iCardia4HF: A patient-centered mobile health intervention to promote self-management and improve patient outcomes in chronic heart failure

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TABLE OF CONTENTS

Page

Table of Contents 3
List of Abbreviations 4
1.0 Project Summary/Abstract 5
2.0 Background/Scientific Rationale 6
3.0 Objectives/Aims 6
4.0 Eligibility 7
4.1 Inclusion Criteria 7
4.2 Exclusion Criteria 7
4.3 Excluded or Vulnerable Populations 7
5.0 Subject Enrollment 7
6.0 Study Design and Procedures 8
7.0 Expected Risks/Benefits 13
8.0 Data Collection and Management Procedures 14
9.0 Data Analysis 16
10.0 Quality Control and Quality Assurance 16
11.0 Data and Safety Monitoring 17
12.0 Statistical Considerations 18
13.0 Regulatory Requirements 18
13.1 Informed Consent 18
13.2 Subject Confidentiality 18
14.0 Unanticipated Problems 19
15.0 References 20

LIST OF ABBREVIATIONS

Co-I	Co-Investigator
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
OHRP	Office of Human Research Protections
OPRS	Office for the Protection of Research Subjects
PHI	Protected Health Information
PI	Principal Investigator
RA	Research Assistant
RN	Registered Nurse
SMC	Safety Monitoring Committee

1.0 Project Summary/Abstract

Approximately 6.5 million people have heart failure (HF) in the United States, and 960,000 new cases are reported each year. HF is one of the most common hospital diagnosis among older adults. About 40% of patients are readmitted within 1-year following their first admission for HF and hospitalization accounts for approximately 80% of the costs of HF management. Evidence from recent trials and systematic reviews suggests that adherence to HF self-care strategies reduces the risk of hospital readmission and improves health-related quality of life. However, self-care among older adult patients with HF is commonly poor. Our team has partnered with industry-leading companies (Self-Care Catalysts, Fitbit, and Nokia) to develop *iCardia4HF*, an innovative and age-appropriate mobile health (mHealth) intervention that promotes adherence to HF self-care through a smartphone-enabled point of care system. This application proposes a randomized controlled trial to examine the feasibility, acceptability and preliminary efficacy of *iCardia4HF*, compared to usual care, in older adult patients with HF (≥40 years). We will enroll 40 patients from the University of Illinois Hospital & Health Sciences system and randomly assign them to either *iCardia4HF* or usual care for 60 days. Patients in the *iCardia4HF* group will receive the *Heart Failure Health Storylines* mobile app developed by Self Care Catalysts in collaboration with the Heart Failure Society of America, three connected health devices from Fitbit and Nokia that interface with the mobile app, and tailored text-messages targeting health beliefs, self-care efficacy, and knowledge about HF. The control group will receive standard care which involves patient education and outpatient follow up with physical and laboratory examinations as needed. The primary study outcome is change in self-care behaviors from baseline to 60-days. Secondary outcomes include hospital readmissions and change in health-related quality of life, self-care efficacy, health beliefs, and HF knowledge from baseline to 60-days. A key translational challenge with mHealth is that many commercial mobile apps have not been tested empirically, and many apps with empirical data are not commercially available. This study represents an important step in addressing this gap by testing a mHealth intervention that incorporates commercially available technologies optimized for older adult users with HF. This pilot study will be crucial in further refining our intervention and serve as a basis for seeking future extramural funding from NIA or NINR for an adequately powered clinical trial.

2.0 Background/Scientific Rationale

With an annual incidence of 960,000, HF remains a major public health issue and is the leading cause of hospitalization among older adults in the United States.[1-3] Despite major improvements in outcomes with medical therapy,[4,5] admission rates following a HF-related hospitalization remain high with 25% of patients readmitted to the hospital within 30-days.[5-7] Recent studies show that the implementation of the Hospital Readmissions Reduction Program,[8-11] a quality care incentive program mandated by the Affordable Care Act, has been successful in reducing 30-day and 1-year hospital readmission rates. But a concomitant increase in short-term (30-day) and long-term (1 year) mortality rates has raised concerns about the unintended consequences of HRRP.[12,13]

Several trials and systematic reviews have demonstrated that better **self-care,** reduces the risk of 1-year mortality and hospitalization, and improves *health-related quality of life (HRQoL)* in patients with HF.[14-20] Furthermore, recent evidence from two rigorously conducted trials suggests that mechanistically, improved self-care is associated with a decline in myocardial stress and inflammatory biomarkers important to HF pathophysiology serum levels of amino-terminal pro-B-type natriuretic peptide (NT-proBNP), an index of myocardial stress, and soluble tumor necrosis factor α receptor 1 (sTNFaR1), an index of systemic inflammation and marker of HF pathogenesis.[21] However, self-care has generally been found to be poor among HF patients. Nonadherence to medication taking and symptom monitoring is remarkably high even among recently discharged patients hospitalized for an HF exacerbation.[22] There are several factors influencing patient decisions about self-care, including health beliefs,[23-26] self-care efficacy,[26-29] and self-care knowledge.[23,30,31] Effective and scalable interventions addressing the complex array of adherence barriers are critically needed to reduce the burden of HF.

Recent advances in commercially available **mobile health (mHealth)** technologies, such as **smartphones** and **connected health devices***,* offer scalable and affordable solutions for promoting self-care and expanding delivery of care services to communities that are difficult to reach.[32] Mobile apps and wearable sensor devices can enhance self-monitoring of HF-related parameters, enable the exchange of physiological data between patients and healthcare providers in real-time, and facilitate the delivery of just-in-time behavior change intervention to promote self-care, with a goal of reducing HF-related hospitalizations and mortality.[33] However, to our knowledge, no study has examined the utility and efficacy of **commercial** mHealth technologies in HF patients.[34,35]

Our team has developed ***iCardia4HF***, a novel mHealth intervention that promotes adherence to HF self-care through commercial smartphone technologies and connected health devices. **We propose a pilot randomized controlled trial (RCT) to evaluate the feasibility and preliminary efficacy of iCardia4HF on patients with HF.** iCardia4HF consists of: **(1)** a **patient-centered mobile health app (*Heart Failure Health Storylines*)** that interfaces with multiple **connected health devices** (Fitbit activity tracker, Nokia blood pressure monitor and Cardio Body weight scale) and comprises a number of self-monitoring, patient education, and adherence reminder tools for improving self-care; and **(2) nurse-led, individually tailored text-messages targeting health beliefs, self-efficacy, and self-care knowledge**. The mobile app has been developed in partnership with the ***Heart Failure Society of America*** and is available for free in the Apple and Google Play stores. The text-messaging component is based on the *Heart Messages* program that has been developed, studied, and refined by Dr. Pressler (Co-I).[36,37] We will enroll 40 patients with HF from the University of Illinois Hospital & Health Sciences System (UI Health) and randomize them 1:1 to receive usual care alone or combined with the iCardia4HF intervention for 60 days.

3.0 Objectives/Aims

The specific aims and hypothesis to be tested are:

Aim 1: Assess the feasibility and acceptability of the iCardia4HF intervention.

Aim 2: Determine the preliminary efficacy of iCardia4HF on self-care, HRQL, and hospital readmissions compared to usual care.

Hypothesis 1: Participants in the iCardia4HF group will report better self-care and HRQL than the usual care group at 60 days.

***Hypothesis 2*:** Hospital readmission rates will be lower in the iCardia4HF group than the usual care group at 60 days.

4.0 Eligibility

Eligible for inclusion in the study are patients with a definitive diagnosis of heart failure who meet all the inclusion criteria described below in sections 4.1. The source of subjects will be the UI Health Cardiology clinic and the Outpatient Heart Failure Program. Subject eligibility will be determined by a trained research assistant under the guidance of PI Dr. Kitsiou and Co-I Dr. Kansal (Co-I). Eligibility will be documented using the "Patient Eligibility Assessment form", which will be implemented in REDCap (Research Electronic Data Capture) – a secure web-based application for building and managing online surveys and databases. The patient inclusion and exclusion criteria for our study are described below.

4.1 Inclusion Criteria

- Inpatients or outpatients with a diagnosis of HF as defined by the International Classification of Diseases (ICD-10) codes
- Stage C, NYHA I, II or III
- ≥ 40 years of age
- Own a smartphone with text-messaging and internet plan
- Ability to speak and read English
- Live within 30 miles from UI Health

4.2 Exclusion Criteria

- On an active waiting list for implanted ventricular assist device or heart transplant
- End-stage HF (hospice candidate)
- Active cancer
- Individuals who are not their own primary caregiver
- Discharge to a setting other than home
- Patients with baseline Montreal Cognitive Assessment (MoCA)[38] score of < 22 (adjusted by adding 2 points for education 4-9, 1 point for education 10-12 years) will be excluded because this score indicates possible dementia[38] and in our past study patients with MoCA < 22 were unable to use a computerized intervention[39].

4.3 Excluded or Vulnerable Populations

This study does **not** focus on vulnerable populations (e.g. decisionally impaired, minors, children, prisoners, pregnant women, or economically and educationally disadvantaged).

Non-English speaking patients will be excluded due to the fact that the heart failure mobile app is currently available only in English. A Spanish version will be developed sometime in the near future and be tested in a different study, but not this one.

5.0 Subject Enrollment

We will enroll 40 adult HF patients in this study. Participants with a diagnosis of HF will be recruited directly from the outpatient Heart Failure program or the inpatient cardiology clinic at UI Health. A HIPAA Preparatory to Research is requested in section 13.1 in order to review the registry to identify potentially eligible participants.

Patient screening for eligibility will be conducted in two Phases as follows:

Phase I: Under the guidance of PI Dr. Kitsiou and Co-I Dr. Kansal, a research assistant (RA) will review the patient registry and clinic schedule on a daily basis to identify potentially eligible patients using all Phase I inclusion/exclusion criteria shown in the Patient Eligibility Assessment form.

Phase II: Outpatients with upcoming clinic appointments who meet all Phase I inclusion criteria will be contacted via telephone by a RA who will briefly explain the study and ask the participant whether they agree to be approached by an RA after their visit to further discussion of the study and assessment of eligibility. Phase I eligible patients who are hospitalized at UI Health will approached by an RA before they are discharged from the hospital will receive information about the study and be screened against all Phase II inclusion/exclusion criteria in the Patient Eligibility Assessment Form to determine eligibility for participation in the study. A Waiver of Consent for Recruitment Purposes is requested in section 13.1. The RA will access the online form in REDCap using a secure (password-protected and encrypted) study laptop.

Patients who meet all the eligibility criteria and agree to participate in the study will be asked to sign the informed consent statement and HIPAA authorization, and then be scheduled to complete baseline assessment measures. Informed consent will be obtained using procedures and language understandable to the subjects.

All patient subjects will be informed that their participation in the study is voluntary and their decision to not participate will not affect the care they receive now or in the future at the UI Health Heart Failure clinic. In order to minimize the possibility of coercion or undue influence on potentially eligible subjects for participation in our study, subjects will only be approached for study consent after they have been evaluated and treated by their physician. Subjects will also be informed that participation is voluntary and will not affect their relationship with the university/hospital if they decline to participate. Also, patients that are being cared for by Co-I Dr. Kansal will not be consented by him but rather another member of the study team.

6.0 Study Design and Procedures

This is a single-site, pilot randomized controlled trial to test the feasibility, acceptability, and preliminary efficacy of iCardia4HF. As shown below in Figure 1, the study includes the following stages: 1) Identify potential participants by reviewing the UI Health HF patient registry against all Phase I criteria of the Patient Eligibility Form; 2) Approach potentially eligible patients and present study opportunity; 3) In-person screenings for eligibility using the Phase II criteria in the Patient Eligibility Assessment Form; 3) Obtain written informed consent if patient is eligible and wants to participate in the study; 4) Complete baseline assessment; 4) Randomize participants in one of the two groups and follow for 60-days; 5) Perform 30-day assessment of self-care (primary outcome) and intervention target variables by telephone; and 6) Perform post-intervention assessment at 60 days. We will track recruitment/retention rates and patient adherence to using the mobile app and digital devices to perform self-care maintenance and self-management of HF throughout the study; obtain post-intervention validated measures of treatment satisfaction among patients; and conduct post-intervention interviews with patients to identify barriers and suggestions for intervention improvements. The primary outcome of interest is change in self-care mean scores using the Self-Care Heart Failure Index v6.2 from baseline to 60-days. Additional outcomes are all-cause and HF-related hospitalizations at 60-days, and changes in health-related quality of life (HRQoL) from baseline to 60 days.

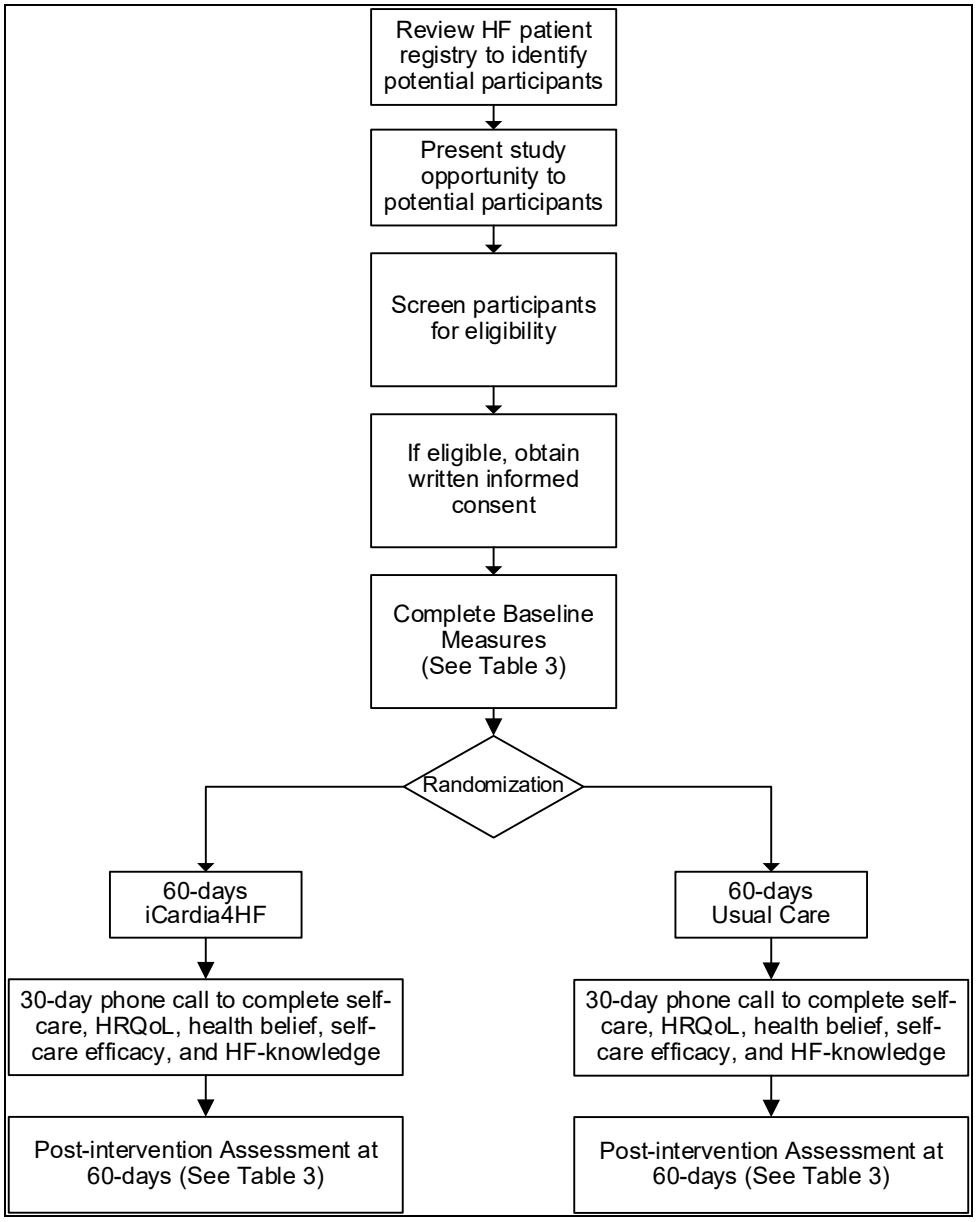


Figure 1: Overview of Study Design

Participants will be randomly assigned in a 1:1 ratio to the usual care or iCardia4HF intervention group using Pocock and Simon's "minimization" procedure[40] to assure better-than-chance group balance at baseline in terms of age, sex, and NYHA functional class. We will use MinimPy,[41] a random allocation program that has been validated and successfully used in previous trials. MinimPy is an open source program (i.e. does not require a license) that can be used for sequential allocation of subjects to treatment groups in clinical trials by using the method of minimization. It can be installed locally on a desktop/laptop computer or accessed online for free. In this study we will install MinimPy in a secure (password-protected and encrypted) desktop computer in Dr. Kitsiou's mHealth Innovation Lab at UIC. A designated RA who does not have ability to influence the execution of the randomization will have access to the computer program and will be responsible for the execution of the randomization sequence and the generation of the allocations. No patient identifiers will be entered in the MinimPy program. The program's computational algorithm automatically adjusts the randomization probability on each occasion based on the entered baseline characteristics (age, gender, and NYHA functional class) of all participants previously randomized to each arm, thus minimizing the total covariate imbalance between study arms after a new patient is randomized.

6.1 Setting and Population

Patients will be recruited from UI Health, which includes both inpatient and outpatient facilities serving a diverse population in Chicago. This setting is ideal because HF patients receive therapies based on national practice guidelines and the UI Health electronic health record (EHR) is available to facilitate data collection. Based on a recent aggregate report from the UI Health Clinical Research Data Warehouse (CRDW) provided to our team by the Biomedical Informatics Core group of the Center for Clinical and Translational Science at UIC, approximately 1200 patients ≥ 18 years of age are hospitalized annually at UI Health with a primary or secondary diagnosis of HF, and 450 patients are enrolled in the outpatient HF program. Patient demographics include 51% women, 60% African-Americans and 15% Hispanics. We anticipate that a significant percentage of participants will be minorities and lower-income. We will enroll equal numbers of women to maximize generalizability of our findings.

6.2 Treatment Arms

6.2.1 Usual Care

Participants assigned to the usual care group will receive standard medical care, which includes nurse-led patient education about HF self-care before discharge, and follow-up visits at the Outpatient Heart Failure Clinic at UI Health a week after hospital discharge and once a month thereafter, depending on the severity of the patient's condition. Patient education at UI Health includes literacy-sensitive, education material about HF self-care developed by the Sheps Center for Health Services Research,[42] and a 40-minute education session with an APN and a dietician to review and discuss the education material provided to the patient. During informed consent, patients will be clearly instructed that they continue to receive medical care as usual, but no medical care is covered by the research study. For patient safety, no usual care will be withheld at any time after enrollment.

6.2.2 iCardia4HF Intervention

In addition to usual care, participants in the intervention group will receive the Heart Failure Health Storylines mobile app, three connected health devices (Fitbit Charge 2 activity tracker and FDA-approved Nokia BP monitor and Cardio Body weight scale), and a program of tailored text-messages.

Mobile app and connected health devices: Heart Failure Health Storylines is a web-based, cross-platform[43] mobile app that has been developed in collaboration with the Heart Failure Society of America and includes 5 core features: 1) *vital signs monitoring*; 2) *assessment of HF symptoms*; 3) *medication tracking*; 4) *physical activity (PA) tracking*; and 5) *HF education*. *Vital signs* (e.g. weight, water mass, blood pressure, heart rate) and *physical activity* data (e.g. steps, intensity of activity, sedentary time, and sleep) are captured by the Nokia and Fitbit devices and are automatically transferred to the phone via Bluetooth. The *symptom tracking* feature prompts patients to answer daily short questions about their HF symptoms (e.g. shortness of breath, fatigue, ankle swelling) using a 10-point Likert scale. The *medication tracking* feature allows patients to add and edit their medications, and setup automated reminders (push notifications) to take their medications as needed. The *HF education* feature contains information about the importance of low-salt diet, exercise, symptoms management, and medication adherence. The app collects all data (Table 1) and provides patients with graphic feedback using a color-coding scheme and a weekly calendar format to assist with detection of important fluctuations between time periods. Patients have the option to share the data from each feature with their "circle of support" to which the user can add a provider, family member, or friend. A goal-based approach will be used to promote self-care via these mHealth tools. The primary **daily** goals are: (1) self-monitoring of weight and BP each morning before breakfast and medications; (2) self-recording of HF symptoms; (3) recording of medication-taking by replying (yes/no) to the push notifications; (4) 30 minutes or three 10-minute bouts of moderate PA per day on most days of the week in concurrence with the healthcare provider's recommendation and clinical guidelines for patients with HF; and 5) following a low-sodium diet (2000-3000 mg of sodium/day). These goals are critical because each represents a key aspect of successful HF self-care.

Tailored text-messages: The goal of the tailored text-messaging program is to improve patients' health beliefs, self-care efficacy, and HF knowledge by decreasing identified barriers and increasing perceived benefits of action. The messages and tailoring algorithm have been developed and validated by Dr. Pressler (Co-I) in the "*Heart-Messages*"[36] and "*PUMP*"[37] studies. Tailoring of the text-messages will be guided by each

person's responses to valid and reliable assessments of intervention target variables at baseline and 30-days. Items on the Health Belief scales are divided into benefit and barrier questions about medications, diet, and self-monitoring compliance. Each item on the scales receives a five-point score ranging from 1 (strongly disagree) to 5 (strongly agree). Participants who score 4 or above on a barrier question or below 3 on a benefit question, will receive 2-3 text-messages per week, tailored to that specific barrier or benefit item (Table 1). Content to enhance self-care efficacy and knowledge will also be incorporated into the messages. If a participant scores 4 or above on a benefit question or below 3 on a barrier question, then a message will not be sent because it is presumed that the patient already understands the barriers or benefits identified in that question. Text-messages will be sent through the iCardia platform.[44]

Table 1: Sample of tailored text-messages.

Diet	
Benefit question: Salty food is not good for me	**Barrier question:** Food does not taste good on a low-salt diet.
Text-message: Salt is not good for you because salt causes your body to hold more water and your heart has to work harder to pump blood through your body.	**Text-message:** Foods can still be flavored with other spices and also salt substitutes. You can see a dietitian or refer to cookbooks on low-salt cooking.
Medications	
Benefit question: If I take my water pills, I will lower my chance of being hospitalized.	**Barrier question:** Taking water pills makes it hard to go away from home.
Text-message: Taking your pills at the time and in the amount ordered by your doctor will help keep your body from holding extra fluid. Getting rid of this extra fluid will prevent swelling in your body and may make you feel better.	**Text-message:** Try to take your pills earlier in the day when you are going out so that they will work before you leave the house. Also, when you go out be sure to find the bathroom wherever you go.

6.3. Study Measures and Data Collection Schedule

Table 3 presents all measures and data collection schedules. Baseline and post-intervention (60-days) data collection visits will take place at UI Health. Thirty-day assessments will be conducted by telephone by trained RAs.

Table 3: Measures and Data Collection Schedule

Measure	Method and Description	Schedule
Personal and Clinical Characteristics		
Demographics	Demographic questionnaire includes date of birth, race, gender, marital status, employment status, education, family income, insurance status, and contact information for the participant and two other family members.	Baseline
Cognition	Montreal Cognitive Assessment (MoCA) is a validated instrument (*r*=.83) with 16-items and 11 categories for assessing cognitive impairment.[38]	Baseline
Clinical HF characteristics	Clinical HF characteristics including duration of HF, etiology, left ventricular ejection fraction, New York Heart Association (NYHA) functional class will be extracted from the medical record by ~~Dr.~~ Kansal (cardiologist at UI Health)	Baseline
Depression	Depression will be examined with the Patient Health Questionnaire (PHQ-9)[45], a 9-item tool with well-established diagnostic validity(*r=.82)*. Scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe, and severe depression, respectively. Patients with high depressive symptoms (score >10) and/or suicidal thoughts will immediately be referred to a UI Health physician for further assessment.[46]	Baseline
Comorbidities	Comorbid conditions will be scored using the updated Charlson comorbidity index (C statistic=.825)[47]	Baseline
Aim 1 Feasibility and Acceptability Measures		
Recruitment/ Retention	We will keep track of the recruitment length; number of patients screened and enrolled in the study; refusal rates for participation and for randomization; retention and follow-up rates, and any recruitment obstacles or issues.	Throughout the study
Compliance	We will assess the number of days patients were compliant with the use of the mobile app and digital devices to record their weight, blood pressure, symptoms, and medication intake based on the timestamped data recorded on the study server. We will also track compliance with wearing the Fitbit device using validated methods.	Throughout the study
Acceptance	Acceptance of the intervention will be assessed with the widely employed Technology Acceptance Model (*r*=.94-.98).[48] TAM is derived from the Theory of Reasoned Action and posits that the strongest predictor of technology use is behavioral intention, which in turn is influenced by the individual's "perceived ease of use" and "perceived usefulness" of the technology. TAM has been	60 days

	used in numerous studies in healthcare,[49] including mHealth studies for patients with HF,[50] and is shown to account for 30% to 70% of technology acceptance.	
Satisfaction	Post-study interviews will be conducted with participants from the intervention group to evaluate their overall satisfaction with the intervention. This process data will be used to refine the intervention.	60 days
Aim 2 Primary and Secondary Outcome Measures		
Self-care (primary outcome)	Self-care will be measured with the Self-Care Heart Failure Index (SCHFI) v.6.2, which includes three subscales self-care maintenance (*r*=.56), self-care confidence (*r*=.70), and self-care management (*r*=.70).[51] Each scale score ranges from 0 to 100. Higher scores indicate better self-care. Scores ≥70 indicate adequate self-care.	Baseline, 30 and 60 days
Health-related Quality of life (HRQoL)	HRQoL will be measured with the Kansas City Cardiomyopathy Questionnaire[52], which contains 23-items that can be quantified into five subscales: physical limitations, symptoms (frequency, severity, and change over time), quality of life (QoL), social interference, and self-efficacy (*r*=.66-.95). Lower scores indicate worse HRQoL.	Baseline, 30 and 60 days
Hospitalizations	The number of hospitalizations during the study will be measured with both self-report and the electronic medical record. The principal diagnosis for each hospitalization will be assessed using the primary ICD-10 code and categorized into 1 of 2 categories: HF-related or all-case hospitalizations.	60 days
ER visits	The primary source of data for this measure will be the UI Health EMR system. Participants in both groups will be asked to self-report any additional out-of-system visits to the emergency room.	60 days
Intervention Target Variables		
Health Beliefs	Health Beliefs will be assessed using three validated scales developed by Co-I, Dr. Pressler: 1) Beliefs about Medication Compliance Scale (12-items; *r*=.87-.91)[53,54]; 2) Beliefs about Dietary Compliance Scale (12 items; *r*=.69-.84)[53]; and 3) Beliefs about Self-Monitoring Scale (18 items; *r*=.83-.89).[54]	Baseline, 30 and 60 days
Self-care efficacy	Self-Care Efficacy will be measured with the SCHFI Self-Care Confidence Subscale (6-items; *r*=.70) which quantifies HF patient's self-confidence to perform self-care maintenance and self-care management.[51]	Baseline, 30 and 60 days
HF-Knowledge	HF-specific knowledge will be assessed with the Dutch Heart Failure Knowledge Scale (DHFK), a 15-item (*r*=.62*)* questionnaire measuring general knowledge about HF, symptom recognition, and treatment (e.g. diet and fluid restriction).[55]	Baseline, 30 and 60 days

6.4. Procedures

Patient Screening, Recruitment, and Informed Consent. Under the guidance of Dr. Kitsiou (PI) and Dr. Kansal (Co-I), a trained RA will review the UI Health heart failure patient registry on a daily basis to identify potentially eligible patients using all Phase I inclusion/exclusion criteria of the Patient Eligibility Assessment Form. To avoid screening the same patients more than once and to accurately keep track of the number of patients who were screened, we will create a Screening Log file in REDCap that will be accessible only by key research personnel at UIC and contain the following elements: Screen ID Number, Patient's Name, Birthdate, and Medical Record Number. This file will be kept separately from the Patient Eligibility Form and all other data collection forms. Patients who meet Phase I inclusion criteria will be approached by the RA for further eligibility assessment while they are hospitalized at UI Health or during their follow-up appointment at the Outpatient Heart Failure clinic. The RA will briefly describe the study to the patient, invite participation, and further assess participants for eligibility using Phase II criteria in the Patient Eligibility Form. Face-to-face screenings will be conducted in private exam rooms at UI Health. Eligible patients who agree to enroll in the study will be consented (i.e. sign the informed consent statement and HIPAA authorization), and be scheduled to complete all baseline measures at UI Health. The informed consents will be filed in a locked cabinet in the PI's research office at the College of Applied Health Sciences. We will create a Master List in REDCap with identifiers of the enrolled patients. The Master List will be kept separately from all other data collection forms/questionnaires and contain the following indicators: name, date of birth, phone numbers, street address, city or state, zip code, email address, medical record numbers, elements of dates, and contact information of two family /next of kin members.

Data collection procedures. Baseline data will be collected via face-to-face interviews in private exam rooms at UI Health. The study RAs will administer/read to the participants the questionnaires described in Table 3 (Demographic questionnaire, Patient Health Questionnaire (PHQ-9), Self-Care Heart Failure Index (SCHFI), Kansas City Cardiomyopathy Questionnaire, Health Beliefs Scales, Self-Care Efficacy Scale, and Dutch Heart Failure Knowledge Scale) and enter all data in REDCap using Subject ID codes. The self-care

efficacy scale is part of the Self-Care Heart Failure Index Scale. We anticipate that baseline data collection will take approximately 60 minutes to complete. We will offer patients rest periods every 20 minutes.

Data pertaining to clinical HF characteristics, comorbidities, and healthcare utilization will be collected by Dr. Kansal (Co-I) and the study RAs from the UI Health Electronic Medical Record of each participant.

Follow-up data at 30 days for the measures described in Table 3 will be collected via telephone by RAs blinded to randomization.

Post-intervention data at 60 days (see Table 3) will be collected via scheduled face-to-face interviews which will be conducted in private exam rooms at the Outpatient Heart Failure Clinic at UI Health.

All face-to-face and telephone surveys/assessments will be administered/read to the participant by trained RAs and responses will be directly entered in REDCap using Subject ID codes. We will use password-protected and encrypted study laptops for data entry in REDCap.

Intervention. After randomization, an intervention RA will install the app in the phone of each patient in the intervention group, pair the app with the devices, explain and demonstrate the intervention, answer questions, and assess patients giving a return demonstration. Personalized medication and symptom reminders, along with PA goals will be entered in each patient's mobile app in concurrence with the healthcare provider's recommendation. These can be updated during the study by the patient or the intervention RA through the app/web interface. We will emphasize to all patients that the app is not a substitute to usual care and does not serve as a telemonitoring system or for reporting emergencies.

Retention. Strategies to minimize attrition will include: compensation for data collection, technology incentive (subjects in the intervention group will get to keep the connected health devices given to them as part of the intervention), collection of names of two family members/friends who would know how to contact the patient, reminder text-messages 24 hours prior to data collection appointments; and public transit or parking vouchers as needed. Our team has demonstrated success in participant retention in numerous studies involving minority and underserved populations.

Fidelity. To ensure intervention fidelity, we will implement strategies recommended in best practices. We will review all text-messages and data from the mobile app and devices daily to ensure participants' receipt of and adherence to the intervention. We will call intervention participants to address any technical issues or barriers to intervention receipt when data have not been recorded in the app for > 4 days. In the event of persistent technical issues that cannot be resolved by phone we will ask permission from the patient to send a research assistant to their home to fix any technical issues with the application or devices.

Participant incentives: Due to the time commitment required to participate in the study, enrolled subjects will receive $40 in cash for completion of study measures/assessments at baseline and $45 for completion of post-intervention study measures/assessments at 60-days for a total possible compensation of $85. Subjects will receive their compensation in cash after the completion of the assessments at UI Health. Both groups will receive the same amount of compensation.

7.0 Expected Risks/Benefits

Expected Risks. The potential risks associated with this study include: 1) a small risk that subjects will feel annoyed by receiving study text-messages; 2) a small risk of participant burden with the study procedures and assessments; 3) potential for loss of privacy or confidentiality of health information; and 4) skin irritation, redness, or rash from the Fitbit activity tracker. It is unlikely that any of these risks would result in serious consequences or harm. For all patients, an alternative to enrolling in the study is not participating (patients may continue usual health care services at UI Health outside of the study, including HF education).

Protections Against Risk

Feeling annoyed by text messages: Subjects will receive regular scheduled text-messages during the study. Participants who no longer wish to receive reminders or text-messages may reply with "STOP." iCardia automatically will stop sending messages if this is received; thus, messages will be immediately discontinued without requiring contact with research team. However, patients have the option to re-subscribe with "START" again and resume messages. *iCardia* provides confirmation regarding successful delivery of messages and color-codes blocked or undelivered messages. This allows our team to identify problems including loss of mobile

service. Text messages will not include any identifying information nor will any personal health information be disclosed by our team. Patients will be instructed not to use text-messaging to share health information. Patients will be reminded that text messages are sent in an automated fashion by computer. Thus, any replies may not be read in a timely fashion. Text messaging by patients should not be considered an Emergency Response System. Furthermore, they will be told and reminded that urgent health questions should be directed to their physician and not sent in a text message. If an individual does share e-PHI through text messaging, the information will be permanently deleted and the patient will be educated regarding this process.

Participant Burden: Study participants are free to withdraw from the study at any time if they feel that the study procedures are too time consuming or if they no longer want to particiapate in the study. This is explicitly stated in the consent form.

Loss of Privacy or Confidentiality: The RAs who will administer the study questionnaires/instruments will be able to view the participants' responses to each question. To this end participants will be informed when they enroll in the study and also before each assessment that if they do not feel comfortable having their response to a question known by the RA, they can simply skip that question, refuse to complete the assessment, or choose to withdraw from the study altogether as stated in the Informed Consent Form. Patient responses will never be discussed with others outside of the study. All key research personnel working in this study have successfully completed all mandatory investigator training courses required by standards of the Office for the Protection of Research Subjects (Human Subjects Research, Information Privacy & Security, and HIPAA).

There is a small risk of breach of confidentiality, regarding health information and collected research data. The following measures/protections will be taken to minimize risk: All research staff will have formal IRB human subject protection and HIPAA training. Additional RA training provided through this study includes discussions on maintaining confidentiality of health information, including communication with health providers. For data collection, all human subjects will be assigned a Subject ID code, which will be used during data collection throughout the study. All computerized and database systems used in this study for data collection and analysis are password protected and encrypted, and will be accessible only by UIC key research personnel identified in Appendix P. Hard copies of the patient consent forms will be maintained in locked cabinets in the PIs office at the College of Applied Health Sciences. After six years, and in accordance with federal regulations, all patient identifiable data will be destroyed as follows: (a) paper-based informed consent forms will be shredded using a commercial shredding machine in the Department of Biomedical and Health Information Sciences; (b) the Screening and Master List with all the human subject identifiers collected during the study, will be permanently deleted from the REDCap using standard procedures already in place for these systems by ACCC.

Skin irritation from the Fitbit device: Subjects in the intervention group will be asked to wear their Fitbit device for ≥10 hours each day, ≥4 days of the week. There is a small risk of mild skin irritation caused by the Fitbit device. To minimize the risk, participants will be shown at baseline how to properly wear and clean the device. In addition, they will be advised to give their wrist a break by removing the band for an hour after extended wear. In case of skin irritation or any other discomfort with the Fitbit, participants will be advised to discontinue its use immediately and contact the study staff for further assistance.

Expected Benefits. The risks to subjects are low when compared to the potential benefits of participation. Patients in the intervention group may derive physiologic and symptom benefits by improving HF self-care. This study is an important step in identifying an affordable and scalable mHealth solution that has the potential to bring about a new paradigm in self-care management of HF. This study may provide additional, generalizable knowledge regarding the impact of mHealth on self-care management of HF.

8.0 Data Collection and Management Procedures

The original (paper-based) signed informed consent forms will be stored in a locked cabinet in the PI's office at the College of Applied Health Sciences. They will be kept separately and securely from all other data files, and will only be accessible by the PI and UIC key research personnel. In order to protect the privacy of study participants and to maintain the confidentiality of the data, all datasets created in this study (questionnaires and data collected from the mobile app and connected health devices) will be stored

electronically on secure, password-protected and encrypted databases (REDCap, iCardia, Fitbit, Nokia Health and Heart Failure Health Storylines) housed in HIPAA compliant environments using project-specific Subject ID codes that are not derived from or related to information about the study participants. Only the PI and key research personnel at UIC will be able to access these databases through password-protected and encrypted laptops/desktops. Co-Investigators Dr. Susan Pressler & Dr. Susan Buchholz from University of Indiana and Rush University respectively will **NOT** have access to the study databases or any identifiable information collected in this study. Any research data shared with them via UIC email, BOX, and/or printed format will be provided either in aggregated or de-identified form using hash record IDs (i.e. unrecognizable values that are not related to the Subject IDs or Master List).

All study questionnaires and data collection forms (Table 3) will be administered/read to the participants by a research assistant, and all responses will be directly entered into REDCap. The Master list containing the Subject ID codes and key linking patient identifiers collected in this study will be stored in REDCap, but kept separately from all other research data at all times. Only the PI and authorized key research personnel at UIC will be able to access the Master List for the purposes of the study. Only the PI will have access rights to export research data from REDCap (e.g. in cvs or spss form) for statistical analysis. Any data exported from REDCap will be de-identified using standard de-identification options implemented in REDCap.

Text-messages will be send through the iCardia platform, a secure, internet-based application that has been developed at UIC and is currently hosted in a HIPAA-compliant server at the ACCC Secure Research Environment.[44] Text-messages will be programmed in the iCardia system by the RAs and the PI, based on each person's responses to the intervention target scales at baseline and 30-days (Table 3), and will be sent to study participants at a scheduled date and time based on their preferences captured at baseline. Participants will be able to change their preferred days/hours by responding to the text-messages sent. Participants who no longer wish to receive reminders or text-messages may reply with "STOP." iCardia automatically will stop sending messages if this is received; thus, messages will be immediately discontinued without requiring contact with research team. However, patients have the option to re-subscribe with "START" again and resume messages. iCardia is password protected and will only be accessed by the PI and key research personnel at UIC through an encrypted, Secure Sockets Layer/VPN connection. iCardia will be used in this study for two purposes: (1) to send motivational text-messages about self-care to study participants in the intervention group; and (2) to remotely collect Fitbit data pertaining to participants' physical activity (steps, minutes of activity, intensity of activity, sedentary minutes, etc.). Storing and exportation of Fitbit data from iCardia is done using Subject ID codes only. Text-messages send from iCardia will not contain patient health information or any other sensitive data.

This study also involves the use of the Heart Failure Health Storylines mobile app and three lifestyle/wellness devices that are commercially available (Fitbit activity tracker, Nokia Health blood pressure monitor, and Nokia Health weight scale). Both the mobile app and devices require the creation of individual online accounts with the respective companies (Selfcare Catalysts, Nokia, and Fitbit) for all study participants allocated to the intervention group, for data collection. To ensure the privacy and confidentiality of human subjects, we will use Subject ID codes for the creation of online accounts. No personal or private identifiers will be stored in any of these systems at any point in time. Furthermore, the data collected from these devices will NOT be integrated with the medical record of the patient or used for clinical decision making. Our team has expertise in the use of these mobile health technologies in human subject research studies and has procedures in place, including a data safety monitoring plan, that complement the existing security measures (e.g., encryption) implemented by the respective companies to protect the privacy and confidentiality of human subjects.

In accordance with HIPAA regulations [45 CFR Part 160], signed informed consent forms and research records of this study will be retained for 6 years after the close of the study. Once the 6 year period has passed, the signed informed consent forms will be effectively destroyed using a commercial shredding machine in the Department of Biomedical and Health Information Sciences at the College of Applied Health Sciences. The electronic Screening and Master Lists with all the subject identifiers will also be permanently deleted from REDCap after 6 years from the close of the study using standard procedures already in place for these systems by ACCC.

9.0 Data Analysis

Statistical analyses of outcome measures will be conducted by Dr. Chen, in collaboration with the PI, within the UIC College of Applied Health Sciences. Descriptive statistics will be used for all measures. Scores will be examined for outliers and appropriate strategies used if needed. Distributions based on density plots will be examined; transformations will be used as appropriate to decrease deviations from normality. We will apply the independent samples t-test and Chi-squared test to evaluate sociodemographic and clinical variables for baseline equivalencies prior to hypothesis testing, although the RCT design will likely balance these factors. The significance level will be set at <.05 for all analyses.

The primary analyses comparing the two groups will use the intent-to-treat (ITT) approach, in which patients are considered to be in groups to which they have been randomly assigned, not on treatment or amount of treatment they actually receive. This approach is taken because it is the best method for evaluating potential effects of a treatment, which is one of our objectives. Another implication of this approach is that patients who are lost to follow-up are included, ensuring that observed differences between conditions are not due to differential drop out. Use of a mixed model analysis helps achieve this goal.

Aim 1 is to test the feasibility (recruitment, retention, compliance) and acceptance of the iCardia4HF intervention. Standard descriptive statistics will be used to describe recruitment/retention, compliance, and intervention acceptance scores. Simple linear regression will be used to test the relationship between the main constructs of the Technology Acceptance Model (perceived usefulness, perceived ease of use, attitude toward use, behavioral intention to use, and actual use). Hierarchical regression analysis will be used to determine the specific contribution of the main model variables in explaining intention to use iCardia4HF above and beyond study covariates (age, gender, race, educational attainment, and income).

Aim 2 is to determine the preliminary efficacy of iCardia4HF on self-care, HRQoL, hospitalizations, and emergency room (ER) visits at 60-days. Mean differences between the two groups in self-care (measured with SCHFI) and HRQoL (measured with the Kansas City Cardiomyopathy Questionnaire) from baseline to 60-days will be quantified, and Cohen's d will be calculated as a standardized index of effect size with 95% CI. Further analysis of self-care and HRQoL will be conducted using mixed model analysis of repeated measures data including randomization group, time, and interactions between group and time while adjusting for personal and clinical characteristics (e.g. age, gender, race, NYHA class) that are significantly associated with the outcome variable ($p<.05$) in the first block of the model. Given the current sample size and follow-up period of 30-days, Poisson regression with robust variance will be used to study the relative risk of hospital readmission and ER visits. Poisson regression is regarded as an appropriate approach for analyzing rare events when subjects are followed for a variable length of time. When Poisson regression is applied to binomial data, the error for the estimated relative risk can be overestimated. However, using a robust error variance procedure can rectify this problem. Results from prior trials and simulation studies indicate that this approach is very reliable with small sample sizes.

10.0 Quality Control and Quality Assurance

Our team includes interdisciplinary expertise in mHealth (Dr. Kitsiou), text-messaging interventions for health promotion and behavior change (Drs. Gerber and Buchholz), self-care interventions for patients with HF (Dr. Pressler), clinical cardiology with a specialization in HF (Dr. Kansal), and biostatistics (Dr. Chen).

This interdisciplinary team will evaluate the quality of data and adherence of data with the protocol. Following recommendations for behavioral intervention studies, we have standardized all intervention materials and procedures, and will provide staff with rigorous training and weekly oversight to ensure intervention fidelity and patient safety. To monitor and support participants' receipt of and adherence to the intervention, we will review on a daily-basis all electronic logs and timestamps of patient-generated data recorded in the dashboard of the app, and document participants' mastery of protocol-specific objectives. The frequency and content of delivered text-messages will be reviewed weekly to ensure that the messaging program is delivered as planned. The study coordinator will call intervention participants twice a week during the first two weeks of the

study and once a week for the remaining weeks to inquire about barriers to intervention receipt, recommend problem-solving strategies, and address any technical issues that may arise. Exit interviews (see Satisfaction Measure in Table 3) will be conducted at 60 days to elicit feedback on the relevance and acceptability of the intervention, perceived benefits, problems encountered, overall satisfaction with the intervention, and suggestions for changes. This process data will be used to refine the intervention.

11.0 Data and Safety Monitoring

Data safety monitoring will be ongoing. A data safety monitoring committee (SMC) will be established to meet and review data and adverse events. The following members of the research team will serve on the committee and participate in the SMC meetings: Spyros Kitsiou (PI); Mayank Kansal (Co-PI); Susan Pressler (Co-I); and Ben Gerber (Co-I). Dr. Kitsiou will be responsible for overall monitoring of the study and for submitting necessary reports to the IRB. Dr. Kansal will be involved with recruitment, intervention delivery, and monitoring of the usual care group. Dr. Pressler will participate in the SMC meetings by teleconference and be particularly involved with delivery and fidelity of the text-messaging program of the intervention, as well as the assessment of self-care and health beliefs. Dr. Gerber will be involved in monitoring of the mobile app and connected health devices data to ensure the protection and confidentiality of participants' data.

Procedures for monitoring study safety, minimizing research associated risk, and protecting the confidentiality of participant data.

Schedule. The SMC will meet quarterly to review the final protocol, initial progress, and the data integrity of the study protocols.

Auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements. First, research team members (RAs, Project Manager) will meet weekly with the PI and review all aspects of the study, including preparation of materials and mHealth equipment, recruitment, data collection, data entry, and protocol adherence. Questions or concerns will be addressed. Second, data will be monitored biweekly by Drs. Kitsiou, Kansal, and Gerber for the first 3 months of data collection and monthly thereafter to ensure the accuracy and completeness. Two cases will be selected and reviewed for compliance at each meeting.

Minimizing research-associated risk. Protocols for patient safety have been established and will be followed for patients who have abnormally low scores on measures for general cognitive function (MoCA), and for patients who have scores on the Patient Health Questionnaire (PHQ-9) suggestive of high depressive symptoms (scores>10). Drs. Kitsiou and Kansal will assist with follow-up with patients' individual physicians for patients with scores suggesting cognitive impairment and/or high depressive symptoms.

Adherence to the safety protocols will be reviewed at weekly team meetings with the PI and at monthly Co-Investigator meetings. In addition, Dr. Kitsiou, will provide continuous, close monitoring of protocol adherence and referral of patients if needed.

Protecting the confidentiality of participant data. All patient data collected in this study are confidential and therefore, we will use Subject ID codes for each subject. The master list file will be stored in REDCap and kept separately from all other data files. Only the PI and UIC key research personnel will have access to identifiable health information. Paper copies of signed informed consent forms will be maintained in locked filing cabinets in a locked research office at UIC accessible only to team members.

We will use the Research Electronic Data Capture (REDCap) for data management and entry. REDCap is a secure web application for building and maintaining online surveys and databases. This application allows users to create a database for data entry, a built-in project calendar, export data to data analysis packages,

build custom queries and reports, and easily manage contact lists of respondents. It also has advanced features which include auto validation, file uploading, and calculated fields and branching logic within electronic forms.

The data will be entered by the data collection RAs trained and supervised by Dr. Kitsiou. The computers that will be used for data collection will be password-protected, encrypted, and maintained in secure, locked offices. No identifiable data will be transmitted electronically. Dr. Kitsiou will monitor the data from the mobile app and devices weekly.

12.0 Statistical Considerations

We will run standard checks for outliers and other errors common to complex data entry and processing. When data are missing at random, that is, the "missingness" may depend on the data that are observed but not on data that are unobserved, the mixed models will still produce valid estimates assuming that models are correctly specified. Data that are not missing at random (NMAR) are expected, but all missing data will be assessed regularly to ensure there are no unforeseen biases that might affect results. As part of data collection, we will collect information about reasons for missing data and use pattern mixture models and sensitivity analyses to investigate and adjust for potential NMAR mechanisms. More complex strategies will be developed if warranted.

13.0 Regulatory Requirements

13.1 Informed Consent

A HIPAA Preparatory to Research is being requested to allow us to review medical records to identify potentially eligible research participants who might be interested in enrolling in the study. Consistent with our patient inclusion/exclusion criteria, we will access the medical record of each patient in the UI Health HF registry to review the following information: name, gender, date of birth, diagnosis and severity of heart failure (echocardiography results, NYHA class, Left Ventricular Ejection Fraction [LVEF]), etiology of HF, hospital admission date(s), follow-up appointment dates, and comorbidities.

A Waiver of Consent for Recruitment Purposes is also being requested for this study. Participants will be asked questions as part of this research project in order to determine their eligibility, but signed informed consent will not be obtained from them until they have been determined eligible.

Written informed consent will be obtained by the PI and/or qualified research assistants from eligible participants who want to enroll in the study. All key research personnel affiliated with the study have successfully completed all mandatory investigator training courses required by standards of the Office for the Protection of Research Subjects (Human Subjects Research, Information Privacy & Security, and HIPAA).

Potential subjects will be given as much time as they need to review the consent document and develop any questions or commentary before moving forward with participation. Should subjects prefer to take the consent form home with them before study procedures commence, they will be encouraged to do so. In such an event, they will be contacted to reschedule their appointment.

All singed informed consent forms will be stored in a locked cabinet in the PI's office at the College of Applied Health Sciences at UIC. Consent forms can be made available to the Co-Is and research personnel through the PI upon request.

13.2 Subject Confidentiality

To ensure that subjects' confidentiality is strictly maintained, we will assign screen ID numbers to subjects who are assessed for eligibility and subsequently subject ID numbers to patients who are consented and enrolled in the study. These ID numbers will be entered into REDCap, which will be accessible by password-only by key research personnel at UIC, and used on all data collection forms and procedures (e.g. Patient Eligibility Assessment Form, Demographic Questionnaire, MoCA, etc.). The collection of personally identifiable data during the recruitment and screening process (i.e. name, birth date, and medical record number) is necessary to avoid screening the same patients more than once. The use of private health information is also a necessary provision in this study to aid with study recruitment by more easily and efficiently identifying

prospective research subjects who meet the clinical criteria of our study. The Screening and Master Lists with all identifiers will be deleted from REDCap after 6 years from the close of the study, using standard procedures already in place by ACCC. As this study is funded by the National Institute of Aging through the Roybal Center, a certificate of confidentiality is automatically granted.

14.0 Unanticipated Problems

Dr. Kitsiou will be responsible for reporting adverse events (AE) and unanticipated problems as required by the UIC IRB and the Midwest Roybal Center (sponsor). Members of the research team will be trained as to what situations constitute AE and unanticipated problems. The UIC IRB will be notified in writing of AE within 72 hours of identification of events. All AE will be reviewed within one week of identifying them by the PI and at investigator team meetings. The SMC will review all AE at the scheduled meetings.

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