If you have questions about your rights as a research subject, you can call the IRB Director at:

New Brunswick/Piscataway Art & Sciences Institutional Review Board
Rutgers, the State University of New Jersey
335 George Street, Suite 3200 New Brunswick, NJ 08901-8559
Telephone: 732-235-9806
Email: humansubjects@orsp.rutgers.edu

Or you can contact the Rutgers Human Subjects Protection Program at (732) 235-8578 in New Brunswick, email them at human-subjects@research.rutgers.edu., or write them at 335 George Street, Liberty Plaza Suite 3200, New Brunswick, NJ 08901.

PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What Is The Purpose Of The Research And How Will My Information Be Used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What Information About Me Will Be Used?

- Assessments, questionnaires, and tasks you complete
- Audio recordings from intervention sessions
- Activity watch for physical activity data
- Information from medical records

Who May Use, Share or Receive My Information?

The research team may use or share your information collected or created for this study

with the following people and institutions:

- Rutgers University Investigators Involved in the Study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- The National Institutes of Health

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I Be Able To Review My Research Record While The Research Is Ongoing?

No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I Have To Give My Permission?

No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I Say Yes Now, Can I Change My Mind And Take Away My Permission Later?

Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him or her of your decision:

Samantha Farris, Ph.D.
Rutgers Emotion, Health and Behavior Laboratory
Department of Psychology
Rutgers, the State University of New Jersey
1 Spring Street, Suite 200 New Brunswick, NJ 08901

How Long Will My Permission Last?

There is no set date when your permission will end. The information you provide in this study may be used in research for many years.

AGREEMENT TO TAKE PART IN RESEARCH

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____
Date:_____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____ Date:_____

<u>ADDENDUM</u>: CONSENT TO AUDIO-/VISUALLY RECORD OR PHOTOGRAPH SUBJECTS

You have already agreed to take part in a research study entitled **Be**havioral **F**actors **I**nfluencing **T**reatment Outcomes in Cardiac Rehabilitation (BE-FIT) conducted by Dr. Samantha Farris. We are asking your consent to allow us to audiotape intervention sessions with research staff you as part of the research. You do not have to consent to be audio recorded in order to take part in the main research.

The audio recordings will be used for:

- Analyzing effectiveness of the intervention
- Analyzing comprehension of use of intervention tools
- Analyzing comprehension of intervention goals and methods
- Supervising research staff delivering the treatment sessions

The recording will include your assigned arbitrary ID number. You will not be identified by name on the audio recording. We are not videotaping so no identifying features will be recorded. The recordings will be stored in a locked filing cabinet with no personal identifiers at RWJ Fitness & Wellness or the Rutgers Emotion, Health and Behavior (REHAB) Laboratory overseen by Dr. Farris, until such time that a member of research staff extracts data from them and enters information into a secure computer platform that is password protected. Recordings will be destroyed upon completion of data entry.

Your signature on this form grants Dr. Farris and clinical staff permission to record you as described above during participation in the above-referenced study. The investigator will not use the recording(s) for any other reason than that/those stated in the consent form without your written permission. The audio recordings will not be used by us or distributed to investigators for other research after the study is over.

AGREEMENT TO BE RECORDED

Subject Name (Print):_____

Subject Signature _____ Date _____

Investigator/Person Obtaining Consent Name (Printed):_____

Signature _____ Date _____

Appendix D - MOP Modification Log

MOP MODIFICATION LOG

Section #	Version #	Date Modified	Page #	Text Location	Brief Modification Summary

Appendix E - Assessments

BL EOT F1 F2 F3 ID: _____ Date: ____/____/_____

BE-FIT RCT Study Measures

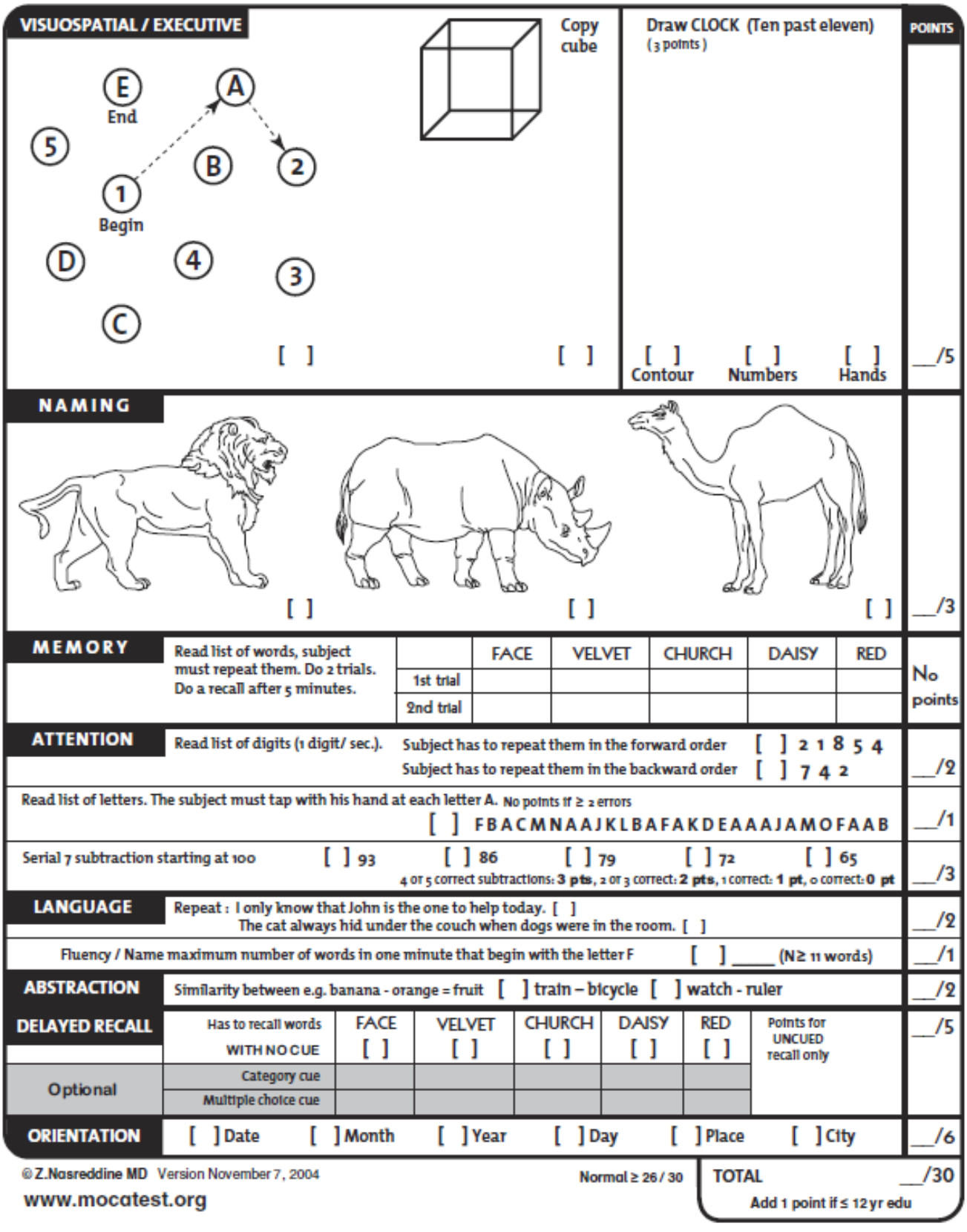
(1) Medical History & CR Attendance
- Medical Data Extraction Form

(2) Exercise Questionnaires
- Exercise Vital Signs (EVS)
- Exercise Sensations Questionnaire (ESQ)
- Fear of Activity in Patients with Coronary Artery Disease (Fact-CAD)
- Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q)

(3) Psychological Factors
- Montreal Cognitive Assessment (MOCA)
- Cardiac Anxiety Questionnaire (CAQ)
- Safety Behaviors Assessment Form (SBAF)
- Threat Perceptions
- Valuing Questionnaire (VQ)
- Intolerance of Uncertainty Scale Short Form (IUS-12)
- Falls Efficacy Scale-International (Short FES-I)
- Discomfort Intolerance Scale (DIS-R)
- Body Vigilance Scale (BVS)
- Multidimensional Assessment of Interoceptive Awareness (MAIA)
- Anxiety Sensitivity Index (ASI-3)
- General Anxiety Disorder 7-Item Scale (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)

Measure	Screen	BL	EOT	F1	F2	F3	method
MoCA							Interview
Medical History							EHR
CR Attendance							EHR
Exercise Vital Signs							Self-Report
ESQ							Self-Report
CAQ							Self-Report
Fact-CAD							Self-Report
PRETIE-Q							Self-Report
SBAF (relevant items)							Self-Report
Threat Perceptions							Self-Report
VQ							Self-Report
IUS-12							Self-Report
FES-I							Self-Report
DIS-R							Self-Report
BVS							Self-Report
MAIA							Self-Report
ASI-3							Self-Report
GAD-7							Self-Report
PHQ-9							Self-Report
HR, BP							Psychophys
Steps/Day		continuous					Fitbit
MVPA Minutes/Day		continuous					Fitbit

Montreal Cognitive Assessment (MOCA)



VISUOSPATIAL / EXECUTIVE

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING

[ ]

[ ]

[ ]

___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Medical Data Extraction Form

This form is meant to be used ONLY by the clinical staff at Robert Wood Johnson Cardiac Rehabilitation and trained, IRB-approved researchers from the Rutgers Emotion Health and Behavior Lab. Patients must give written consent prior to extraction of medical data.

Date of Birth _____ Race _____

Height _____ Ethnicity _____

Weight _____ Marital Status _____

BMI _____ Highest Degree _____

Sex _____ Employment _____

Insurance: Medicare Non-Medicare

Cardiovascular Tests:

Blood Pressure _____/_____

Target Exercise Heart Rate Range_____-_____

Cardiac Diagnoses: Date of **most recent** qualifying condition

_____/_____/_____

- ☐ Myocardial infarction
- ☐ Heart failure
- ☐ PCI: angioplasty/stenting
- ☐ Heart valve repair/replacement
- ☐ Coronary bypass surgery
- ☐ Stable angina
- ☐ HOCM (cardiomyopathy)
- ☐ ICD (implanted cardiac device)
- ☐ Other _____

Other Medical Conditions:

- ☐ CAD/PAD/atherosclerosis
- ☐ Hypertension
- ☐ Hyperlipidemia
- ☐ Type II diabetes
- ☐ Smoker
- ☐ Arthritis
- ☐ Back pain, other chronic/inflammatory pain
- ☐ Cancer
- ☐ Other _____

☐ Psychiatric Diagnoses
☐ Psychiatric Diagnoses

Psychiatric Diagnoses:

☐ GAD
☐ Panic disorder
☐ Social anxiety disorder
☐ Specific phobia
☐ OCD
☐ PTSD
☐ Depressive disorder
☐ Bipolar disorder
☐ Psychotic episode/disorder
☐ Somatic disorder/Illness anxiety

Medications:

_____
_____
_____
_____
_____

Cardiac Rehabilitation:

Risk stratification: High Medium Low
Rehab Start Date: _____ BE-FIT Start Date: _____
# of Sessions Attended prior to BE-FIT session 1: _____
# of Sessions Prescribed: _____
# of Sessions Attended Total (by end of Rehab program): _____

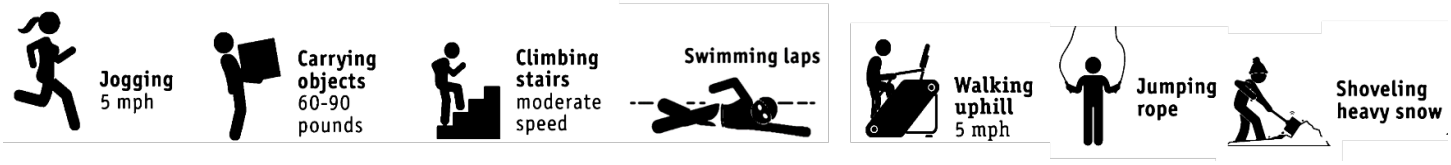
Exercise Vital Signs (EVS)

Moderate Intensity Exercise

• You can talk, but not sing, while performing the activity.
• Examples: brisk walking, slow biking, doubles tennis, various forms of dance, active home chores and gardening, etc.

Vigorous Intensity Exercise

• You can no longer talk easily during the activity and are somewhat out of breath.
• Examples: jogging, fast bicycling, singles tennis, aerobic exercise class, swimming laps, etc.



1. On average, how many days per week do you engage in moderate to vigorous physical activity (like a brisk walk; see examples above)?
_____ days

2. On average, how many minutes (per day) do you engage in physical activity at this level?
_____ minutes

For research staff use only:
Total minutes per week of physical activity (multiply #1 by #2) _____ minutes per week

Exercise Sensations Questionnaire (ESQ)

For each statement below, circle the *one* number that best represents your level of concern about each sensation if it happened **while you were doing aerobic exercise, like fast walking or running**.

		Not at All	A Little	Some	Much	Very Much
1	It would scare me if I had joint pain during exercise.	0	1	2	3	4
2	It would scare me if my muscles were sore during exercise.	0	1	2	3	4
3	I would worry if my lower back hurt during exercise.	0	1	2	3	4
4	It would scare me if I had a heavy feeling in my arms/legs during exercise.	0	1	2	3	4
5	It would scare me if I felt tired during exercise.	0	1	2	3	4
6	I would worry if my vision was blurry during exercise.	0	1	2	3	4
7	It would scare me if my body ached during exercise.	0	1	2	3	4
8	I would worry if I had a chest pain during exercise.	0	1	2	3	4
9	It would scare me if I had neck pain during exercise.	0	1	2	3	4
10	It would scare me if I didn't have much energy during exercise.	0	1	2	3	4
11	It would scare me if I felt tingling or numbness during exercise.	0	1	2	3	4
12	I would worry if I felt dizzy during exercise.	0	1	2	3	4
13	I would worry if my heart was pounding or racing during exercise.	0	1	2	3	4
14	It would scare me if I had difficulty breathing during exercise.	0	1	2	3	4
15	It would scare me if I felt faint during exercise.	0	1	2	3	4
16	I would worry if my head was pounding during exercise.	0	1	2	3	4
17	I would worry if I felt tightness in my chest during exercise.	0	1	2	3	4
18	It would scare me if my muscles felt tense during exercise.	0	1	2	3	4

CAQ

Please rate each item by choosing the answer (number) that best applies to you.

	Never	Rarely	Some-times	Often	Always
1. I pay attention to my heartbeat.	0	1	2	3	4
2. I avoid physical exertion.	0	1	2	3	4
3. My racing heart wakes me up at night.	0	1	2	3	4
4. Chest pain/discomfort wakes me up at night.	0	1	2	3	4
5. I take it easy as much as possible.	0	1	2	3	4
6. I check my pulse.	0	1	2	3	4
7. I avoid exercise or other physical work.	0	1	2	3	4
8. I can feel my heart in my chest.	0	1	2	3	4
9. I avoid activities that make my heart beat faster.	0	1	2	3	4
10. If tests come out normal, I still worry about my heart.	0	1	2	3	4
11. I feel safe being around a hospital, physician, or medical facility.	0	1	2	3	4
12. I avoid activities that make me sweat.	0	1	2	3	4
13. I worry that doctors do not believe my symptoms are real.	0	1	2	3	4
When I have chest discomfort or when my heart is beating fast:	Never	Rarely	Some-times	Often	Always
14. I worry that I may have a heart attack.	0	1	2	3	4
15. I have difficulty concentrating on anything else.	0	1	2	3	4
16. I get frightened.	0	1	2	3	4
17. I like to be checked out by a doctor.	0	1	2	3	4
18. I tell my family or friends.	0	1	2	3	4

FAct-CAD

The aim of this scale is to evaluate whether there is fear of activity related to your heart disease. Please answer all the questions regarding your heart disease.

	Never	Seldom	Some-times	Mostly	Always
1. I can walk on level road as long as I want to despite my heart problem.	0	1	2	3	4
2. I am afraid of any physical activity since I learned of my heart problem.	0	1	2	3	4
3. I feel uneasy when I walk uphill due to my heart problem.	0	1	2	3	4
4. My body doesn't allow me to do certain activities even though I would like to.	0	1	2	3	4
5. Morning exercises relax me.	0	1	2	3	4
6. I have difficulty in performing my duties at home due to my heart problem.	0	1	2	3	4
7. I feel chest discomfort if I exert myself a little.	0	1	2	3	4
8. I cannot carry loads heavier than six pounds after my heart problem.	0	1	2	3	4
9. I do the shopping for my home despite my heart problem.	0	1	2	3	4
10. It is not possible to maintain my usual physical activities after learning about my heart problem.	0	1	2	3	4
11. I now try to protect myself from strenuous activities.	0	1	2	3	4
12. I feel physically insufficient.	0	1	2	3	4
13. My sexual life is as it used to be.	0	1	2	3	4
14. I refrain from staying alone due to my heart problem.	0	1	2	3	4
15. I am worried that I may hurt my heart/incision if I exercise.	0	1	2	3	4
16. I feel demoralized to see that my spouse/relatives are more protective of me.	0	1	2	3	4
17. I will exercise if my doctors say so.	0	1	2	3	4
18. It is natural that I am unable to do certain activities that I used to do.	0	1	2	3	4
19. My heart problem may get worse if I stay inactive.	0	1	2	3	4
20. I am worried that I will not be able to be as strong as I was after my heart problem.	0	1	2	3	4
21. Being physically active makes me feel good.	0	1	2	3	4

PRETIE-Q

Please, read each of the following statements and then use the response scale on the right to indicate whether you agree or disagree with it. There are no right or wrong answers. Work quickly and mark the answer that best describes what you believe and how you feel. Make sure that you respond to all the questions.

		I totally disagree	I disagree	Neither agree nor disagree	I agree	I totally disagree
1	Feeling tired during exercise is my signal to slow down or stop.	0	1	2	3	4
2	I would rather work out at low intensity levels for a long duration rather than at high-intensity levels for a short duration.	0	1	2	3	4
3	During exercise, if my muscles begin to burn excessively or if I find myself breathing very hard, it is time for me to ease off.	0	1	2	3	4
4	I'd rather go slow during my workout, even if that means taking more time.	0	1	2	3	4
5	While exercising, I try to keep going even after I feel exhausted.	0	1	2	3	4
6	I would rather have a short, intense workout than a long, low intensity workout.	0	1	2	3	4
7	I block out the feeling of fatigue when exercising.	0	1	2	3	4
8	When I exercise, I usually prefer a slow, steady pace.	0	1	2	3	4
9	I'd rather slow down or stop when a workout starts to get too tough.	0	1	2	3	4
10	Exercising at a low intensity does not appeal to me at all.	0	1	2	3	4
11	Fatigue is the last thing that affects when I stop a workout; I have a goal and stop only when I reach it.	0	1	2	3	4
12	While exercising, I prefer activities that are slow-paced and do not require much exertion.	0	1	2	3	4
13	When my muscles start burning during exercise, I usually ease off some.	0	1	2	3	4
14	The faster and harder the workout, the more pleasant I feel.	0	1	2	3	4
15	I always push through muscle soreness and fatigue when working out.	0	1	2	3	4
16	Low-intensity exercise is boring.	0	1	2	3	4

SBAF

Below is a list of behaviors that people sometimes use to make themselves feel more comfortable. For each behavior, please pick the response that most accurately describes how often you engage in that behavior.

	Never	Some-times	Often	Always
1. Stay within certain distances from home (or other safe places)	0	1	2	3
2. Call doctors' offices (or health-lines) frequently	0	1	2	3
3. Take it easy when I exercise (or do other activities that require physical exertion) so my heart rate does not get too high	0	1	2	3
4. Check my body for problems (pain, discomfort, symmetry, discoloration, new growth, etc.)	0	1	2	3
5. Carry medication in case I need it	0	1	2	3
6. Research medical symptoms on the internet	0	1	2	3
7. Check my body temperature	0	1	2	3
8. Ask others for reassurance (e.g., about a decision or worry)	0	1	2	3
9. Check my pulse or heart rate	0	1	2	3
10. Talk to others about my health or health-related activities	0	1	2	3
11. Pay attention to body for physical symptoms or sensations	0	1	2	3
12. Check that I can swallow without choking	0	1	2	3
13. Request specialized medical exams from providers	0	1	2	3

Threat Perceptions

Below is a list of feelings and thoughts that people sometimes have in response to engaging in physical activity. We are interested in understanding how you feel when you have the most symptoms during exercise or physical activity (e.g., heavy breathing, sweating, increased heart rate). Please read the list below and indicate to what extent you agree with the following statements.

	Not at all	A little bit	Moderately	Extremely
1. I feel vulnerable.	0	1	2	3
2. I am worried that I am not in control.	0	1	2	3
3. I am worried that my symptoms are severe.	0	1	2	3
4. I feel helpless.	0	1	2	3
5. I am worried that I am going to die.	0	1	2	3
6. I am afraid.	0	1	2	3
7. I think this event will have a big impact on my life.	0	1	2	3

VQ

Please read each statement carefully and then circle the number which best describes how much the statement was true for you DURING THE PAST WEEK, INCLUDING TODAY.

	Not at all true						Completely true
1. I spent a lot of time thinking about the past or future, rather than being engaged in activities that mattered to me	0	1	2	3	4	5	6
2. I was basically on "auto-pilot" most of the time	0	1	2	3	4	5	6
3. I worked toward my goals even if I didn't feel motivated to	0	1	2	3	4	5	6
4. I was proud about how I lived my life	0	1	2	3	4	5	6
5. I made progress in the areas of my life I care most about	0	1	2	3	4	5	6
6. Difficult thoughts, feelings or memories got in the way of what I really wanted to do	0	1	2	3	4	5	6
7. I continued to get better at being the kind of person I want to be	0	1	2	3	4	5	6
8. When things didn't go according to plan, I gave up easily	0	1	2	3	4	5	6
9. I felt like I had a purpose in life	0	1	2	3	4	5	6
10. It seemed like I was just 'going through the motions', rather than focusing on what was important to me	0	1	2	3	4	5	6

IUS-12

Please circle the number that corresponds to how much you agree with each of the following statements as a general rule.

	Not at all	A little	Somewhat	Very Much	Entirely
1. Unforeseen events upset me greatly.	0	1	2	3	4
2. It frustrates me not having all the information I need.	0	1	2	3	4
3. Uncertainty keeps me from living a full life.	0	1	2	3	4
4. One should always look ahead so as to avoid surprises.	0	1	2	3	4
5. A small unforeseen event can spoil everything, even with the best of planning.	0	1	2	3	4
6. When it's time to act, uncertainty paralyses me.	0	1	2	3	4
7. When I am uncertain I can't function very well.	0	1	2	3	4
8. I always want to know what the future has in store for me.	0	1	2	3	4
9. I can't stand being taken by surprise.	0	1	2	3	4
10. The smallest doubt can stop me from acting.	0	1	2	3	4
11. I should be able to organize everything in advance.	0	1	2	3	4
12. I must get away from all uncertain situations.	0	1	2	3	4

FES-I (Short)

Below are some questions about how concerned you are about the possibility of falling. Please reply thinking about how you usually do the activity. If you currently don't do the activity (for example, if someone does your shopping for you), please answer to show whether you think you would be concerned about falling IF you did the activity. For each of the following activities, please check the box which is closest to your own opinion to show how concerned you are that you might fall if you did this activity.

	Not at all concerned	Somewhat concerned	Fairly concerned	Very concerned
1 Getting dressed or undressed	0	1	2	3
2 Taking a bath or shower	0	1	2	3
3 Getting in or out of a chair	0	1	2	3
4 Going up or down stairs	0	1	2	3
5 Reaching for something above your head or on the ground	0	1	2	3
6 Walking up or down a slope	0	1	2	3
7 Going out to a social event (for example, religious service, family gathering or club meeting)	0	1	2	3

DIS-R

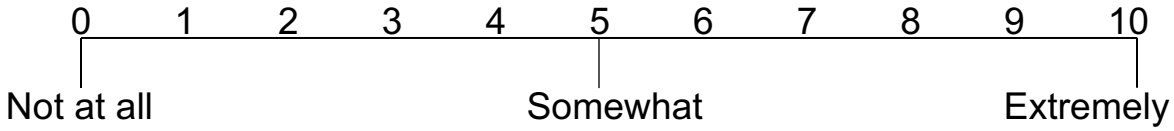
Instructions: Below are statements about how some people feel and behave. For each statement below, circle the number which best describes the degree to which the statement applies to you.

	Not at all like me			Moderately like me			Extremely like me
1. When I feel any physical discomfort, I am unable to continue with my daily activities.	0	1	2	3	4	5	6
2. Experiencing any type of physical discomfort is almost unbearable.	0	1	2	3	4	5	6
3. When I feel physically uncomfortable, it's difficult for me to function.	0	1	2	3	4	5	6
4. When I feel physical discomfort, all I can think about is how bad I feel.	0	1	2	3	4	5	6
5. I can't handle feeling physical discomfort	0	1	2	3	4	5	6
6. There is nothing worse than experiencing physical discomfort.	0	1	2	3	4	5	6
7. When I feel physical discomfort, I can't help but concentrate on how bad it feels.	0	1	2	3	4	5	6
8. Feeling physical discomfort scares me.	0	1	2	3	4	5	6

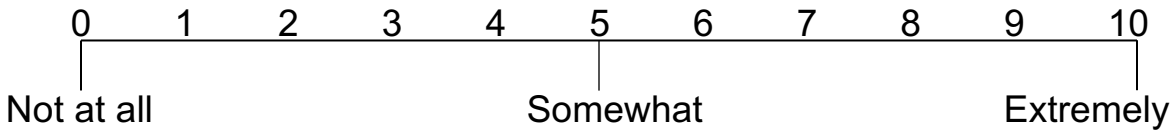
BVS

This scale is designed to index how sensitive you are to internal bodily sensations such as heart palpitations or dizziness. Fill it out according to how you have felt for the **past week**.

1. "I am the kind of person who pays close attention to internal body sensations."



2. "I am very sensitive to **changes** in my internal body sensations."



MAIA

Below you will find a list of statements. Please indicate how often each statement applies to you generally in daily life.

	Circle one number on each line					
	Never					Always
1. When I feel physical pain, I become upset.	0	1	2	3	4	5
2. I start to worry that something is wrong if I feel any discomfort.	0	1	2	3	4	5
3. I can notice an unpleasant body sensation without worrying about it.	0	1	2	3	4	5
4. I can stay calm and not worry when I have feelings of discomfort or pain.	0	1	2	3	4	5
5. When I am in discomfort or pain I can't get it out of my mind.	0	1	2	3	4	5
6. I listen for information from my body about my emotional state.	0	1	2	3	4	5
7. When I am upset, I take time to explore how my body feels.	0	1	2	3	4	5
8. I listen to my body to inform me about what to do.	0	1	2	3	4	5
9. I am at home in my body.	0	1	2	3	4	5
10. I feel my body is a safe place.	0	1	2	3	4	5
11. I trust my body sensations.	0	1	2	3	4	5

ASI-3

Circle the number that best corresponds to how much you agree with each item.

If any items concern something that you have never experienced (e.g., fainting in public), answer based on how you think you might feel if you had such an experience.

Otherwise, answer all items based on your own experience.

Be careful to circle only one number for each item and please answer all items.

	Very little	A little	Some	Much	Very much
1. It is important for me not to appear nervous.	0	1	2	3	4
2. When I cannot keep my mind on a task, I worry that I might be going crazy.	0	1	2	3	4
3. It scares me when my heart beats rapidly.	0	1	2	3	4
4. When my stomach is upset, I worry that I might be seriously ill.	0	1	2	3	4
5. It scares me when I am unable to keep my mind on a task.	0	1	2	3	4
6. When I tremble in the presence of others, I fear what people might think of me.	0	1	2	3	4
7. When my chest feels tight, I get scared that I won't be able to breathe properly.	0	1	2	3	4
8. When I feel pain in my chest, I worry that I'm going to have a heart attack.	0	1	2	3	4

ASI-3 Continued…	Very little	A little	Some	Much	Very much
9. I worry that other people will notice my anxiety.	0	1	2	3	4
10. When I feel “spacey” or spaced out I worry that I may be mentally ill.	0	1	2	3	4
11. It scares me when I blush in front of people.	0	1	2	3	4
12. When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.	0	1	2	3	4
13. When I begin to sweat in a social situation, I fear people will think negatively of me.	0	1	2	3	4
14. When my thoughts seem to speed up, I worry that I might be going crazy.	0	1	2	3	4
15. When my throat feels tight, I worry that I could choke to death.	0	1	2	3	4
16. When I have trouble thinking clearly, I worry that there is something wrong with me.	0	1	2	3	4
17. I think it would be horrible for me to faint in public.	0	1	2	3	4
18. When my mind goes blank, I worry there is something terribly wrong with me.	0	1	2	3	4

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? Circle your answer.

	Not at all	Several Days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you marked any problems on this page, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? Circle your answer below.

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

PHQ-9

Over the last 2 weeks, how often have you been bothered by the following problems? Circle your answer.

	Not at all	Several Days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself— or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite— being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you are better off dead or of hurting yourself in some way	0	1	2	3

If you marked <u>any</u> problems on this page, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people? Circle your answer below.

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

Appendix F – Adverse Event Form

Adverse Event Form

BE-FIT RCT

Interventionist Name:_____

Pt ID:_____

This form is cumulative and captures adverse events of a single participant throughout the study.

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious Adverse Event (SAE)
1 = Mild 2 = Moderate 3 = Severe	0 = Not related 1 = Unlikely related 2 = Possibly related 3 = Definitely related	0 = None 1 = Dose modification 2 = Medical Intervention 3 = Hospitalization 4 = Intervention discontinued 5 = Other	1 = Resolved 2 = Recovered with minor sequelae 3 = Recovered with major sequelae 4 = Ongoing/Continuing treatment 5 = Condition worsening 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (if yes, complete SAE form)

At end of study only: Check this box if participant had no adverse events ☐ None

Adverse Event	Start Date	Stop Date	Severity	Relationship	Action Taken	Outcome of AE	Expected?	SAE?

Appendix G – Serious Adverse Event Form

BE-FIT RCT

Protocol Number:_____ **Interventionist Name:**_____

Pt ID:_____

Date Participant Reported/Date of Site Awareness:

__ __ / __ __ __ / __ __ __ __
d d m m m y y y y

1. SAE Event Term (Diagnosis, ex: Stroke, Myocardial Infarction).
2. SAE onset date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
3. SAE stop date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___
   d d m m m y y y y
4. Location of SAE:_____
5. Was this an unexpected adverse event? ☐ Yes ☐ No
6. Brief description of participant with no personal identifiers:
   Sex: ☐ F ☐ M Age: _____
   Diagnosis for study participation:_____
   _____
7. Brief description of the nature of the SAE (attach description if more space is needed):
   _____
   _____
8. Category of the SAE:
   ☐ Date of death___/_____/_____
   (dd/mmm/yyyy)
   ☐ Life threatening
   ☐ Hospitalization – initial or prolonged
   ☐ Disability/incapacity

☐ Congenital anomaly/birth defect
☐ Required intervention to prevent permanent impairment
☐ Other:_____

9. Intervention type:
   ☐ Medication or nutritional supplement (specify):_____
   ☐ Device (specify):_____
   ☐ Surgery (specify):_____
   ☐ Behavioral/lifestyle (specify):_____

10. Relationship of event to intervention:
   ☐ Unrelated (clearly not related to the intervention)
   ☐ Possible (may be related to the intervention)
   ☐ Definite (clearly related to the intervention)

11. Was study intervention discontinued due to event? ☐ Yes ☐ No

12. What medications or other steps were taken to treat the SAE?

    _____

13. List any relevant tests, laboratory data, and history, including preexisting medical conditions.

    _____

14. Was this event a study related endpoint?

15. Type of report:
   ☐ Initial
   ☐ Follow-up
   ☐ Final

Signature of principal investigator: _____ Date: _____

Appendix H - NIA Single-Site Clinical Trial Closeout Procedures

I. INTRODUCTION

Purpose

The purpose of this document is to describe an orderly approach to the separation of participants from a clinical trial and the administrative procedures associated with the trial's completion.

Types of Closeout

A. Scheduled - upon completion of the trial.

B. Unscheduled - as a result of failure to obtain continuation funding, negative or positive findings, findings in other studies that impact on the clinical trial, or other unforeseen events.

II. SITE CLOSEOUT

The study site is responsible for ensuring the following activities are completed prior to study closeout along with the Participant Closeout Procedures described in Section III below.

A. ***Study Forms***

- All outstanding forms should be collected, organized, and corrections made, where necessary.
- All data queries should be corrected and resolved.

B. ***Safety Reporting***

- All adverse events (both serious and non-serious) should be recorded and followed up to resolution in accordance with procedures detailed in the protocol.
- All serious adverse events (SAEs) should have been reported to the Data and Safety Monitoring Committee (DSMC) or Safety Officer, Institute, Institutional Review Board (IRB), and other organizations, as specified in the protocol and Data and Safety Monitoring Plan (DSMP).
- All adverse events should have been reported as specified in the protocol.

C. ***Study Files***

- The investigator's study files should be complete and up to date with originals of the following maintained in the Study Binder, as relevant:
  - Investigator(s) Curriculum Vitae(s) (CVs), Licenses and Training Records
  - IRB approval letters for the protocol, all amendments, Informed Consents, annual reviews and advertisements (including updated approvals)
  - IRB membership list
  - All IRB correspondence
  - Institute correspondence

- Site signature log
- Copy of randomization code for randomization, if applicable

- All informed consents should be signed and on file.
- Record retention procedures should be documented with respect to type and length of retention and consequences of improper record retention and should conform to protocol and institutional requirements. The site should be completely familiar with required record retention policies.

D. ***Clinical Supplies***

- Clinical supplies, including any treatment intervention materials, must be disposed of according to protocol directions.

E. ***Laboratory Records and Specimen Retention***

- The site should ensure that the laboratory records are complete and up to date (reference ranges, laboratory certifications, specimen tracking records, specimen storage records).

F. ***Notifications and Equipment Removal***

- A final report should be submitted to the IRB and should conform to institutional reporting requirements. The report is likely to include, but is not limited to, study conduct and outcome, pertinent safety and efficacy observations, complete disclosure of any SAEs experienced during the course of the study, and the study closeout date.
- As relevant, arrangements should be made for the removal and shipment of any study- specific equipment received by the site (e.g., computers, diagnostic equipment, and participant monitoring devices).

Figure 1 provides a sample study documentation list, and Figure 2 provides a sample Closeout Checklist.

Study Documentation List

Document	Purpose
Treatment intervention product(s) accountability at site	Documents that the treatment intervention product(s) have been used according to the protocol. Documents the final accounting of treatment product(s) received at site, dispensed to participants, returned by the participants, and returned or destroyed.
Final report by investigator to IRB, as required	To document completion of the trial
Final Trial Closeout Monitoring Checklist, if relevant	To document that all activities required for trial closeout are completed, and copies of essential documents are held in the appropriate files
Audit Certificate (if relevant)	To document that audit was performed

Study Closeout Checklist

____ Investigator has signed and dated all forms.

____ Forms for all participants have been filed or transmitted as described in the Manual of Operating Procedures.

____ All appropriate documents are in the study files.

____ The final study close-out report has been submitted to the IRB.

____ Documents are retained as specified in the Manual of Operating Procedures or IRB directives, whichever is longer.

____ There is a plan in place in the event of an audit by the NIA, as relevant.

____ Final report has been submitted to the NIA.

III. PARTICIPANT RIGHTS AND NOTIFICATION

The study site should prepare a letter that thanks each study participant. The letter should be circulated to each site for distribution. The letter may include but not be limited to the following information:

- Study findings
- Treatment assignment, as relevant
- Treatment options, as relevant, whether continued treatment with the assigned intervention is indicated, and how and where treatment may be obtained
- Transfer of care responsibilities
- Rights to confidentiality, privacy, and to no further contact from study staff, if that is participant's preference
- Subsequent updates or recalls if new and important information emerges following separation
- Contact information of study staff

A copy of the letter should be included in the participant's file.

IV. INSTITUTE RESPONSIBILITIES

The NIA may wish to send staff or a Contractor to ensure that closeout procedures are appropriately conducted at any of the study sites.