HeartMapp: Assessment and Training for Heart Failure

HeartMapp: A Closed-Loop Assessment and Treatment Mobile Application for Heart Failure. A Pilot Randomized Clinical Trial

Principal Investigator

Ponrathi Athilingam, PhD, RN, ARNP
Associate Professor
University of South Florida, College of Nursing

Supported by:

The National Institute of Nursing Research

R43NR018415-01
ClinicalTrials.gov Identifier: NCT03827954

Version 3
February 22, 2019
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY TEAM ROSTER</td>
<td>4</td>
</tr>
<tr>
<td>PRÉCIS</td>
<td>5</td>
</tr>
<tr>
<td>1. Study objectives</td>
<td>7</td>
</tr>
<tr>
<td>1.1 Primary Objective</td>
<td>7</td>
</tr>
<tr>
<td>1.2 Secondary Objectives</td>
<td>7</td>
</tr>
<tr>
<td>1.2a Exploratory Objective</td>
<td>7</td>
</tr>
<tr>
<td>1.3 Background</td>
<td>7</td>
</tr>
<tr>
<td>1.4 Study Rationale</td>
<td>8</td>
</tr>
<tr>
<td>2. STUDY DESIGN</td>
<td>11</td>
</tr>
<tr>
<td>3. SELECTION AND ENROLLMENT OF PARTICIPANTS</td>
<td>12</td>
</tr>
<tr>
<td>3.1 Exclusion Criteria</td>
<td>13</td>
</tr>
<tr>
<td>3.2 Study Enrollment Procedures</td>
<td>15</td>
</tr>
<tr>
<td>4. STUDY INTERVENTIONS</td>
<td>16</td>
</tr>
<tr>
<td>4.1 Interventions, Administration, and Duration</td>
<td>20</td>
</tr>
<tr>
<td>4.2 Handling of Study Interventions</td>
<td>22</td>
</tr>
<tr>
<td>4.2.1 Allowed Interventions</td>
<td>22</td>
</tr>
<tr>
<td>4.2.2 Required Interventions</td>
<td>23</td>
</tr>
<tr>
<td>4.2.3 Prohibited Interventions</td>
<td>23</td>
</tr>
<tr>
<td>4.3 Adherence Assessment</td>
<td>23</td>
</tr>
<tr>
<td>5. STUDY PROCEDURES</td>
<td>23</td>
</tr>
<tr>
<td>5.2 Description of Evaluations</td>
<td>28</td>
</tr>
<tr>
<td>5.2.1 Enrollment, Baseline, and/or Randomization</td>
<td>31</td>
</tr>
<tr>
<td>5.2.2 Follow-up Visits</td>
<td>32</td>
</tr>
<tr>
<td>5.2.3 Retention</td>
<td>32</td>
</tr>
<tr>
<td>6. SAFETY ASSESSMENTS</td>
<td>33</td>
</tr>
<tr>
<td>6.1 Adverse Events and Serious Adverse Events</td>
<td>37</td>
</tr>
</tbody>
</table>
STUDY TEAM ROSTER

MAIN RECRUITMENT SITES

USF Health Morsani Center for Advanced Healthcare
13330 USF Laurel Dr, Tampa, FL 33613
Telephone: 813-974-2201

Florida Hospital Tampa and the Pepin Heart Institute
3100 East Fletcher Avenue
Tampa, Florida 33613
Telephone: 813-971-6000

Florida Cardiology Division of USF
509 S Armenia Ave #200, Tampa, FL 33609

PRINCIPAL INVESTIGATOR (Site PI)
Ponrathi Athilingam, PhD, RN, ARNP

CO-INVESTIGATORS

Miguel Labrador, PhD, Professor, Department of Computer Science and Engineering
Jerri Edwards PhD, Professor, Department of Psychiatry and Behavioral Neurosciences
Joel Fernandez, MD, FACC, Assistant Professor, USF Cardiology, and Florida Cardiology Division at S. Armenia Avenue, Tampa

SPONSOR/PI on the Grant)
Tom Van Vleet, PhD, Director of Sponsored Programs / Senior Scientist,
Posit Science Inc. San Francisco, CA

OTHER STUDY STAFF

Aimon C. Miranda, PharmD, BCPS, Assistant Professor, Department of Pharmacotherapeutics and Clinical Research, USF, College of Pharmacy

Kristen Dolan, ARNP, Florida Hospital, Tampa

TBD. Study coordinator and Research Assistants, USF College of Nursing
PRÉCIS

Short Study Title
HeartMapp: Assessment and Treatment for Heart Failure

Full Study Title
HeartMapp: A Closed-Loop Assessment and Treatment Mobile Application for Heart Failure: A Randomized Clinical Trial

Aims/ Objectives

Development Phase (Project months 0-3)
During the development phase, the team will finalize the cognitive training (CT) modules from BrainHQ (BHQ) of Posit Science Corporation within HeartMapp, complete the software development and release the app through the quality management system.

Feasibility and Efficacy Testing Phase (Project months 4-12)

- **Primary** objective is to establish the feasibility of the HeartMapp Plus [+] CT from BrainHQ. Feasibility will be assessed by App usage and engagement (HeartMapp + BHQ and CHF (Congestive Heart Failure) Info App + control games from BHQ) by HF patients.
- **Secondary** objectives are: to test the initial efficacy of HeartMapp + BHQ to improve cognitive function and heart failure (HF) self-care. We will also explore the efficacy of HeartMapp to improve quality of life, global health, medication adherence, heart rate variability (HRV) and reducing hospital admissions.

Design and Outcomes

We will conduct a prospective, parallel arm, double blinded, randomized, controlled pilot clinical trial to examine feasibility and initial efficacy of the HeartMapp + BHQ compared to an attention control condition who will use the CHF Info App + control games. Approximately 49 participants aged 40 and older with a diagnosis of HF, will be consented to ensure the successful completion of 40 participants (post ~18% attrition). Eligible participants will be randomized to either HeartMapp + BHQ or an active control condition using the CHF Info App +BHQ. Both groups will complete follow-up assessments at 3- and 6-months after enrollment.

- **The primary outcome** is the feasibility of using HeartMapp + BHQ, which will be quantified by measuring app usage and engagement with the apps. Engagement with CT of BHQ will be calculated as percentage of participant's who complete at least 20 hours of assigned CT included in HeartMapp. App feasibility and engagement will be assessed by App access by participants; Accessing App components at least 80% of the days (72 days out of 90-days) will be used to determine app engagement.

- **The secondary outcomes** are improvement in cognitive function and HF self-care. If we see effect sizes on Cohen’s d of d=0.25 or greater relative to controls for these outcomes, HeartMapp will be considered potentially efficacious.

- **Exploratory outcomes** include improvement in quality of life, global health, medication adherence, HRV and hospital admission. We will calculate effect sizes using Cohen’s d on these outcomes to inform future studies.
Interventions and Duration

**Intervention HeartMapp Plus BHQ.** The HeartMapp includes 7 features of self-care components and cognitive training. Participants will receive daily alerts to complete self-care assessments and receive feedback based on their HF symptoms using a clinically based built-in algorithm. They will use all seven features of HeartMapp (see figure 1) plus two CT exercises. The CT includes: Useful Field Of View (UFOV)\(^1,2\) and Tonic And Phasic Alertness Training (TAPAT)\(^3\) exercises in a 30-hours of training schedule to be delivered over a 12-week period (**30 minutes per day, 4 days per week**). The program will offer 24 hours of UFOV and 6 hours of TAPAT (30 total hours) to be completed in 12-weeks. Although the minimum hours necessary to determine feasibility, as outlined in the primary outcome as supported in our earlier study\(^4\) is 20 hours of assigned CT included in HeartMapp, participants are encouraged to complete a total of 60 sessions or 30 hours of CT. Completing 20 hours of CT is considered feasible.

The Attention control or CHF Info App Plus Control Games (**CHF Info App +BHQ**). The CHF Info App (one component of the HeartMapp) has 14 HF education modules (see Figure 2) and three control games to mimic CT. Three control games included are Bricks Breaking Hex, Double Klondike Solitaire, and Gem Swap. The participants will be encouraged to use 30-minutes a day for 4-days a week to complete 30-hours. Participants will access at least one education module per week until 14 are completed in 12-weeks.

Both groups will complete a follow-up assessment at 3- months to determine initial efficacy and at 6-months to assess long-term engagement with HeartMapp.
Sample Size and Population

A diverse sample of 49 adults aged 40 and older with clinical diagnosis of HF will be recruited from USF Morsani Health Center, Florida Cardiology Division at S. Armenia Avenue Clinic of Dr. Fernandez, and Florida Hospital, Tampa. Eligible participants will be randomized to either an Intervention group (HeartMapp +BHQ n=25) or attention control group (CHF Info App group +BHQ, n=24). Randomization will be stratified by age (<65 or ≥ 65 years of age) and cognitive status (Montreal Cognitive Assessment (MoCA) score 20-25 and ≥ 26.

1. STUDY OBJECTIVES

1.1 Primary Objective
The primary objective of this study is to establish feasibility of the proposed intervention. App usage and engagement (HeartMapp +BHQ and CHF Info App +BHQ) by HF patients will be automatically tracked by the apps.

1.2 Secondary Objectives
The secondary object is to test the initial efficacy of HeartMapp +BHQ to improve cognitive function and HF self-care measured using cognitive assessments and validated questionnaires.

1.2a Exploratory Objective
Explore improvement in quality of life, global health, medication adherence, HRV and reduced hospital admissions among HeartMapp +BHQ group compared to CHF Info App +BHQ group.

BACKGROUND AND RATIONALE

1.3 Background
Chronic heart failure (HF) is a progressive disease that affects 6.5 million Americans with costs exceeding $37 billion annually. Incidence of HF is increasing, with more than 650,000 new cases diagnosed annually and 10 million cases expected in the U.S. by 2020. Presently, treatments for HF are largely comprised of drug therapies targeting pathophysiology or complex educational interventions targeting self-care practices. Despite increasing adherence with treatment guidelines, hospital readmission rates remain high. In fact, half of all HF patients are re-admitted within the first six months of initial hospitalization, suggesting that education does not often translate to changes in self-care practice.

A significant limiting factor for the success of HF treatment is cognitive deficit
Cognitive deficits are prevalent in 25-80% of all patients with HF. Slower speed of processing, poor memory and executive function, and limited attention span result in reduced ability to understand and adhere to self-care recommendations that subsequently affect functional abilities leading to disability. Several studies have shown that cognitive decline in HF is associated with delays in seeking care for HF symptoms, poor medication adherence, poor quality of life, 30% increased incidence of hospital readmissions and is an independent predictor of 12-month all-cause mortality. Also, poor self-care in HF patients is
linked to a four times higher risk of developing mild cognitive impairment relative to age-matched healthy older adults.22 Despite increased prevalence of HF and the detrimental effects of cognitive decline,10,11,13–17 current treatment guidelines do not include appropriate tools to evaluate23 or address cognitive vulnerabilities, nor track cognitive status over time.24

There is increasing evidence to support an association between cognitive deficits and HF outcomes.25–27 The efficacy of cognitive interventions, such as cognitive training (CT) demonstrated to attenuate HF related cognitive and functional impairments.28 These merging evidence on CT supports improved quality of life and functional outcomes in HF4,11,28 and reduced third party payer on healthcare resource allocations,29 thus cognitive training is recommended by current HF guidelines.6 As of January 2017, the Centers for Medicare & Medicaid Services launched “HF Bundled Payments for Care Improvement initiative” in which hospitals, physician groups, and post-acute care providers are held accountable for total Medicare episode payments for 90-days.30 Accordingly, high risk HF patients are routinely discharged with homecare with telemonitoring for the first 30-days to avoid readmission penalty.26 Given the ineffectiveness of this current approach, home health agencies are actively considering alternate cost-effective products, with the goal of keeping patients at home.31,32

Mobile digital health applications hold great potential to improve efficiency in HF care via lower costs, better adoption, improved outcomes (see Preliminary Studies), and higher patient satisfaction. Although 30+ HF related apps are commercially available, the majority are unimodal and lack support for usability and potential efficacy.33 An exception, Heart-Keeper, has been tested for usability, but Heart-Keeper is not specific for HF and had flaws and undergoing update currently, does not offer user feedback and does not address cognition.34 Given the increased adoption of smartphones by older adults35,36 to address the rising incidence of chronic diseases,37,38 and the current shortcomings in remote HF-specific digital health, the team created a novel patient-centered mobile intervention app (HeartMapp) to fill the current unmet medical need in HF.39 HeartMapp provides an immediate and interactive means of HF self-care practice and monitoring, including ecological momentary assessments of mood, physiology and cognitive status. HeartMapp also includes cognitive exercises, demonstrated to improve executive abilities28 to enhance self-care management, decrease healthcare utilization costs by 50%24 and reduce functional impairments.4,40 Individualized cognitive and physiological assessments and treatments capture users’ mood, physical behaviors, and cognitive status in their natural environment;3,41 as a point-of-care (POC) device, HeartMapp allows clinicians to remotely monitor patients’ status continuously, in ways that can inform treatment and significantly increase scientific knowledge (e.g., examining the influence of cognition on treatment adherence).

1.4 Study Rationale

While several HF related apps now track symptoms or address a self-care activity in HF, no apps currently address cognitive function or include cognitive training; a central and limiting factor in HF recovery. The etiology of HF related cognitive deficits is believed to be vascular in
origin due to hypoperfusion to the brain during periods of reduced cardiac function. The approach to CT in HeartMapp first targets cognitive operations most vulnerable to the effects of hypoperfusion: sustained goal-directed attention, speed of processing and executive functions. This approach has been successfully applied in several clinical and sub-clinical populations to improve sustained attention and inhibitory control, with training benefits extending to untrained executive functions and IADLs (see preliminary studies). This neuroplasticity-based approach to treatment employs progressive learning to improve core aspects of brain dysfunction. Neuroplasticity-based treatments utilize progressive learning to induce selective positive physical changes in synaptic numbers and strengths that result in the “specialization” of neuronal response representations supporting emergent behaviors. Over three decades of research has documented the remodeling of distributed cortical and sub-cortical responses as the brain is engaged in new, important experiences, or as an individual acquires new perceptual, cognitive, motor, or executive control abilities. In Phase I, individuals with HF will be trained on cognitive exercises improving their speed and accuracy of visual, auditory and cross-modal information processing, while also learning to sustain their goal-directed attention over increasingly longer intervals, producing sustained improvements in processing efficiency and improving functional resource availability (i.e., increasing feed-forward power). As training progresses, participants will be trained to maintain more items in working memory, switch between competing demands and more effectively manipulate information in memory. These ‘higher-level processes’ positively increase the excitability of activities that feedback to perceptual processing (i.e., increasing the feed-backward power of the brain). This approach has been successfully applied in several vulnerable populations and recent evidence suggests that HF patients also benefit.

**Preliminary Studies.** **Preliminary HeartMapp Studies.** A pilot RCT of the CT intervention in HeartMapp was conducted at USF by Co-Investigators Drs. Athilingam and Edwards; HF patients (n=17) were randomized to 40 hours of CT (n=8 completers), or a wait-list control (n=6 completers). Estimated mean difference (See Figure 3) between the CT and the control group, using Cohen’s d, indicated that CT enhanced processing speed (d=0.78), speech processing (d=0.88), working memory (d=0.44-0.50), and memory span (d=0.57). In addition, CT improved functional outcomes, as shown in a HF specific quality of life measure relative to controls (d’s=0.22-0.38). Dr. Edwards has previously completed many RCTs of computerized, process-based, cognitive training among both healthy older adults and those with chronic disease. Using these data, Drs. Edwards and Athilingam performed secondary analyses of the ACTIVE data set, including patients with HF (n=54), and found that the patients randomized to CT
performed significantly better on a composite of everyday speed of processing from pre- to post-training compared with 31 participants who were randomized to the control group (p <0.001). Other parallel research in HF patients has similarly documented that the neuroplasticity-based CT approach is efficacious. Benefits from the CT program is generalized to a 50% reduction in healthcare utilization costs in HF patients, and resulted in significant increases in serum brain-derived neurotrophic factor, as well as significant improvements in HF population.

In a recently completed pilot RCT of the six core features of HeartMapp, but without CT, Dr. Athilingam enrolled 18 patients with HF, mean age = 53 years; 56% female; 61% lived alone; 49% were minorities; 6% had less than high school education. About 90% had non-ischemic cardiomyopathy, mean ejection fraction was 28%, 67% were in HF stage C, and 61% were in NYHA class II. Mean Montreal cognitive assessment score was 26 indicating that mostly everyone had normal cognition. All participants had a mobile phone and 83% reported using their mobile phone to acquire health information. Participants were block randomized to HeartMapp (n=9) or HF education (n = 9), and the interventions were administered via mobile phone. Mean change scores (30-days post app use - baseline) on key HF outcomes showed significant trends in improvement in the HeartMapp versus the education group, despite small sample size. Improvement comprised the following: patients in the HeartMapp group improved self-care maintenance by 2 points, while the HF group declined 5 points (p=.083); mean score change in HF knowledge improved 3 points in the HeartMapp group, while the HF education group declined (p=.37); depression measured by PHQ-9 improved in the HeartMapp group relative to the education group (p=.07); quality of life measured by the Kansas City Cardiomyopathy questionnaire improved in the HeartMapp group while the HF group declined 9.0 points (p=.18). Medication adherence improved among both groups and no age or gender differences were observed (manuscript in prep). Given the positive results of the pilot CT trial of using HeartMapp in HF and parallel research indicating benefits of CT in HF, the researchers anticipate that outcomes will improve significantly in the full-feature HeartMapp in phase I (SBIR).

These cognitive training exercises not only improve cognitive function, but have also been shown to protect against depression, improve instrumental activities of daily living, enhance walking speed, and maintain health-related quality of life, all of which are particularly relevant to HF patients. In phase I, the team will incorporate CT exercises accessible via HeartMapp, which will collectively target attention, speed of processing, basic visual and auditory perception, divided attention, and response inhibition. The team will determine the optimal algorithm-directed approach for successful and efficient epochs of engagement.

Finally, the development of HeartMapp has benefitted from Dr. Athilingam’s clinical expertise in this area. Recently, she was awarded the National Science Foundation Innovation-Corps grant that enabled her team to explore The Business Model Canvas for commercializing HeartMapp. Given the complexity of the healthcare ecosystem, the application of Business Model Canvas provided an in-depth understanding and testing of the nine-key building blocks, particularly the customer discovery process aligned with the value proposition towards
commercializing HeartMapp. Stakeholders (n=125) including patients, physicians, nurses, and administrators from hospitals, nursing homes, home healthcare agencies, and insurance companies—were interviewed around the US over a 3-month period. Results indicated that most hospitals establish affiliations with home healthcare service providers to provide HF patient care (i.e., home care is not part of a unified continuum of care). Home healthcare professionals reported that because their current remote telemonitoring equipment is bulky, obsolete, difficult to transport, and costly to maintain, they are eager to implement alternatives to meet the demand. The results of the investigation concluded that HeartMapp may offer the desired solution and merited further exploration.

Dr. Athilingam also completed a survey of 37 participants (25 HF patients and 12 healthcare workers) after navigating the HeartMapp features for up to two hours. The usability questionnaire examined four dimensions: ease of use; usefulness and problem solving capabilities; presentation accuracy and clarity; and satisfaction with use and design. All participants completed a self-confidence questionnaire and was able to navigate features of HeartMapp with little or no help and reported moderate self-confidence in using the app. The healthcare workers (n=12) reported high confidence in recommending HeartMapp to their patients and high confidence in using HeartMapp data for clinical decision-making in patient care. Dr. Athilingam also assessed the readability of the HF education modules, the CHF Info App, that are materials included within HeartMapp. The results demonstrated that the materials included are at 5th grade to 8th level.

2. STUDY DESIGN

A prospective, parallel arm, double blinded, randomized, controlled pilot clinical trial will be conducted among 40 adults with HF to determine feasibility and potential efficacy of using a mobile technology-based intervention (HeartMapp +BHQ) among patients with HF. The goals in the current project are:

1. To finalize the development of HeartMapp +BHQ modules (0-3 project months).
2. To examine feasibility and potential efficacy of HeartMapp +BHQ (4-12 project months).

The proposed timeline for completion of the current project milestones is one-year. The team propose to enroll 40 with oversampling by 18% totaling up to 49 patients with HF.

Randomization

To avoid biased allocation, we propose to use a stratified randomization of all 40 participants into two groups by age (<65 or ≥ 65 years of age) and cognitive status [Montreal Cognitive Assessment (MoCA score 20-25 and ≥ 26)]. We will use the online, REDCap system to generate treatment allocation of groups.

The research staff who randomize the patients, Joel Fernandez, MD, Cardiologist and Ms. Dolan a cardiology Nurse Practitioner will care for the welfare of study participants, and Pharmacist (Dr. Miranda), will be un-blinded to the treatment allocation. Participant randomization and allocation into an intervention group will be performed after inclusion and exclusion data and baseline data has been collected and verified. Unblinded research staff from
the Sponsor, Posit Science Corporation will be provided access to the REDCap system for auditing purposes and may access randomization records at any time to monitor the randomization assignments for accuracy and integrity. Participants will be randomized with their assigned de-identified participant identification number, and no personally identifying information will be accessible to Posit Science unblinded research staff and deviations will be discussed at the bi-weekly meetings. A separate blinded research assistant will complete the follow-up assessment of all participants. The PI (Dr. Athilingam) and Co-Is (Drs. Edwards and Labrador) will be blinded to the participant assignment. They won’t obtain consent document or collect data from participants. Dr. Athilingam and Edwards will be involved in data analysis. Dr. Tom Van Vleet from Posit Science Corporation, San Francisco, CA, the Sponsor PI will not be involved directly in any participant related study activities of the RCT, but will be involved in the overall design and execution of the study protocol, including oversight and coordinating of study activities between the Sponsor and USF study personnel, and data analysis of the deidentified data.

3. SELECTION AND ENROLLMENT OF PARTICIPANTS

Selection of participants is based on their condition of HF and is not based on gender or ethnic considerations. Race and ethnicity in this study will be determined via self-report or self-identification by participants. The diverse demographics of the Tampa Bay area and Dr. Fernandez, a Spanish speaking provider will enable us to recruit a diverse representative sample.

Upon obtaining approval by the USF Institutional Review Board, participants will be recruited from Florida Hospital, Tampa, which provide advanced cardiac care, USF Morsani Health Center and Florida Cardiology Division of USF at S. Armenia Avenue Clinic of Dr. Fernandez. The team projects recruiting three participants per week to enroll the required sample of 49 in three months and follow them at 3- and 6-months after enrollment.

Materials for recruitment will include an IRB-approved brochure that explains the research in layperson’s language and will be made available at the inpatient units of the Florida Hospital, cardiology clinic at S. Armenia Avenue, and USF Morsani Health Canter where recruitment is approved and supported. The Nurse Practitioner (NP) Ms. Dolan, Pharmacist Dr. Miranda, and
the discharge care coordinators will identify participants with HF and give the brochure about the study to potential participants in Florida Hospital. They will refer these potential participants to the study staff. The study staff will confirm from the providers if these potential participants are medically stable to participate in this research, confirm their NYHA class (that is Class II-III) and other inclusion and exclusion criteria.

Inclusion Criteria
The inclusion criteria were designed to assure that the participants could properly perceive and understand the testing and training stimuli as was done in the pilot study.

- Age 40 years or above,
- Clinical diagnosis of HF as defined by the International Classification of Diseases (ICD-10 codes) and recent hospitalization for HF,
- New York Heart Association (NYHA) classification II-III,
- Potential participant must be a fluent English speaker, based on self-report and as determined by the screening clinician, to ensure reasonable and valid results on key assessments.
- Potential participant must have adequate sensorimotor capacity to perform study activities, including motor capacity adequate to control a mobile device to perform both assessments and mobile-based intervention activities, in the judgment of the study personnel. Therefore,
  - Adequate hearing will be determined by response to a pure-tone stimulus at 70 dB at 1 & 2 kHz in each ear, measured using the Welch Allyn.
  - Intact vision (visual acuity of 20/50 or better, as assessed by a Snellen chart per standard procedure).

3.1 Exclusion Criteria
Participants meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Listed for heart transplant as status 1A,
- Enrolled in a palliative or hospice care program,
- Enrolled in a concurrent clinical trial (involving investigational pharmaceutical, behavioral treatment, or other medical device) that could affect the outcome of this study.
- Previous participation in CT at the USF Cognitive Aging Lab, and/or the participant is actively using any form of cognitive training program or has used it within a month of the consent.
- Self-reported vision, hearing, or motor difficulties that would interfere with the ability to complete the study interventions,
- Self-reported diagnosis of dementia, stroke, traumatic brain injury, brain tumor, epilepsy, or a neurological disorder (e.g., Parkinson disease, multiple sclerosis) that affects cognition or would interfere with the ability to benefit from the study intervention,
• Other unstable medical conditions and/or untreated conditions that may affect cognition, including substance abuse/dependence disorders, endocrine, ongoing chemotherapy or other cancer treatment that could cause chemo brain, or conditions with predisposition to imminent cognitive or functional decline,
• Presence of a disability (e.g., aphasia) that may prevent them from completing study related activities or has problems performing, comprehending or following spoken instructions during assessments, or those with behaviors during screening that are likely to present significant problems performing assessments will be excluded,
• Severe depressive symptoms screened using the Patient Health Questionnaire (PHQ-9) with a score of 7 or greater,
• History or current diagnosis of organic mental disorder including schizophrenia, schizoaffective disorder, delusion disorder, psychotic disorder, bipolar disorder, and/or mood congruent or mood incongruent psychotic features or disorders.
• Evidence of dementia with a score of <20 in MoCA,
• Participant that shows signs of intoxication due to current substance abuse (including alcohol and/or illegal drugs) will be excluded.
• Participants will be screened using the Columbia-Suicide Severity Rating Scale (C-SSRS with suicidal thoughts or ideation). Potential participants who have answered ‘yes’ to:
  o Question 5 (Active Suicidal Ideation with Specific Plan and Intent) or,
  o To any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the C-SSRS “Suicidal Behavior” portion will be excluded from the study if the ideation or behavior occurred within 2 months from participant’s date of consent (as recommended by the FDA for treatment trials). Participants excluded for this reason will be referred for appropriate treatment.

Participants who are excluded due to depression, suicidal thoughts or ideation and/or dementia, poor vision or hearing will be referred to the appropriate professionals for thorough evaluation and treatment.

Follow-up: Once enrolled in the study, the study staff will call all participants three times at the first week, once a week for 12-weeks and once a month up to 6-months. Participants will come to the USF College of Nursing at 3-months and 6-months. Participants who are unable to come to the College of Nursing for follow-up visits will be scheduled a visit per participants’ preference either in their homes or at doctor’s office. Participants will receive written follow-up reminders a week earlier and a phone call 24- hours prior to visits. Participants will complete the same online questionnaires and cognitive assessment, and a measure of HRV using BioPatch™. They will be asked about number of emergency room visits and hospital admissions and data confirmed by chart audit. The C-SSRS form will also be administered to all participants at follow-up visits. Participants meeting these criteria for suicidal thoughts or ideation at any time throughout the study will be asked to complete a final assessment, if appropriate, then withdrawn from the study and referred for appropriate treatment. Participants that show signs of intoxication due to current substance abuse
(including alcohol and/or illegal drugs) during any in person follow-up visit will have that visit re-scheduled; participants with this problem occurring more than once may be excluded and dropped at the discretion of the PI and referred for appropriate treatment.

3.2 Study Enrollment Procedures

Recruitment

At the start of the study, the study team will enroll individuals from USF Morsani Health Center, Florida Cardiology Division of USF at 509 S. Armenia Avenue and Florida Hospital where recruitment is approved. The study staff, who are credentialed by Florida Hospital will approach participants referred by the discharge care coordinator or providers from Florida Hospital, who are medically stable and ready for discharge, after an index HF admission. The study staff (study coordinator) will approach these patients who are referred and ask of their willingness to participate in the study. The study staff will explain the study requirements about the need for screening for eligibility and two follow-up visits to the College of Nursing or doctor’s office. The study staff will also explain the consent process and HIPAA authorization required to allow study staff to access participant health records relevant to the study. For participants contacting the Study Staff independent of a provider or clinician referral, the study staff must verify that they are receiving treatment by a clinician at the associated clinics to ensure that clinical reports can be retrieved to assess eligibility for participants that enroll in the study. Participants will also be requested to provide secondary contact information such a family member or friend. The secondary contact will serve as an emergency contact in the unlikely case of an emergency. If the participant agrees to provide this, the participant authorizes the study staff to contact this individual when the participant has been unresponsive to study staff communication efforts and/or will serve as an emergency contact in case of an emergency. Once consented, participants will be screened for eligibility (see below consent process). Participants who fail screening due to depression, dementia, suicidal ideation, poor vision and hearing will be referred for further clinical evaluation with a referral letter for appropriate specialists.

Once, consented and deemed eligible, the research assistants, who have completed human subject training and are credentialed by Florida Hospital will collect baseline data by helping participants access REDCap to complete online questionnaires. Participants will complete cognitive assessments and measure of heart rate variability. The study staff will extract clinical variables including medications, ejection fraction and HF functional class of participants from the patient portal in EPIC. The study coordinator who is unblinded will randomly assign eligible participants to intervention and attention control group stratified by age (<65 or ≥ 65 years of age) and cognitive status (Montreal Cognitive Assessment (MoCA score 20-25 and ≥ 26). The study coordinator will train the participants on the use of HeartMapp or CHF Info App. The blinded research staff will collect the follow-up data.

Informed Consent

During the informed consent process, the participant will be provided with a copy of the informed consent form which includes the HIPAA waiver. The informed consent discussion will take place
in a private room at the hospital or in clinic at the Study Site. Participants will be encouraged to take time to consider whether or not they wish to participate in the study. Written informed consent from participants will be obtained prior to enrollment at the first study visit before screening and baseline data collection. The study staff, who has completed human subjects training and are approved by the Institutional Review Board will explain the study procedures, answer any questions, and obtain informed consent. The study staff will read and/or summarize key sections of the consent document with the patient, as appropriate, and clarify any questions. The participant will be provided an opportunity to ask questions prior to signing the consent form (as well as throughout the study at each of the follow-up visits). A copy of the signed consent form will be provided to the participant. To proceed in the study, the individual must willingly sign the informed consent form. No study procedures will commence until a signed informed consent form is obtained by the research staff.

4. STUDY INTERVENTIONS

Intervention Features of the HeartMapp
Presently, the HeartMapp has now 7 HF features with multiple HF self-care components included. During the first three months of this grant, cognitive training (CT) from BHQ will be added within HeartMapp making it have 8 features. (See Figure 1)

1) Medication Tracker: this feature allows patients to add and edit their medications and activate reminders to take medications (e.g., SMS or push notification). This feature can also assist home health nurses to update their patients' medications list collaboratively. A systematic review of 57 studies reported reduced readmission and mortality with improved medication adherence and a recent pilot study of MedSentry, a mobile app, usage improved medication adherence, improved quality of life and decreased readmissions.
2) Symptoms Tracker: Tailored automated reminders are provided to patients to check their weight, complete HF symptom assessment questions, as well as brief cognitive and mood assessments. While symptoms are the hallmarks of HF severity, patients experience of symptom clusters and symptom intensities vary and may reflect the personal and social experiences of illness, cultural differences in the interpretation of symptoms, and responses to the illness; all of which may influence HF self-care practices and care seeking behavior. Often patients misinterpret symptoms of HF and decline seeking early medical care resulting in higher readmission rates as symptom recognition may be impaired in the elderly population, reinforcing the importance of bolstering cognition.

Once a user is registered in HeartMapp with baseline height, weight, and health care provider information, they receive tailored daily prompts and are provided access to the assessment window to check weight, blood pressure, and answer the short questionnaires on HF symptoms and cognitive and mood status. HeartMapp then classifies users via the HF severity index based on the New York Heart Association functional classification and provides automated cues for action; a method shown to identify mild deterioration in symptoms for early medical care and assess functional improvements upon intervention. Including, a) Green Zone, if HF symptoms are reported as stable or no change in weight; b) Yellow Zone, if HF symptoms are reported as mild and a weight gain of three pounds in one day or 5 pounds in a week; c) Orange Zone, if symptoms are moderate and a weight gain of more than 5 pounds; or d) the Red Zone, if HF symptoms require immediate attention. These data entered in HeartMapp will be followed daily by study staff using the companion app that will provide daily alerts to the study staff on the color zone, weight, and health during the study period for triage and decision making for further care.

A pre-post pilot study that provided text messages to patients with HF (n=15) reported significant and large increases in mean composite score of HF self-care maintenance ($p < 0.01$) and self-care management ($p < 0.01$) at four weeks. Given the prevalence of cognitive impairment, HeartMapp includes a memory screener and a simple naming task to measure cognition (see Boston Naming Test with 9-items), as patients with early vascular dementia due to cerebral hypoperfusion in HF display memory problems and increased naming errors. Finally, given the incidence of depression in HF (prevalence rate of approximately 40%), which is an independent risk factor for hospital readmission, functional decline, and mortality. HeartMapp administers the Patient Health Questionnaire-9 (PHQ-9) to capture mood state biweekly, and in phase I, the team will add the novel Immediate Mood Scaler (IMS) which, unlike PHQ-9, captures current mood state and can be administered daily.

3) CHF Info (HF related education): Lack of knowledge is a key barrier for self-management and HF outcomes and evidence indicates that traditional patient education using printed materials does not adequately support self-management in HF patients. HeartMapp includes audio-enabled HF education and reference materials in 14-modules, and includes push notifications-based educational tips (i.e HF symptom management; low salt dietary tips;
information regarding heart and brain connection). Readability analysis of the education modules in the app is assessed at fifth grade to eight grade level as recommended by American Medical Association. To match the intervention protocol, three control games of BHQ are added within CHF Info App. (See Figure 2)

4) Exercises: This feature includes a) deep breathing exercise for stress reduction and walking to enhance physical activity and tracks distance walked in 6-minutes (6-minute Walk Test) using the accelerometer built in the mobile device when they carry the device with them as a mean to track improvement in physical health. If they are unable to walk or wheel chair bound, they don’t have to walk, but they can use other components of HeartMapp. Patients with HF have 2-3 times higher incidence of psychological distress and depression compared to general population and deep breathing results in decreased salivary cortisol levels, indicating a greater reduction in stress compared to the control group. Conscious control of breathing influences the autonomic nervous system that controls heart rate, and heart rate variability. This was seen in HF (n=81) patients who practiced controlled breathing at six breaths/minute compared with spontaneous breathing of 15 breaths per minute in healthy controls (n=21) due to its effect on baro-reflex sensitivity. HeartMapp is designed to teach patients via auditory/visual biofeedback to attain six breaths per minute and offers performance feedback. Patients are encouraged to breathe as tolerated and may breathe more times in the beginning, but the goal is to achieve 6 breaths per minute. Given the importance of physical activity in HF patients and its positive association with increased functional independence for activities of daily living such as walking, dressing, bathing, toileting, and eating. HeartMapp includes the b) 6-Minute Walk Test (6MWT) an informative metric for patients with chronic heart and lung diseases, validated for independent remote administration. Additionally, heart rate variability (HRV) is considered the best indirect prognostic assessment of cardiac autonomic activity for patients with HF. The large Whitehall II study (N=3328) reported a positive association between physical activity and HRV, and a dose-response relationship of baroreflex sensitivity and improved HRV to individually-tailored exercise training in patients with HF has also been shown. Also, HRV is highly sensitive to overall demands of sustained attention over and above the influence of other cognitive processes. Collectively, overtime, CT, deep breathing and walking may reduce stress and improve HRV, thus influence cardiac function.

5) Vital signs: Data on weight, heart rate and blood pressure entered in HeartMapp by the participants are tracked and performance shown as graphs under stats. HeartMapp has the capability of syncing data from wearables such as Moto 360 and Fitbit, but for this study, we are not using any wearable.

6) Communication feature. HeartMapp also includes a communication feature (A companion App) to offer social support to the participants. Evidence indicates that lack of social support is a barrier to self-care.
and care-seeking behavior of patients. The communication feature allows patients to create a self-identified support circle enabling access to performance statistics of the patients and facilitate communication and support between self-identified circle members via text messages (e.g., study staff, family members, home health nurses, and health care providers). The self-identified circle member will act as a coach or companion and will have downloaded HeartMapp as a coach. This feature was added in response to the pilot study completed by the PI, and is based on patients and family members’ feedback. The study staff will serve as the coach in this study. The coach will receive notification on HF zone (Severity of HF symptoms) of the participants alerting if their HF symptoms worsened or if they have not taken their medications. These notifications will help the study staff to track performance statistics and communicate with patients via text messages within HeartMapp and call participants for triage and help with further medical care.

7) Performance feedback (Stats) feature displays patient performance trends in weight, blood pressure, HF symptoms assessments (Zones status indicating symptom severity), medication compliance, exercise history and vital sign statistics (i.e. weight, heart rate and blood pressure) over time to facilitate informed communication with healthcare teams during office visits and with home health nurses for triage and decision making. Evidence support performance feedback improve the technical and behavioral effectiveness. The number of times patients access the stats feature along with responses to alerts serves as indicators of patient engagement.

8) Cognitive Training. Neuropsychology-based CT will be a new feature added to HeartMapp within the exercise tab and will be tested in this application. During the first 3-month of the study, the team will include CT modules that will be linked in the exercise feature of the HeartMapp. The CT includes Useful Field Of View (UFOV) and Tonic And Phasic Alertness Training (TAPAT) exercises in a 30-hour training schedule delivered over a 12-week period (30 minutes per day, 4 days a week, for 12 weeks). The algorithm included in the CT program generates a continuously updated user profile derived by recording changes of performance of each user in every exercise session, referenced to an a priori sequence of exercises identified to be the ideal sequence in which a typical user (the average of thousands of normal users) should complete this deficit-targeted exercise suite. For example, if performance gains are maintained as predicted, the algorithm positively elaborates current treatment parameters and strategies. HeartMapp will employ reminders according to adaptive control of thought-rational theory of cognition; an approach shown to improve the adoption of health-related behaviors. In addition, the design features of the cognitive exercises promote greater engagement of neuromodulatory systems. This is accomplished by wrapping the exercises in a game format, in which users trigger the start of the stimuli or engage a stream of stimuli deployed in a continuous performance format (engaging cholinergic selective attention systems); users are also presented with multiple varying stimuli over time in which task relevant items require increasingly greater discrimination from foils (engaging noradrenergic novelty detection and tonic and phasic alertness systems), and earn positive, unexpected, and fun rewards when trials are correct (engaging dopaminergic reward systems).
4.1 Interventions, Administration, and Duration

**Intervention, HeartMapp +BHQ:** The study coordinator will launch HeartMapp in participants' own mobile device or a loaned device. This staff will set up tailored alerts, and demonstrate the functionality of HeartMapp for those enrolled to receive HeartMapp. Participants will be instructed to use HeartMapp daily by responding to the alerts provided four times a day, a time recommended in an earlier feasibility study by HF patients for completing symptom assessment, exercises and medications. They are instructed to complete 2 hours of CT per week at 15 minutes per session twice a day (30 minutes a day) to avoid fatigue, at home on their own. Participants will be allowed up to 12 weeks to complete training, which is 60 sessions for a total of 30-hours that has demonstrated improved cognitive function and impacted self-care and quality of life of patients with HF. (See Figure 1)

The HeartMapp's features include responding to daily alerts and performing CT of BHQ will be demonstrated to the participants. HeartMapp will alert participants four times a day. First alert is in the morning to complete weight and answer the HF symptom questionnaire and perform cognitive training. Second alert will occur in the evening to report change in symptoms, encouraging, walking and deep breathing exercises. The third and fourth alerts are reminding participants on medication management. CT exercises are in a 30-hour training schedule delivered over a 12-week period (30 minutes per session, 4 sessions per week, for a total of 60 sessions).

*The topics that will be covered for participant at training include:*

- Daily alerts to complete daily weights, blood pressure and symptom and mood assessment
- Alert to take medication as per participants' schedule
- Responding to automated feedback and cues for action provided by HeartMapp.
- Demonstrate how to use the brain training exercises in HeartMapp.
- Demonstrating deep breathing exercise to achieve six-breaths per minute.
- Six-minute walk-test using accelerometer of the mobile device and setting goal.
- Navigating the 14-modules of HF education and receiving text messages on HF education tips on self-management, diet, medication and physical activity.
- The user interface feature of zoom and audio function of HeartMapp.
- Use of information (statistics) displayed as graph in HeartMapp on weight, symptoms, blood pressure, medication compliance, breathing and walk test.
- How to respond to cues such as, if HF symptoms seem to be getting worse, as in Yellow Zone, they will be advised to seek medical help from a primary care doctor or the study NP or call 911 if they are in red zone. At times, these cues could be false alarms, therefore, participants will be educated to call the study staff (unblinded staff who trained them) with concerns for additional triage and management guidance to participants. They will be educated that the study staff will be calling them for declining HF symptoms and send them text messages.
The Attention Control, CHF Info App + BHQ Group will have the CHF Info App downloaded on their mobile device or a loaned device by the unblinded study staff. The study staff will teach participants how to access each module, check their knowledge, use control games and maintain a paper version for weight and symptom monitoring which is the standard care. The CHF Info App, is one of the components of the HeartMapp (See Figure 2). The readability of the education materials included in CHF Info App is assessed to be in fifth grade to eighth grade level, which is recommended by American Medical Association. Participants will be trained to use the CHF Info App to complete at least one module a week for 12-weeks to complete the 14 modules. Participants will be trained to use the three control games, 30-minutes a day for 4 days a week to complete 30 hours of BHQ games. The topics that will be taught include:

- Daily text message on key HF health topics
- Navigate the 14-modules at one module per week which include:
  - what is heart failure and types of heart failure?
  - what causes heart failure,
  - how to care for yourself with heart failure at home,
  - heart failure medications and treatments,
  - importance of exercise and physical activity,
  - why low salt diet with few good low salt recipes,
  - managing feelings and thinking ability
  - how to care for other chronic conditions,
  - vaccinations and preventive care
  - follow-up care and cardiac rehabilitation
- Check your knowledge module to review what you have learned
- Use of the three control games of BHQ. We previously vetted casual video games requiring minimal attention, memory and executive function will be used for the active control condition.
- The games included are:
  - Bricks Breaking Hex (Candy Crush inspired): The goal of this game is to connect and remove bricks of the same color to clear the board.
  - Gem Swap: Participants are presented with a grid of gems on the screen. The goal of this game is to swap adjacent gems to line up 3 or more identical gems to score.
  - Double Klondike Solitaire: Participants are presented with a row of standard playing cards in the middle of the screen and a stack of the remaining cards on the top left corner of the screen. The goal of this exercise is to move all cards from to the 8 foundations (standard suits) from Ace to King. Participants are asked to click and drag cards from the row presented to the foundations.
- Paper version for weight and symptom monitoring prescribed by “My Heart Failure Action Plan” which is the standard care.

All Participants who do not own a weighing scale or blood pressure monitor will be given one. The medium of treatment for the two-arm in this clinical trial is the use of mobile technology for both groups and complete same questionnaires and data collection.
All participants will receive the same number of contacts from study staff at three times during the first week after enrollment, and once a week for the first three months and once a month for the remainder of the study period.

4.2 Handling of Study Interventions

The apps are not available on the market for download. Therefore, the study staff will download the apps in patients own mobile device or a loaned device and train the participants in using the app. Prior to start of the study, Posit Science will use their research portal to add the CT exercises within HeartMapp and three control games within CHF Info App. All usage data from HeartMapp and CHF Info App are timestamped and saved in a secure portal with pass word protection at USF Department of Computer Science and Engineering. The USF currently use the Advanced Encryption Standard (AES) to encrypt location data as it is transferred using UDP to ensure a secure Location-Based Services (LBS) for wireless communications.

For both the HeartMapp +BHQ and CHF Info App +BHQ, a participant opens a standard application on their own device or a loaned device. The participant then logs into the program platform (using a study provided user name that contains no personally identifiable information). The participant is directed, as randomized, to use the HeartMapp +BHQ or CHF Info App +BHQ. When it is time to complete the BHQ exercises in HeartMapp or control games, respectively, the participant will choose that feature within the respective apps. When doing so, the participants will be redirected to the BrainHQ application and have access to either CT exercises or control games. A game-like experience begins, where the participant is encouraged to earn points and in-game rewards to advance.

All usage and progress data from BrainHQ delivered exercises is encrypted then transmitted to a central server. In a research study such as this one, no personally identifiable information is stored on the server (including internet protocol addresses). On the server, the data are available for review by the un-blinded Cognitive Remediation Coach, Study Coordinator and/or clinician through a secure web portal. The Cognitive Remediation Coach, Study Coordinator, and/or clinician in particular will use the secure web portal to regularly check on usage and progress of each active participant to customize their weekly phone/in-person discussions to provide helpful guidance and coaching.

At the end of this Phase I Clinical Trial, following completion of the data analysis phase, if one intervention is found to be more effective than the other, study, participants will be given access to the intervention that is deemed more effective.

Concomitant Interventions

4.2.1 Allowed Interventions
Participants will be allowed to receive standard HF treatment and any prescribed medical treatment for any health conditions.

4.2.2 Required Interventions
None

4.2.3 Prohibited Interventions
Other forms of cognitive training or use of similar mobile apps for HF treatment or care.

4.3 Adherence Assessment
Participants will be considered adherent to using the BHQ exercises, if they complete at least 20 hours of the initial amount of CT training (at least 40 sessions) in HeartMapp. Adherence to app usage will be determined if participants accessed HeartMapp components 80% of the days, which is 72-days. The HeartMapp will record number of times each HeartMapp components are accessed and number of CHF Info modules and control games in BHQ completed.

5. STUDY PROCEDURES

At the screening and baseline visit, all participants will complete the consent and HIPAA waiver form prior to testing for eligibility and completing prescreening documents with demographic data. They will complete the MoCA and PHQ-9, as well as answer questions to ascertain their eligibility, and indicate their interest in participating in research. Those who score <20 on the MoCA or ≥7 on the PHQ-9 will be referred for further evaluation and treatment. Once a patient is consented and deemed eligible to enroll in the trial, the data collected will undergo a verification process. After which, the study staff, who is unblinded will randomize participants using the REDCap system to generate treatment allocation to one of the two groups. A total of 49 subjects, 25 to HeartMapp +BHQ, and 24 to CHF Info App +BHQ will be enrolled.

Once randomized (either HeartMapp +BHQ or CHF Info App +BHQ) the apps will be downloaded in patients own mobile device or a loaned device by the study staff and will be trained to use the apps at home. All participants will be given a weighing scale and a blood pressure monitor if they do not have one and will be trained to use them. If participants are discharged from hospital prior to enrollment in the study or those who prefer to start the study at a later time will have a visit scheduled in the clinic or in their homes within the first week after discharge. Participants that are not enrolled within the week following discharge, but return for reevaluations to the cardiology clinic after their first week of discharge for a follow-up may be approached and enrolled. The PI (Dr. Athilingam) and Co-Is (Drs. Edwards and Labrador) will be blinded to participant assignment. They will NOT obtain consent document or collect data.
Consent Process

The informed consent discussion will take place in a private room at the hospital or in clinic prior to any study related activities. Individuals who are interested and potentially eligible for the study will be provided with a copy of the informed consent statement with HIPAA waiver. Participants will be encouraged to take time to consider whether or not they wish to participate in the study. Written informed consent from participants will be obtained prior to enrollment at the hospital or clinic or at home. Study staff who have completed human subjects training and are approved by the Institutional Review Board will explain the study procedures, answer any questions, and obtain informed consent. The participant will be provided an opportunity to ask questions prior to signing the consent (as well as throughout the study). No study related activity including screening will take place until the consent document is signed. Potential participants may invite a friend or family member to be present during the visit, to further discuss their decision to enroll and/or contact (e.g., phone call) a friend or family member who are their secondary contact that is not physically present for discussion before deciding to enroll. At the potential participant’s request, study staff may be asked to ‘step-out’ of the room to provide privacy for such discussions. In addition, potential participants will be provided the option to defer their decision, bring the consent form and other study information forms home to discuss their decision with friends or family members, and later return to the study site to enroll. A copy of the signed consent form will be provided to the participant. No study activities will take place prior to completion of the consenting process.

- Informed consent will be an agreement between the investigators and each participant having the capacity to understand and make an informed decision. Consent will be obtained prior to each potential participant’s participation in this study.
- Each individual participating in this study will be made aware of the fact that his or her participation involves research and the intent of the research, the expected duration of their participation and a description of the procedures that will be followed. Participants will be informed that their participation in the study will not influence their clinical care or their relationship to the Florida Hospital, Florida Cardiology Division of USF, and/or the USF Morsani Health Canter.
- Each participant will be made aware of the reasonably expected benefits he or she might receive, as well as any risks or potential discomfort that are involved.
- Each participant will be made aware of alternative procedures that are available to him or her.
- Each participant will be made aware that his or her records will remain confidential, but the NIH and IRB have the right to inspect his or her records.
- Each participant will be told that his or her participation in the study is voluntary, without force or influence from the investigators or research staff.
- Each participant will be given the name and method of contacting the appropriate person(s) to answer his or her questions about the research and in the unlikely event of research-related injury.
Each participant will be informed about compensation for their participation in the study, as well as the methods, schedule and conditions for payment.

**Training of Participants**

Once enrolled and randomized, the unblinded study staff will download the app in their own mobile device or a loaned device and train them. Participants that use their personal mobile device, given that it meets systems requirements, must allow the study staff to install and remove the necessary application(s) and configure the settings as needed on their personal device prior to program use. The study staff will use teach-back methods to ensure proper understanding to use the Apps. The teach-back methods have shown to be beneficial in our pilot study in educating participants. This study staff will call them three times during the first week to ensure a smooth transition to the mobile delivered intervention activities. If it is not feasible to complete this training at the Baseline Visit or the participant is experiencing difficulties using the mobile apps, the study staff may schedule retraining at home or at the recruitment site, as needed. The study staff will also call participants on whom they receive notification on declining to other than green zone, whose performance statistics demonstrated declining HF symptoms. Participants who do not own a weighing scale or blood pressure monitor will be given one and trained to use them at home. A training manual with link to YouTube will be provided to participants.

[https://www.youtube.com/watch?v=jdJ7rjdHUIA](https://www.youtube.com/watch?v=jdJ7rjdHUIA)

**Follow-Up**

A blinded study staff will help participants complete the same questionnaires in REDCap, complete online cognitive assessments, and collect HRV data using BioPatch™ at 3- and 6-months at the College of Nursing, or patients' home or cardiology clinics. To ensure privacy in data collection, they will be completed in a private secured room. Once the participants complete the outcome measures, they will receive compensation as allowed.

Participants will receive a follow-up reminder a month prior to the schedule follow-up date. An email from REDCap will be sent a week prior to the follow-up date and a phone call 24-hours prior. Participants who miss a follow-up will be contacted within three days and requested to reschedule. If the team loses contact with the participants for 2-weeks or more, the team will reach out to the participant’s secondary contact. If participants cannot be successfully reached within three weeks, a letter requesting a reply will be mailed. If no response, they will be considered dropouts after 4-weeks of trying the above methods. If it was the patients first follow-up visit and a contact was established after the 4-weeks window, they be considered a drop out for visit 1, but will be scheduled for visit 2 (6-month follow-up), if appropriate. The same window of 4-week will be considered for visit 2 and after that time period, they will be considered dropouts.
Participant Payment

The consenting study team member will inform participants about compensation for their participation in the study. Specifically, we will provide

- $20 for the consent, initial screening and baseline assessment visit (V0),
- $2 for each training session completed (maximum of $120 for completing all 60 sessions or 30 hours of training) during the Program Use period,
- $50 each for completing the post-intervention 3-month assessment (V1) and
- $25 for the 6-month follow-up assessment (V2).

Participants that complete the study in its entirety will earn $215.

Compensation will be provided through a reloadable debit card. Payment for assessment visits will occur following completion of that visit. In the event that a participant must repeat an assessment visit due to administrative assessment or Site Study personnel errors, participants may be provided additional compensation for that session. If, for any reason, eg. technical or vendor issues, prevent the study staff from issuing the reloadable debit card, adding funds to the reloadable debit card, or making any other changes to the card, participants will be compensated through a gift card (eg. Amazon eGift Card, Visa Gift Card, etc). Each training session will consist of HeartMapp or CHF Info App activities and training exercises (cognitive training or control games). Compensation for training will occur on a weekly basis and participants will be paid for all sessions completed over the course of that week.

If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or treatment sessions they have completed.

For participants who are loaned a mobile device for the duration of the study, compensation for all study activities completed during the Program Use period will occur after the participant returns the loaned mobile device to the study staff at the 3-month follow up assessment visit. If participants are unable to meet with the study staff in person to return the iPad, the participant will be sent a pre-paid label and box (if necessary) to return the mobile device at no cost to them. Participants who withdraw from the study will be compensated for all study visits they have completed once the loaned mobile device has been returned to the study staff. For participants who do not return the mobile device, all forms of appropriate means and communication (eg. phone contact, email, mailed letters) will be used in an effort to retrieve the study mobile device. The mobile device that we loan out may have GPS enabled so that we can identify where they are in the event that they go missing. If a loaned mobile device is not returned to us at the end of the study, we may remotely deactivate the device so that it is unusable. Participants who do not return the mobile device will not be compensated for study-related activities.
5.1 Schedule of Baseline and Follow-up Evaluations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening, Enrollment, &amp; Randomization</th>
<th>Baseline</th>
<th>FU Visit 1 (3-4months)</th>
<th>FU Visit 2 (6-7months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescreening Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics &amp; Medical History*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Health Questionnaire-9*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbia-Suicide Severity Rating Scale (C-SSRS) *</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vision and Hearing**</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montreal Cognitive Assessment*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Variable*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Health Literacy Scale**</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Support Questionnaire**</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment/Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH EXAMINER***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neuro QoL ***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Self-Care of Heart Failure***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Quality of Life (KCCQ)***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Promise Global Health***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Heart Rate Variability***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hospital and ER admissions***</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse Events Reporting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Data Management</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates Covariates

* Screening
** Potential Covariates
*** Outcome Measures
5.2 Description of Evaluations

All of the outcome measures and procedures are standard. The researchers proposed to use routine assessments and standard questionnaires that are commonly used in clinical practice and research. No experimental procedures will be used. All of the measures and the intervention exercises have previously been completed by adults with HF. The data collected will not associate any personal identifying information with specific participants.

The researchers propose to use the common data elements (CDE) to advance the science of self-management of chronic diseases as well as a Research Electronic Data Capture (REDCap) software application and workflow methodology to collect and manage data in the proposed pilot trial.

The following list comprises and describes the measurements, tests and assessments to be used in this study.

1. Demographic questions included in Prescreening form and Medical History Data
   - Gender at birth and current gender identity
   - Age
   - Education
   - Race and Ethnicity: Caucasian, African American, American Indian, Asian/Pacific Islander, Other
   - Hispanic or Non-Hispanic, if Hispanic then origin (e.g., Mexican, Puerto Rican, Cuban).
   - Marital Status
   - Native and Primary Language
   - Handedness: Right or Left
   - Employment Status
   - Medical History questions

   - Clinical variables including severity of heart failure by NYHA Class and ejection fraction and duration of HF, will be obtained by chart audit.
   - Inclusion/Exclusion questionnaire
   - Secondary contact information for retention will be collected at baseline
   - Test of hearing acuity, as determined by response to a pure-tone stimulus at 70 dB for 1 & 2 kHz in each ear, measured using the Welch Allyn.
   - Test of visual acuity of 20/50 or better, as assessed by a Snellen chart per standard procedure.
   - Montreal Cognitive Assessment (MoCA): The MoCA is a brief tool to assess general cognitive function. Each of the 30 components of the assessment is
scored for a total of 30 points. The MoCA tests visuospatial/executive functioning, naming, memory, attention, language, abstraction, delayed recall, and orientation to time and place. Participants must score a 20 or above to enroll in the study.

- Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 scores each of the 9 DSM-IV criteria for depression as 0 (not at all) to 3 (nearly every day). Sensitivity 88% and a specificity of 88% for major depression, Cronbach’s alpha 0.82. Participants who score 7 or above on the PHQ-9 will be excluded.

C-SSRS will be administered to assess for suicidality. Participants that screen positively for this assessment will be excluded and will be referred for appropriate treatment.

Covariates include:

- Health literacy will be assessed using Brief Health Literacy scale. This brief questionnaire has three questions. Receiver operating curve 0.76 to 0.87.
- Perceived social support reported as feelings of being cared for, supported, and valued as a person. Cronbach’s alpha 0.99.

2. **Primary Outcome Measures**: The primary outcome is the feasibility of app usage and engagement of participants with the apps.

- App usage by participants will be tracked by HeartMapp and synced to a secure USF website to determine number of times HeartMapp components are accessed.
- Patient engagement with the Apps will be assessed using the data entered by participants in response to alerts and interventions in the app. Specifically, patient engagement will be calculated using the following information: the number of times participants access HeartMapp features, the number of times they entered data in response to alerts, education modules deep-breathing and six-minute walk test completed. We anticipate at least 80% of time participants will assess HeartMapp features (72 of 90 days).
- Engagement with CT exercises will be measured as percentage of participants who complete 20 hours of CT.

3. **Secondary Outcome Measures**:

   a) **Cognitive Outcomes**: The efficacy of HeartMapp +BH to enhance cognition will be assessed by measuring outcomes of processing speed and executive function using standardized measures.
   - The National Institute of Health (NIH) Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER)
includes series of tasks targeting inhibition, set shifting, fluency, insight, and planning. Available at [http://memory.ucsf.edu/examiner](http://memory.ucsf.edu/examiner). Confirmatory factor analysis supports both a one-factor model and a three-factor model, and these models formed the basis for an Item Response Theory (IRT)-generated Executive Composite score and smaller scales quantifying Working Memory, Cognitive Control, and Fluency. Test-retest reliabilities range from .78 to .93. NIH-EXAMINER was designed to be applied in multiple ways. The online version will be used for ease of completion by participants on an ongoing basis during training. The NIH-EXAMINER allows researchers the ability to quantify each of the relevant domains. For this study we will include behavioral domain, insight, planning, and set-shifting that are proposed to have an effect by UFOV and TAPAT training.

- The Neuro QoL Cognition 2.0, a validated measure that provides a practical opportunity for multidimensional assessment in neurologic and cognitive assessment in clinical research or practice will be used. The internal consistency for this measure is (Cronbach α) of the 13 short forms ranged from 0.85 to 0.97.

b) **Functional Outcomes**: Common data element recommended by NIH will be used in this study to measure functional outcomes using validated standard questionnaire.

- **Self-care of HF** will be measured using the Self-Care of Heart Failure Index, used in multiple studies of HF patients. This HF specific self-care domains including: Self-Care Maintenance, Self-management, and Self-Confidence. The questionnaire includes 15-items for a total score of 100. Cronbach’s alpha .56 to .82. Test-retest reliability 0.90.

c) **Exploratory Outcomes**

- **Health related quality of life** in HF will be measured using the Kansas City Cardiomyopathy Questionnaire. This questionnaire include five clinically relevant domains: physical limitations, HF symptom (frequency, severity, and change over time), quality of life, social interference, and self-efficacy. Cronbach’s alpha .66 to .95 for each domain.

- **Global health** will be measured using the NIH Patient-reported Outcome Measurement Information System (PROMIS) Global Health Short-Form (4 items on overall physical health, physical function, pain, and fatigue) and global mental health (4 items on quality of life, mental health, satisfaction with social activities, and emotional problems) scales have internal consistency (r=.81-.86, respectively).
• **Heart rate variability (HRV)** will be assessed using a BioPatch™ from Medtronic at baseline and follow-ups. A non-allergenic patch will be used on all participants to avoid skin irritation. The BioPatch™ uses Bluetooth technology to transfer data to USF’s secured server. HRV will be assessed for 10 minutes to determine improvement after CT and breathing exercise. This will be done at the time of enrollment at baseline and at 3- and 6-months after enrollment in the College of Nursing or patients’ home during follow-ups.

• Medication adherence is tracked by HeartMapp as responses entered in HeartMapp for daily alerts when medications are due. If participants did not respond to alert when it is time to take a particular medication, HeartMapp will alert them again after 30-minutes. If still no response, it will consider them as non-adherence or medication not taken. Participants entry are time stamped to measure adherence.

• Number of hospitalizations and number of emergency room visits for HF. These data will be obtained from participants and/or their family members during follow-up visits at 3- and 6-months and will be confirmed via chart audit.

### 5.2.1 Enrollment, Baseline, and/or Randomization

**Enrollment**

Participants will be enrolled at the Florida Hospital prior to discharge, at the cardiology clinic at Florida Cardiology Group of USF at S. Armenia Avenue, or USF Morsani Health center. Patients who are discharged from Florida Hospital prior to enrollment will be visited at home or cardiology clinic within a week after discharge. The study staff will consent participants prior to completing the prescreening form and screening test to ensure that all inclusion and exclusion criteria are met. This requires:

- Signed informed consent
- Completion of eligibility questionnaire
- Prescreening questionnaire with secondary contact information
- Questionnaire on demographics, medical history and clinical data
- Completion of MoCA
- Completion of PHQ-9
- Vision and hearing test
- Brief Health Literacy Scale
- Social Support Questionnaire
- CSSRS
After consent with HIPAA waiver is obtained these screening process will be completed. Those deemed eligible will be enrolled, a participant ID number will be assigned. All participants will complete baseline data in REDCap. Once baseline data is collected and undergoes the verification process, participants will be randomized to either HeartMapp +BHQ or CHF Info App +BHQ group stratified by age and MoCA score.

**Randomization**

Randomization will be completed after the participant’s screening and baseline data has been verified as accurate and complete by the study staff, at the first study visit. Participants will be randomized using a stratified randomization by age (<65 or ≥ 65 years of age) and cognitive status (Montreal Cognitive Assessment (MoCA score 20-25 and ≥ 26). Unblinded Posit Science personnel will monitor randomizations in for accuracy and integrity.

**5.2.2 Follow-up Visits**

Recruitment and baseline data collection and training to use HeartMapp or CHF Info APP is to be completed at the hospital, cardiology clinic at S. Armenia Avenue and/or USF Morsani Health center. Participants who express interest but are discharged prior to enrollment will be visited at home or cardiology clinic within the first week of enrollment.

- Visit 0 (consent, screening, baseline, randomization) completed at the time of enrollment in the hospital, cardiology clinic at S. Armenia Avenue, Morsani Center or participants home.
- Visit 1 (3-month) follow-up data will be completed at the USF College of Nursing, cardiology clinic or patients' homes.
- Visit 2 (6-months) follow-up data is to be completed at the USF College of Nursing, cardiology clinic or patients' homes.

Follow-up data at visit 1 and 2 will be collected by a blinded study staff.

**5.2.3 Retention**

Every effort will be made to retain participants and all participants will be invited to complete data collection. Proven retention strategies as detailed by Robinson et al. will be applied including, but not limited to having consistent staff and flexible appointment times for follow-up at visit 1 and 2 and follow-up reminders. In the consent process, the study time and visit commitment will be emphasized. When consented, participants will be provided with a flow chart of the study visits to USF College of
Nursing with their specific dates indicated. Every effort will be made to accommodate participants’ schedules and to provide convenient testing sites (e.g., patients’ home or a convenient location such as doctor’s office).

Participants will be scheduled and confirmed for the next follow-up visit after each data collection at baseline and 3-months. Each participant information will be collected in the best manner (e.g., email or mobile number) and times to contact them to facilitate communication. Information for a secondary contact person for each study participant will be obtained to facilitate continued follow-up. Participants will receive a follow-up reminder a month prior to the schedule date. An email from REDCap will be sent a week prior to the follow-up date and a phone call 24-hours prior.

Participants who miss a follow-up will be contacted within three days and requested to reschedule. If the team loses contact with the participants for 2-weeks or more, the team will reach out to the participant’s secondary contact. If participants cannot be successfully reached within three weeks, a letter requesting a reply will be mailed. If no response, they will be considered a dropout after 4 WEEKS of trying the above methods.

6. SAFETY ASSESSMENTS

Potential Risks
Participation in the assigned intervention HeartMapp +BHQ or attention control conditions (CHF Info App +BHQ) presents minimal risk. The probability and magnitude of harm or discomfort anticipated in this research study are not greater than those ordinarily encountered in daily life and/or during the performance of routine clinical, physical or psychological examinations or tests.

Serious adverse effects from prior studies of the treatments under study have not been reported. Participants will be encouraged to report any adverse effects (AEs) occurring during the duration of the study to the study staff. The protocol details the following potential risks related to study participation.

The following foreseeable risks will be discussed with potential participants during the enrollment visit, as will the following measures taken to minimize such risks:

- **Discomfort while Completing Online Study Measures.** This study will use REDCap to complete questionnaires online. Participants may struggle to complete online assessment. Those who struggle online completion will be provided a paper and pencil version of the same questionnaires (if they prefer).
- **Discomfort while Learning New Tasks.** There are minimal risks associated with completing the tasks on the mobile device. However, participants may
experience frustration with learning a new task. These risks will be minimized by adequate training and offering a troubleshooting video and training manual, as well as tailored training to each individual's level of performance. We believe adequate training on HeartMapp +BHQ and CHF Info App +BHQ will help relieve or eliminate the stress and fear associated with learning a new task.

- **Risk of False Alarms.** The automated cues for HF symptoms from HeartMapp may at times be false. To minimize this false alarm, participants are advised to call the study staff for additional triage and guidance for management of symptoms.

- **Discomfort During Assessments and Self-Report Measures.** Some participants may experience discomfort in the form of boredom, frustration or embarrassment due to sensitive questioning about their condition and/or while completing the self-reported measures on cognition. To prevent these risks, participants will be reminded during each assessment appointment that their participation in the study is voluntary and that as such, they may skip any question they do not wish to answer. This study will use routine, standardized, non-invasive measures of cognition, and functional assessments. Established protocols will be followed during testing to minimize risk to participants. Assessments may be fatiguing for some individuals. To minimize this potential discomfort, breaks are encouraged and provided within the session; participants will be encouraged to save their assessment and after a break will be encouraged to complete the assessments. In the event that a participant appears to be under undue strain, test sessions will be discontinued and rescheduled.

- **Risk of Skin Irritation:** Participants may develop skin irritation from wearing the BioPatch™ for 10-minutes. We propose to use non-allergenic electrodes to minimize skin irritation. If participants develop allergic to the electrodes, we will use the cloth strap.

- **Unable to perform Walking and/or Breathing Exercise(s):** If participants are unable to walk or perform deep breathing, they do not have to perform them, but will be advised to continue using the other features/modules of HeartMapp.

- **Discomfort During Program Use:** The following risks may be reasonably anticipated as the result of mobile-based exercises in both the HeartMapp +BHQ and CHF Info App +BHQ: fatigue, headache, boredom, eye strain, neck/shoulder discomfort, leg/hip discomfort, arm/wrist discomfort, back discomfort, mood complaint, tremor, and sleep quality. To minimize fatigue or other discomfort, participants are encouraged to sit ergonomically correct while training on their mobile device. The exercises are designed to be entertaining and enjoyable. In addition, the mobile-based exercises may be paused at any time and participants are encouraged to take breaks during the training session.

- **Loss of Privacy:** Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. One reason for this is that the study personnel in some jurisdictions are required by
law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures an error may occur. To mitigate this risk, all information collected on paper will be kept in locked file cabinets of the PI’s office in College of Nursing. Electronic data will be password protected and stored on USF Health network servers which are HIPAA compliant. All data keys will be stored separately and securely. Only study personnel will have access to the study data. No participant names or other identifying information will be used in reports or publications. The Sponsor’s PI and Posit Science personnel will not have access to participants personally identifying information, but will have access to deidentified data and is expected to follow the HIPAA rule proposed by USF.

- **Risks of Email Communication:** This study will rely on the use of email communication between study staff and research participants as part of their participation in the program. Study staff would email participants about their upcoming appointments, provide weekly updates on program usage, or communicate other important study information. Participants may also ask questions of study staff using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:
  
  - Others can intercept messages
  - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages
  - A copy of the message may be saved on a device or computer system, even if it is deleted
  - If an email address is not typed correctly, it can be sent to the wrong person
  - Emails can spread computer viruses
  - Others may be able to access messages on devices that were lost, stolen, or thrown away
  - If a user changes emails without notifying study staff, they may miss communications.

**Note:** The Sponsor, Posit Science Inc., to whom the grant is funded does not provide compensation for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries. Participants will be encouraged to report any adverse effects occurring during the duration of the study to the point of contact within research staff. Any reports that result in changes that could potentially increase risk to study participants will be reviewed with the Principle Investigator of the Sponsor, Dr. Thomas Van Vleet. Any such changes requiring an update to the protocol.
or consent will be submitted and approval will be requested by the reviewing Institutional Review Board prior to implementation.

To address factors that contribute to non-compliance, we have incorporated several elements of flexibility in the BHQ exercise schedule to accommodate the challenges that participants with HF may encounter. These risks and associated accommodations will also be discussed with the participant.

- **Fatigue**: Participants with HF may report symptoms of fatigue, and we expect that some participants will not be able to complete a 30-minute session of cognitive training exercises or control games in one sitting. To accommodate participants experiencing this, they may choose to break the training session into shorter time segments, such as 15 min in the morning and 15 min later in the day. Participants can pause the sessions to take break at any time and continue where they left off. The Study Coordinator or Cognitive Remediation Coach will work out a schedule that is feasible, given participant’s current life circumstances.

- **Extra Time**: Participants who complete fewer than 30 hours in the 12-week schedule because unusual life circumstances or because of health issues will be allowed to continue program use for 4 more weeks (for a total of 16 weeks in the program use period) or until they complete all 30 hours (60 sessions) of training, whichever comes first. To ensure a time-bounded study commitment, after 16 weeks such participants will perform their 3-month post enrollment visit, given that they have met the minimum number of training sessions (40 sessions over the course of 20 hours) required to complete the 3-month and 6-month follow up assessment visits.

- **Variable Number of Cognitive Training Sessions**: We expect that some participants will not be able to complete the recommended 4 sessions per week, every week. To accommodate this, we will be understanding of their circumstances and explain to participants that the study will benefit from them doing as much use of apps as their schedule permits. The Study Coordinator or Cognitive Remediation Coach may work out a schedule that is feasible, given participant’s current life circumstances, as appropriate.

- **Cessation of Program Use While Continuing Participation in the Study**: In some cases, a participant may wish to stop or minimize use of the apps going forward, while remaining in the study. Potential reasons for this decision might include a change in work circumstances, a change in health status, family or personal issues, or a lack of interest in the study activities. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after discussion with the study coordinator, the participant will be permitted to cease using the apps, and be scheduled for a 3- or 6-month post enrollment visit, as needed, at the appropriate time relative to the pre-
assessment (baseline) visit, given they have met the minimum number of training sessions (40 sessions, 20 hours) required to complete the follow-up visits.

- **Training.** Adequate training to use HeartMapp and CHF Info App will eliminate the stress and fear associated with learning a new task.

- **Location of Use Resulting in Poor Compliance:** The mobile-based delivery of the program allows participants to complete their assigned exercises in any location they deem comfortable and convenient, given they are able to access Wireless Internet. Since usage and progress tracking for the program is web-based, participants needing to travel while enrolled in the 12-week intervention may continue with the study activities.

- **Emergency:** All participants will be told how to contact study personnel in the case of an emergency. In such emergency, the study staff will triage the participants via telephone and refer them to the primary care physician or Nurse Practitioner (Ms. Dolan) and Dr. Fernandez for further care as needed.

### Potential Benefits:

Potential benefits include

1. **Benefit to Participants:** Direct benefits to participants cannot be guaranteed. However, participants may indirectly feel supported by being monitored by the study team.

2. **Benefit to Individuals:** Results from this study may benefit adults with HF. If the intervention evaluated in this study is shown to be effective in improving HF outcomes and reduce hospitalizations, it is likely to become a standard treatment for HF, which could help thousands of individuals with HF.

3. **Benefit to Science:** Results from this study will greatly contribute to the understanding of mobile technology and cognitive training as a prevention strategy to improve self-care at home for patients with HF. Understanding if the scientific design principles of this intervention drive superior outcomes to ordinary educational materials and computer games will provide considerable insight to scientists and clinicians working on research for this clinical population.

### 6.1 Adverse Events and Serious Adverse Events

An adverse event (AE) is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

AEs will be assessed at each participant contact using an AE checklist from clinicaltrial.gov. The unblinded study staff will complete this from on all participants.
enrolled in the study during each follow-up and contact. All-cause mortality of the participants enrolled will be obtained from hospital data from EPIC. The study will be stopped if three or more AEs attributable to program use or study activities occurred.

6.2 Reporting Procedures

Study staff will ask about any adverse events during daily data in HeartMapp, as well as weekly and monthly follow-up calls and at each follow-up visits of all enrolled study participants. All such events will be documented on a standardized form. At all in-person contacts and at any other applicable time throughout the study, any potential adverse events reported by a subject or observed by the research staff will be recorded and subsequently evaluated by the primary care physicians or Dr. Fernandez of patients enrolled from Morsani center and Nurse Practitioner (Ms. Dolan) for patients enrolled from Florida Hospital, for its relation to the study research procedures and whether or not any corrective action need be taken. It is unlikely and not expected that any adverse incident will result from implementation of this study protocol. However, any and all adverse events that may occur will be recorded on the appropriate date report forms, and those attributable to study activities or program use will be reported to the governing IRB, as applicable.

Any study related, unanticipated adverse events attributable to program use and study related activities will be reported to the IRB and within 72 hours of awareness occurrence or detection by PI. In the unlikely event of a serious adverse event this report will be made within 72- hours to the NINR Project Officer. In the unlikely case of a study-related serious adverse events, an interim analysis will be performed in order to determine whether a change in the risk/benefit ratio has occurred. If so, this change will be brought to the attention of the IRB for review, current and future participants will be notified of this change, and stopping rules will be considered if three serious adverse events occur, the study will be stopped in such instances.

6.3 Follow-up for Adverse Events

Any false alarm from HeartMapp due to automated cues will be triaged by the unblinded study staff and referred to primary care physician. The study co-investigator and Cardiologist Dr. Fernandez and Nurse Practitioner (Ms. Dolan) will follow-up with the participants for any unresolved adverse events.

6.4 Safety Monitoring

The study co-investigator and Cardiologist Dr. Fernandez, the Nurse Practitioner (Ms. Dolan) and Dr. Miranda from Florida Hospital as well as the unblinded study coordinator who is a nurse will be responsible for ensuring participants’ safety on a daily basis. In addition, the unblinded study coordinator will monitor participant safety and triage daily using the notification they receive and data entered by patients who have declined HF.
symptoms and refer them to Dr. Fernandez or Ms. Dolan for follow-up. The study team will have regular weekly meetings to evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. Dr. Charles Lambert, Cardiologist, Florida Hospital Tampa will serve as independent data safety monitoring personnel for this pilot study. He will independently evaluate the safety of the study and the data collected quarterly to offer feedback and meet with the research team quarterly.

Dr. Tom Van Vleet of Posit Science Inc. San Francisco will be blinded to randomization and have unrestricted access to deidentified data for analysis through REDCap. Unblinded research staff from Posit Science Corporation, will have access to participants randomization and REDCap data to maintain accuracy and integrity of the data and will be responsible for regulatory and reporting procedures to NIH. Posit Science will have signed a research agreement to follow the HIPAA rules to ensure data is kept password protected and secured.

7. INTERVENTION DISCONTINUATION

Given the minimal risks involved in completing the intervention, the researchers do not anticipate intervention discontinuation due to adverse events.

The team will establish the stopping rules for the trial if any adverse incidence occurs. These may not be related to the study, but worsening HF that results in patients referred to palliative or Hospice care. These patients will be deemed unstable to continue using the Apps and such patients will be discontinued from the study and considered as dropouts. However, if the team received adverse events such as repeated HF hospitalizations of patients enrolled in the study and more than three related serious adverse events occur that are attributable to program use and study related activities, the study will be stopped.

Participants may wish to stop or minimize the apps usage going forward, while remaining in the study for reasons such as change in work circumstances, health status, family or personal issues, or a lack of interest in using the apps. They will be informed of their personal commitment to the basic scientific research of the study. In such cases, after discussion with the study coordinator, the participant will be permitted to cease using the apps, and be scheduled for a 3-month or 6-month post enrollment visit at the appropriate time relative to the pre-assessment (baseline) visit and will be allowed to stop their participation.

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to use the program. For participants seeking to withdraw for that reason,
we will offer the alternative of discontinuing use of the program and scheduling and completing the post-intervention assessment visit at the appropriate time relative to their baseline visit, given they have met the minimum training sessions required to complete the post- and follow-up assessment visits. The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of sessions. Participants who still wish to withdraw following that option will withdraw. Other than time required to use the program, we do not anticipate any common reasons for withdrawal that we will plan for in advance.

In rare cases, a Principle Investigator may decide to prematurely discontinue a participant’s involvement in the study for any of the following reasons:
   a) Safety,
   b) Participant non-compliance,
   c) A change in circumstance that would prevent completion of protocol-required assessments or intervention activities,
   d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
   e) Participant displays inappropriate behavior toward study staff members,
   f) Loss of funding, or;
   g) A clinical determination, by the Principal Investigator, that continuation in the study is not in the participant’s best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant’s involvement in the study by arranging for the Site Study Coordinator or Cognitive Remediation Coach to recover the mobile device (if it has been issued to the participant), conducting an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

8. STATISTICAL CONSIDERATIONS

8.1 General Design Issues
This study will test the feasibility of conducting a trial that is designed to determine the effectiveness of a promising non-pharmacological, technology-based intervention that include cognitive training program to improve outcomes among HF patients.

8.2 Sample Size
Sample size. Given the nature of a pilot feasibility study, no power analysis was performed for this study. We proposed to over sample to account for 18% attrition
(n=49) to meet the goal of enrolling 20 subjects per intervention arm. However, the team will perform a power calculation based on the results of this trial to perform a power analysis for a large longitudinal study.

8.2.1 Treatment Assignment Procedures

Randomization. The participants will be randomized stratified by age (<65 or ≥ 65 years of age) and cognitive status (MoCA score 20-25 and ≥ 26) in to the intervention group (HeartMapp +BHQ) or attention control group (CHF Info App +BHQ). For allocation concealment, the research assistants, cardiologist and NP are the ones who will know the group assignment. The PI and Co-Is (Drs. Edwards and Labrador) and Sponsor PI (Dr. Thomas Van Vleet) will be blinded to random assignment of participants. The random assignments will be stored on REDCap and password protected. The study coordinator, research assistant, cardiologist and unblinded Posit Science personnel will be the only persons who can access the randomization list.

Unblinded personnel from the Sponsor, Posit Science, will be given access to REDCap account for auditing purposes and may access the account at any time to monitor the randomizations for accuracy and integrity. Participants will be randomized with their assigned de-identified participant identification number, and no personally identifying information will be accessible by Posit Science research staff. Posit Science Corporation will have regular bi-weekly meetings with USF research team. The unblinded study staff will update the randomization list and create a matching list for the study IDs and their group assignments but denoting the groups as HeartMapp or CHF Info App.

8.2.2 Interim analyses and Stopping Rules

When 20 participants have completed the 3-month follow-up, we propose to perform an interim-analysis for safety monitoring. The interim-analysis will be performed by an independent statistician (USF College of Nursing statistics core), blinded to the treatment allocation. The incidence of adverse events, attributable to program use and study activities, and attrition will be compared between the two randomized conditions. Dr. Tom Van Vleet of Posit Science Corporation, San Francisco will have access to deidentified data for analysis. He is responsible to follow the HIPAA rules approved by the USF SOW agreement and follow NIH criteria on the safety and privacy of the data.

8.3 Outcomes

8.3.1 Primary outcome

The primary outcome measure will be the feasibility of using the apps by HF patients. The feasibility assessment includes the app usage and engagement with the apps, which is tracked by the apps. Engagement with BHQ exercises will be calculated as
percentage of participant’s who complete at least 20 hours of assigned CT included in HeartMapp. Engagement with apps will be calculated as the percentage of participants accessing app components at least 80% of the days during the 3-months, which is 72 days. The team expects at least 80% of those randomized to HeartMapp +BHQ (n=16) will engage in accessing the components of HeartMapp, demonstrating feasibility.

8.3.2 Secondary outcomes

Secondary outcomes include potential efficacy of HeartMapp +BHQ intervention in improving 1) cognitive outcomes measured using NIH-EXAMINER and Neuro QOL and 2) HF self-care measured using the Self-Care of HF Index.

8.3.3 Exploratory outcomes

Exploratory outcomes include improvement in quality of life measured using KCCQ, global health by PROMISE Global health scale, medication adherence stamped by patient entry in HeartMapp, HRV using BioPatch™, number of hospitalizations and emergency room visits from patient interview and confirmed by chart review.

8.4 Data Analysis

The statistician and the data manager core at the College of Nursing will facilitate the data analyses. The statistical software, SAS 9.4 (SAS Institute), will be used for the statistical data analyses in this project. Univariate descriptive statistics will be conducted on subjective and objective outcomes, as well as baseline covariates (age, sex, clinical variables, comorbidity data and health literacy) to describe the sample characteristics of the participants. Data issues such as abnormal values or outliers will be investigated and reconciled by collaborations among the research team. Baseline characteristics of the randomized conditions will be compared by two sample t-tests or nonparametric tests for continuous variables and Chi-Square Test or Fisher's Exact Test for categorical variables. The team proposed to use process evaluation framework to explain the rationale why HeartMapp intervention succeed or failed, and whether there are characteristics or mechanisms involved in the intervention implementation that potentially mediate or moderate outcomes.

A linear mixed model will be used to test the average scores of primary outcomes for the two assigned groups over times (repeated measures at baseline, 3- and 6-months). Due to the dependence among the two primary measurements over time from same subjects, mixed models allow us to take the dependence into account. An explorative analysis will be conducted to uncover relationship between specific intervention
component elements included in HeartMapp and program outcomes using the framework described for health promotion interventions.

Exploratory analysis will be conducted to identify potential significant covariates and type of engagement of the HeartMapp for the analyses, the correlations between the response variables and the covariates and the correlations among the covariates including demographic variables such as age, sex, race, marital status, and socioeconomic status, clinical variables (severity and duration of HF), comorbidities, psychosocial distress, health literacy level, and a lack of social/emotional support will be studied (use either Pearson correlation coefficient or Spearman correlation coefficient depending on variable types). Sex as a biological variable and age as a dichotomized variable (<64 years and >65 years of age) will be explored. Stepwise forward selection method using general linear model (Proc GLM) will be used. Variable selection procedures such as stepwise method work better than univariate one-at-a-time method that tests significance for the covariates separately. Those covariates that are selected from the stepwise method, along with key primary and secondary outcomes measures will be included in the mixed models. The final model will use Proc MIXED for the continuous outcome variables plus the selected covariates including sex, duration and severity of HF, illness burden, and health literacy. Regression analysis also will be performed to examine influence of confounding variables such as age, sex, education, duration and severity of HF, illness burden, and health literacy on outcomes.

Completion of this pilot study will provide data necessary and calculation of effect sizes using Cohen's d by calculating the mean difference between your two groups. This will help the team to formally design and power a large randomized controlled trial in phase 2, testing the efficacy of HeartMapp +CT relative to treatment-as-usual.

9. DATA COLLECTION AND QUALITY ASSURANCE

9.1 Data Collection Forms
The study staff will maintain the data forms versions and participants’ data in REDCap. All physical forms including the eligibility questionnaire and clinical variable data will only be identified with subject number. The consent document with identifying information will be stored separately under lock and key in the PI's office at USF College of Nursing. All outcome data will be collected as direct entry into REDCap. The Sponsor will have access to deidentified data in REDCap and will audit data for accuracy and integrity, and conduct analysis as needed. The study staff will audit all data completed by the participants via REDCap.
9.2 Data Management

All demographic information and subjective outcome measurements will be completed online using validated questionnaire via REDCap. Each participant is identified in the system with participant’s subject number. Participants will provide e-mail for completion of data via REDCap. The unblinded study staff will be the one who have access to participants’ email. This unblinded study staff will work with the data manager from College of Nursing to create the REDCap database prior to starting the trial. The College of Nursing data manager will check data entry in REDCap, manage discrepancies, code data, and develop clean clinical trial data for analysis. Every effort will be made to test participants at each assessment point regardless of intervention compliance.

Unblinded Posit Science research staff will be granted access to the REDCap system. The REDCap system will be configured to prevent Posit Science personnel from viewing the participant’s email address and any identifying information stored within the system. The designated unblinded Posit Science Data Monitor and USF research staff will interact frequently throughout the study to accomplish the quality goals of the data management process through the below process:

- **Data Cleaning:** All electronic data may be automatically reviewed to check for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system, when applicable.
- **Data Editing:** Each data record is evaluated on a regular interval by the Posit Science Data Monitor. Any discovered error is then referred to the designated USF research staff within the REDCap System via the Posit Science Data Monitor. USF research staff will review the queries and make the corrections through the REDCap system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- **Data Update:** The cycle of data editing will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered during review, the Posit Science Data Monitor will request the corrections, as appropriate, such that USF research staff may reconcile the data through the REDCap system.

The PI will work with the statistical core team, the data manager from College of Nursing, and Posit Science research staff to perform data management for the trial. Best practices for data management will be followed to ensure the integrity and quality of the scientific data. The data managers at USF will modify REDCap database to accommodate and create de-identified study data required for analysis by the blinded study personnel. Upon each batch of new data at 3-6 months, the data managers at
USF and Posit Science will perform data quality checks including abnormal values, outliers, range check, etc. Any data problems identified will be discussed and reconciled with the study teams and the data collection staff members. The data managers at USF and Posit Science and Statistician from College of Nursing statistical core will also perform data cleaning, data conversion, data manipulation, data storage and back up, data documentation (such as data dictionary, data audit trail) and data dissemination. Dr. Charles Lambert, Cardiologist, Florida Hospital Tampa will serve as independent data monitoring of assess the data collected team along with the statistical core. Dr. Lambert will meet with the team quarterly.

Long-term data preservation will be through the USF Geoportal and Data Depository. Online data will be retained on a multi-disk configuration that the disk will be partitioned into several volumes with each volume behaving like an individual physical disk to avoid data loss. All materials in paper format, including the consent form collected will be stored for five years in the PI's office in College of Nursing after the completion of the study according to University guidelines and then will be securely shredded by USF authorized entity, frequently throughout the study to accomplish the quality goals of the data management.

9.3 Quality Assurance

9.3.1 Training
The study staff will be trained on consent process, screening for eligibility on administering the MoCA, depression questionnaire, CSSRS, vision and hearing tests in a consistent fashion. They study staff will be trained to help patient complete questionnaires in REDCap and collect cognitive measure using NIH-EXAMINER, and HRV using BioPatch™. The study staff will be trained by PI and Co-Is prior to beginning data collection. The protocol will be reviewed in detail prior to data collection by the Sponsor. The Sponsor will have access data in REDCap and will audit data for accuracy and integrity of randomization without identifiable patient information. The Posit Science Data Monitor will interact frequently with USF research staff to accomplish the quality goals of the data management process and deviations will be addressed during monthly meetings. The study staff will have regular at bi-weekly staff meetings. The study staff will review and audit all data forms for consistence and errors. A quarterly assessment of the data will be completed independently by Dr. Lambert. Staff will complete retraining of the study protocol and procedures prior to follow-up data collection at 3-and 6-months.
9.3.2 Quality Control Committee
The data manager from College of Nursing and the unblinded research staff from Posit Science Corporation will perform routine data management tasks. The USF data team will double check data entry, data quality checks, data cleaning, merging data from REDCap to SAS for data analysis by the team. The data manager from College of Nursing will be responsible in opening and managing a REDCap account on the USF Health Information Service server. All data on USF Health servers are HIPAA compliant with automatic daily data back-up. In addition, Dr. Lambert will independently assess the quality and safety of the data collection activities quarterly.

9.3.3 Protocol Deviations
A standard protocol deviations form will be used to track any deviations. The study staff will maintain the protocol deviations log. The study staff will also record deviations discovered in auditing the data and reconcile errors. Deviations will be reported to Posit Science during the monthly meetings and documented in a note to file by study staff.

9.3.4 Monitoring
A manual of operations will be used. The study staff will observe daily data entered in HeartMapp for triage and decision making. Protocol procedures will be reviewed regularly at the bi-weekly research meeting with the study staff and the unblinded study staff from Posit Science and by Dr. Lambert quarterly. Study staff will regularly observe and evaluate one-another to ensure consistency in data collection.

10. PARTICIPANT RIGHTS AND CONFIDENTIALITY

10.1 Institutional Review Board (IRB) Review
The informed consent document will be included in the appendix and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The signed consent forms will be kept separate from the data forms in a locked cabinet.

10.2 Informed Consent Forms
All participants will have the capacity to provide informed consent at the screening and baseline visit. A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The HIPAA waiver included in the consent form will allow study staff to access the participants’ clinical reports in medical records (EPIC) to verify eligibility. A copy of the signed consent document will be given to each participant and this fact will be documented in the participant’s record.
10.3 Participant Confidentiality

Any data, forms, reports, and other records will be identified only by a participant identification number (Participant ID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, and the NINR. Posit Science will have access to REDCap randomization data and will extract data as needed for monitoring. They will only use deidentified data for analysis and follow the privacy and confidentiality of data as required by USF and NIH.

10.4 Study Discontinuation

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

11. COMMITTEES

Given the nature of the feasibility study, the data safety monitoring will be carried out methodically by the research team, not a separate DSMB. The research team will have regular meetings to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial.
12. REFERENCES


57. Ruppar TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication Adherence Interventions Improve Heart Failure Mortality and Readmission Rates: Systematic Review and Meta-Analysis of Controlled Trials. Journal of the American Heart Association 2016;5.

13. SUPPLEMENTS/APPENDICES

13.1 Modifications

Any modification to the protocol will be annotated here. The annotation will note the exact words that are changed, the location in the protocol, the date the modification was approved by the IRB, if needed, and the date it became effective.

The IRB approved informed consent will be added