A multifaceted adaptive mobile application to promote self-management and improve outcomes in heart failure: ManageHF

National Clinical Trial (NCT) Identified Number: NCT04755816

Principal Investigator: Michael Dorsch, PharmD, MS

Funded by: The National Institute on Aging

Version Number: 3.1

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.2, 1.3, 5.1, 5.2	Update inclusion and exclusion criteria	Due to lower-than-expected recruitment, the inclusion and exclusion criteria have been revised to include a broader pool of patients with heart failure. The changes were approved by the DSMB.

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STATEMENT OF COMPLIANCE

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

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

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

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

I confirm that I have read and understand the protocol referenced above. I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission from the Protocol Chairs and the IRB.

Institution Name: _____

Site Principal Investigator Name (PRINT): _____

SITE PRINCIPAL INVESTIGATOR SIGNATURE: _____ DATE:_____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A multifaceted adaptive mobile application to promote self-management and improve outcomes in heart failure	
Study Description:	The Manage HF study is a multicenter 12-week randomized controlled double-blind 2x2 factorial clinical trial. This study will investigate the effectiveness of two contextual just-in-time adaptive interventions (JITAIs) delivered via a mobile app for heart failure patients. The clinical worsening intervention targets self-management of behaviors to prevent worsening of a patient's heart failure symptoms. The dietary sodium intervention promotes lower sodium intake. Eligible participants will be randomized to the dietary sodium intervention, the clinical worsening intervention, both interventions, or no intervention in a 1:1:1:1 manner, stratified by site, gender, and HF type (HFpEF versus HFrEF).	
Objectives:	Primary Objective:	Determine the impact of two unique adaptive mobile application interventions on death, HF readmissions, and health-related quality of life (HRQOL) in HF patients.
	Secondary Objectives:	Examine the effect of the two interventions on the individual components of the primary composite endpoint and relative change in heart failure symptoms and establish the effect of each intervention on its intermediate outcomes of reduction in dietary sodium and clinical worsening events.
Endpoints:	Primary Endpoint:	The hierarchical composite of time to death from any cause, time to first HF readmission, and change from baseline to week 12 in quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ).
	Secondary Endpoints:	Time to all-cause mortality Time to first HF readmission HF hospitalization within 30 days of discharge Days alive and out of hospital over 12 weeks Change in MLHFQ over 12 weeks Change in estimated sodium intake over 12 weeks Percent time in a clinically worse state over 12 weeks
Study Population:	500 adult heart failure patients	
Phase:	III	
Description of Sites/Facilities Enrolling Participants:	The administrative site and data coordinating center for this clinical trial are located at the University of Michigan. Nine clinical sites in the United States will recruit and enroll participants for the clinical trial.	

Description of Study Intervention:	The mobile app includes two interventions that are turned on or off based on the randomization assignment for the clinical trial. The clinical worsening intervention promotes self-monitoring and self-management with a health status indicator that is linked to adaptive, personalized and contextual push notifications to promote a behavioral change. The dietary sodium intervention facilitates lower sodium choices at home, restaurants and grocery stores using tailored and contextual push notifications.
Study Duration:	54 months
Participant Duration:	12 weeks

1.2 SCHEMA

STUDY FLOW CHART

SCREENING

Prior to consent, all patients will be screened for eligibility using the inclusion/exclusion criteria. All enrolled participants must have left ventricular ejection fraction (LVEF) ≤ 40% or an LVEF >40% (with left atrial size >40mm or BNP > 175 pg/ml or NT-proBNP > 700 pg/ml); have a smartphone with Apple or Android operating system installed; have a personal physician for follow-up; have a valid email address; be able to download ManageHF; and currently be admitted to the hospital, or discharged from the hospital within the last 14 days, for acute on chronic decompensated HF.

CONSENT

BASELINE

Demographics, medical history, vital signs, medications, clinical labs (local), cognitive assessment, anxiety and depression questionnaire, HRQOL questionnaires, nutritional questionnaires, mobile application education and set up

↓

Eligible participants will be randomized to the dietary sodium intervention, the clinical worsening intervention, both interventions, or no intervention in a 1:1:1:1 manner, stratified by site, gender, and HF type.

FOLLOW-UP

6-week follow-up from discharge (+/- 10 days)
Clinical events (death, hospitalizations, other AEs), HRQOL questionnaires, nutritional questionnaires

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12-week follow-up from discharge (+/- 10 days)
Clinical events (death, hospitalizations, other AEs), HRQOL questionnaires, nutritional questionnaires

Notes:
Patients will perform daily self-monitoring which includes a daily survey and remote devices (BP cuff, scale, and wearable activity monitor).
Patients will self-administer the HRQOL questionnaires and nutritional questionnaires via a website.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening and Enrollment** (admission to +14 days from discharge)	**Baseline** (day of discharge +14 days)[3]	**6 weeks from randomization** +/- 10 days	**12 weeks from randomization** +/- 10 days
Enrollment Visit (Inpatient)	SS			
Informed Consent	SS			
Inclusion/exclusion[1]	SS			
Randomization[2]		CC		
App training & application-specific questionnaires	SS			
Demographics	SS			
Medical history		SS		
Follow Up Call & EHR review ● Clinical events (death, hospitalization, other AEs) ● Medications			SS	SS
HRQOL surveys	Participant	Participant	Participant	Participant
Nutritional Surveys	Participant		Participant	Participant
Daily self-monitoring (weight, blood pressure, activity monitor)		Participant----------Participant		
Final Status				SS/CC

Key: EHR = electronic health record, SS = study site, App = mobile application, CC = coordinating center

[1]If screening/enrollment and baseline do not occur on the same day, re-confirm participant's eligibility at baseline.
[2]Randomization to occur remotely after participant completes HRQOL and Nutritional Surveys. The New York Heart Association (NYHA) questionnaire is not required for randomization.
[3]If a participant has been re-hospitalized prior to randomization, re-confirm participant's eligibility, complete a new Health History (Day of Discharge) form in the database with the most recent hospitalization data, and submit a Serious Adverse Event report.

2 INTRODUCTION

2.1 STUDY RATIONALE

Scope of Heart Failure

By 2030, over 8 million Americans will have heart failure (HF), and HF will account for $69 billion/year in medical expenditures.[1] Much of this societal cost is related to hospitalizations for worsening HF, which also take a terrible toll on individuals. Approximately one-third of patients who survive hospitalization for HF die within a year.[2] Hospital readmissions are common, as more than one-fifth of patients with HF are readmitted within 30 days of initial discharge.[3] These recurrent hospital stays not only increase the risk of death[4], but also markedly worsen health-related quality of life (HRQOL)[5], contribute to functional decline, and increase the risk for long-term institutionalization.[6] Hospitals also suffer the consequences; HF is the primary driver for federal 30-day readmission penalties,[7] which now exceed $500 billion/year. Reducing HF readmissions is thus an essential goal across the healthcare spectrum from patients to payers.

Efforts to Reduce Readmissions

Most U.S. hospitals now have dedicated quality improvement teams to reduce readmissions in patients with HF.[8] These efforts typically cover four domains: enhanced patient education, increased use of evidence-based HF therapies, timely post-discharge follow-up, and improved communication between inpatient and outpatient healthcare providers.[9] Although based on a strong rationale, these initiatives have produced mixed results.[10] A recent slight decline in risk-adjusted 30-day readmissions has plateaued, and this improvement partially relates to changes in risk coding[11] rather than definitive improvement in outcomes. Even more concerning, both crude and risk-adjusted 30-day mortality in HF have gradually increased over this timeframe.[4,12] It is clear that new approaches are needed to improve post-discharge outcomes in patients with HF.

Rationale for an Intervention During an Episode of Clinical Worsening

Research on the etiology of HF admissions has been performed to identify better why patients are presenting to the hospital.[13–17] In a recent study, 94 patients were asked to complete a questionnaire about their HF admission.[13] Patient-identified reasons for admission were worsening heart failure (53%), dietary nonadherence (16%) and medication issues (3%). Physicians in this study further identified the most common cause of a preventable admission, which included medication issues, salt restrictions and fluid restrictions. In a similar study of 173 patients readmitted for HF, patients, caregivers, cardiologists and HF nurses completed a questionnaire on the causes of the readmission.[14] Worsening HF as a sole reason for the admission was the most commonly reported factor. In addition to worsening HF, 56% of patients, 36% of caregivers and 63% of health care providers indicated comorbidities, nonadherence and nonoptimal medications were critical factors in the readmission. Respondents reported that 23-31% of the readmissions could be prevented if patients were more adherent, requested help earlier and an

adequate medical professional was available. These identified factors are essential to the creation of the multifaceted intervention within our mobile application in this proposal.

Rationale for an Intervention to Support Dietary Sodium Restriction

Dietary nonadherence, generally understood to mean excess sodium consumption, frequently occurs before HF decompensation and hospitalization.[13–17] As part of the HF syndrome, chronic neurohormonal activation and reduced renal perfusion can promote sodium and fluid retention. This may cause shortness of breath and other congestive symptoms, which are the most common reason for patients with HF to seek emergency care. Current HF guidelines advise dietary sodium restriction of 2,000-3,000 mg/day or less,[18,19] and this guidance is the most common self-care recommendation provided to patients with HF.[20] Cohort studies suggest that lower sodium intake may be particularly important in patients with more severe HF symptoms.[21] Yet, in the large U.S. Heart Failure Adherence and Retention Trial (HART), the median estimated sodium intake was 3,336 mg/day and only 17% of participants reported consuming <2,500 mg/day or less of sodium.[22] An opportunity seemingly exists to reduce HF readmissions and improve HRQOL by promoting adherence to a low-sodium diet.

This study will determine the effectiveness of two unique just-in-time adaptive interventions (JITAIs) within a mobile application that targets the two most common reasons patients are readmitted to the hospital, inability to recognize worsening and nonadherence to a low sodium diet. The study's aims are:

Primary Objectives: Determine the impact of two unique adaptive mobile application interventions on death, hospital readmission and HRQOL in HF patients. Hypothesis 1a: Each intervention will reduce mortality, HF readmission and improve HRQOL (measured by the Minnesota Living with Heart Failure questionnaire (MLHFQ)) compared to control over 12 weeks. Exploratory hypothesis 1b: The two interventions will have an additive impact on all-cause mortality, HF readmission and HRQOL.

Secondary Objectives: Establish the effect of the interventions on intermediate outcomes and confirm that the proximal outcomes mediate the interventions' impact on survival, all-cause mortality, HF readmission and HRQOL. The intermediate outcomes are time clinically worse for the clinical worsening intervention and change in sodium intake for the dietary sodium intervention from baseline to 12 weeks. Hypothesis: The intermediate outcomes facilitate the effects of their respective intervention and clarify how each intervention improves HRQOL and reduces readmission.

Exploratory Objectives: Develop data-driven machine learning models that can predict episodes of clinical worsening. Continuously measured active and passive remote monitoring will be performed over 12 weeks for all patients in the clinical trial. Currently, the clinical worsening intervention is centered on a rule-based model to identify when a patient is experiencing a clinical worsening episode. Hypothesis: Machine learning models can more accurately predict a clinical worsening episode compared to the current rule-based model.

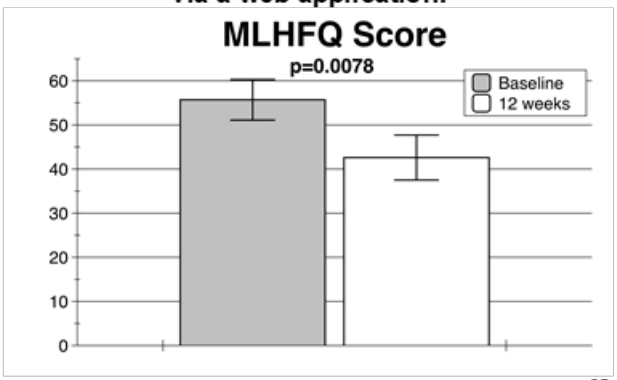
2.2 BACKGROUND

HF is the most common hospital discharge diagnosis among older adults in the United States, affecting 900,000 patients each year.[23] One-fifth of HF patients are readmitted within 30 days of discharge, and readmissions are directly linked to poor health-related quality of life (HRQOL).[13–17] HF readmissions also result in significant, potentially avoidable costs to our already strained healthcare system, since hospitalizations account for nearly 70% of annual HF costs.[15] The most common causes of HF readmission – failure to recognize clinical worsening and nonadherence to dietary sodium restrictions – are related to poor HF self-management.[13–17] Currently, there are no effective HF self-management tools to support older adult HF patients in managing their condition after they transition from the hospital back into the community.

Preliminary Data

Several studies have shown that self-monitoring can improve HRQOL in HF.[24,25] We performed a prospective single-center single-group study to determine the effectiveness of our web application designed to promote self-regulation.[26] Participants were instructed on how to use the web application and to perform self-monitoring daily for 12 weeks. A comprehensive physical exam, assessment of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and an evaluation of self-management were performed in person at baseline and 12 weeks. Participants (N = 24) consisted of older (mean 59 years), predominantly female (63%) adults with NYHA class II or III symptoms. NYHA classification (Pre 2.5 ± 0.13 versus Post 2.0 ± 0.13; p = 0.0032) and MLHFQ score (Pre 55.7 ± 4.6 versus Post 42.6 ± 5.1; p = 0.0078) improved over 12 weeks of self-monitoring. Numerical improvement was also demonstrated in weight (Pre 209 ± 9.6 pounds versus Post 207 ± 9.4 pounds; p = 0.39), number of times exercised per week (Pre 1.29 ± 0.5 versus Post 2.5 ± 0.6; p = 0.30), and walk distance (Pre 572 ± 147 yards versus Post 845 ± 187 yards; p = 0.129). Jugular venous distention (Pre 8.1 ± 0.6 centimeters versus Post 6.7 ± 0.3 centimeters; p = 0.08) and peripheral edema (Pre 29.2% versus Post 16.7%; p = 0.38) decreased after 12 weeks of self-monitoring via the web application.

Figure 1. Preliminary data for self-monitoring via a web application.



Dorsch et al. *Telemedicine and e-Health* 2015.[25]

Clinical Worsening Intervention

We developed a mobile application that can effortlessly assist in self-monitoring, ultimately driving self-management in HF. Version 1 of the application provided patients a health status indicator (HSI) using standard stop light color concept (green, yellow, red) and a message explaining the meaning of the HSI. A deterministic algorithm, based on a daily survey and the change in patient weight compared to dry weight, produces the number for the HSI. See figure 2 for a depiction of the HSI page. We studied this intervention in a randomized clinical trial, which was Aim 1 of an R21 funded by the National Institute on

Aging. We hypothesized that the HSI would accomplish enhanced self-management and improve HRQOL. HF patients at hospital discharge were randomized to the App or usual care (No App) in a 1:1 fashion and followed for 12 weeks. The MLHFQ was collected at baseline, 6 weeks and 12 weeks and HF readmissions were collected over the 12 weeks. Eighty-three patients were enrolled and completed all baseline assessments. Baseline characteristics were similar between groups, except HF type. The average age is 60.2 and 62 years in the App and No App arms, respectively. Most patients were NYHA class III, 58% had ischemic heart disease as the origin of HF, 57% had atrial fibrillation and 35% were female. The App group had a reduced MLHFQ at 6 weeks (p=0.039) but not at 12 weeks (p=0.778) compared to control. The time to first HF readmission was not statistically different between the two groups, but in favor of the App group (App 26.2% vs. No App 19.3%, HR 0.89, 95% CI 0.39-2.02, p=0.781).

Motivational push messages were developed for the clinical worsening intervention to support HF self-management. In addition to the above study, Aim 2 of our R21 grant developed motivational messages to be delivered via the mobile application to improve HF self-management. We performed 3 HF patient and 2 HF nurse focus groups. The messages emphasize knowledge about their disease, behaviors that lead to success and knowledge that encourages positive behavior. Topics of the messages include: avoiding major mistakes with medications after discharge, basics of diuretics, fluid restriction information, the relationship between fluid intake, sodium and volume overload, troubleshooting changes in weight, and medication information. We created 58 messages to test in the focus groups. After the 5 focus groups, we generated a list of 37 messages that HF patients and nurses agreed would promote a behavior change through self-management and be effective at reducing HF readmissions.

Dietary Sodium Intervention

In an R21 grant from the Agency for Healthcare Research and Quality (AHRQ), we have developed a mobile application-based intervention to help patients reduce sodium intake in hypertension. The dietary sodium intervention delivers just-in-time contextual push notifications using the mobile phone sensors and geofencing to promote lower sodium alternatives at home, grocery stores and restaurants. A single center, prospective, open-label study evaluated the effectiveness of the dietary sodium intervention. Patients > 18 years of age diagnosed with hypertension and on antihypertensive therapy for at least 3 months were enrolled. Participants were randomized 1:1, stratified by gender, to receive the mobile app or usual dietary advice for 8 weeks. The primary endpoint was the change in 24-hour urinary sodium excretion. Secondary outcomes included the change in estimated sodium intake from a Block Food Frequency Questionnaire (FFQ), 24-hr dietary recall and blood pressure (BP).

Fifty patients (24 App, 26 No App) were randomized. Baseline demographics were similar between the groups. The average age was 57 years and BP 131/83 mmHg. The reduction in 24-hour urinary sodium excretion from baseline was greater in the App compared to No App group (App -574±1646 vs. No App -52±1708 mg, p=0.30). The reduction in FFQ (App -1554±1764 vs. No App -409±929 mg, p=0.008) and 24-hr dietary recall (App -1537±2692 vs. No App -374±2172 mg, p=0.11) sodium intake from baseline were greater in the App compared to No App group. A standard sodium intake screener also demonstrated a greater reduction in the App group compared to No App group (App -9.5±8.9 vs. No App -3.9±8.8 points,

p=0.036). Systolic BP was reduced from baseline in the App compared to No App group (-7.5 vs. -0.7 mmHg, p=0.12).

Reducing sodium intake has improved HRQOL and reduced hospitalizations. Our research group recently completed the Geriatric OUt-of-hospital Randomized MEal Trial in Heart Failure (GOURMET-HF) pilot study.[27] GOURMET-HF was the first randomized study to evaluate the feasibility and safety of providing home-delivered meals following HF hospitalization. Patients discharged from HF hospitalization at three sites (University of Michigan, Ann Arbor Veterans Affairs Health System, and Columbia University) were randomized to four weeks of home-delivered, low-sodium, nutritionally robust meals vs. usual care. The primary outcome of GOURMET-HF was the between-group change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Score, a measure of HRQOL, from discharge to four weeks post-discharge. Sixty-six patients were randomized 1:1 at discharge to meals versus usual care (age, 71±8 years; 30% female; ejection fraction, 39±18%). The KCCQ Score increased similarly between groups between discharge and four weeks post-discharge (meals 46±23 to 59±20 vs. usual care 43±19 to 53±24, p=0.37) but the KCCQ Clinical Summary Score (average of two KCCQ domains: symptoms of HF and physical limitations) improved to a greater degree in the patients receiving meals (47±22 to 65±19 vs. 45±20 to 55±26, p=0.053). Readmissions within 30 days for HF (11% vs. 27%, p=0.06) and total days re-hospitalized within that timeframe (17 vs. 55 days, p=0.055) trended lower in patients receiving meals.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The main potential risks of the study are loss of protected health information and the potential of "over adherence" to the mobile application. Although the education in the intervention is considered standard of care, over adherence to guideline-based educational interventions (e.g. extreme sodium restriction) could lead to renal insufficiency and/or hypotension.

2.3.2 Known Potential Benefits

The benefits of the research to study participants include gaining information on their own self-management strategies and how they can improve their disease progression. If proven effective, this could potentially benefit others when the mobile application software is fully available to the public. Potential benefits to society include improved understanding of the management of heart failure patients upon hospital discharge. This could ultimately lead to better follow up care and lower morbidity and mortality for patients with heart failure.

2.3.3 Assessment of Potential Risks and Benefits

Study Intervention Risks

The mobile application-based study interventions are push notifications and educational content during a clinical worsening and just-in-time contextual messages to decrease sodium intake that are part of standard HF education. The potential risk to participants is over adherence to either intervention. Over

adherence could result in restricting sodium or food intake too greatly. The risk is small, but important in the clinical trial. A full plan for reducing this small risk is found in the Data Safety and Monitoring Plan.

Risk of Loss of Confidentiality

Information obtained during assessments is confidential and used solely for research purposes. While every effort is made to maintain confidentiality and to protect Patient Health Information (PHI), there always exists a small possibility that some information could be compromised. A full plan for reducing this small risk is found in the Data Safety and Monitoring Plan.

Benefits

If the mobile application-based interventions are effective in the treatment of HF, then it could be possible the participant treated with the app may receive the benefits of improvement in HF. There are only potential benefits to the individual participants in this study. However, direct participation in the clinical trial may be of no benefit to an individual participant.

The knowledge gained from this study will allow us to determine the interventions, pieces of our interventions and groups of individuals that demonstrate improved outcomes over time. This information will be critical to the success of this intervention. The information from this proposal will also allow us to build a more tailored mobile application intervention, if needed, for heart failure patients which has the ability to be impactful in future studies.

3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATIONS
Primary		
Determine the impact of two unique adaptive mobile application interventions on death, hospital readmission and HRQOL in HF patients.	The hierarchical composite endpoint of time to death, time to HF readmission, and change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ).	The composite endpoint is clinically relevant and consistent with the published data. Time to death will be prioritized over time to hospital readmission, which will be prioritized over change in MLHFQ. MLHFQ is a validated HRQOL survey that correlates to many adverse outcomes in HF.
Secondary		
Estimate the effect of the two interventions on the individual components of the primary composite endpoint and relative change in heart failure symptoms.	Time to all-cause mortality Time to first HF readmission 30-day recurrent hospitalizations Change in MLHFQ over 12 weeks Days alive and out of hospital (DAOH) over 12 weeks	Thirty-day all-cause readmission is a quality metric by the Centers for Medicare and Medicaid Services. DAOH is an emerging outcome in HF trials that incorporates both morbidity and mortality and captures disease burden.

	Change in NYHA classification over 12 weeks	
Establish the effect of each intervention on its proximal outcome and the mediation properties of the proximal outcomes on the individual components of the composite endpoint.	Change in estimated sodium intake over 12 weeks Percent time in a clinically worse state over 12 weeks Composite primary outcome	Estimated sodium intake will be used to establish the dietary sodium intervention efficacy. Percent time in a clinically worse state will be used to establish the clinical worsening intervention efficacy.
Tertiary/Exploratory		
Determine whether there is an interaction effect between the two interventions.	The hierarchical composite endpoint of death, HF readmission, and change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ).	The composite endpoint is clinically relevant and consistent with the published data. Death will be prioritized over hospital readmission, which will be prioritized over change in MLHFQ.
Identify differences in associations based on race or sex.	All primary and secondary endpoints.	As health behaviors may vary by race and sex, differences between these groups should be explored.
Develop data-driven machine learning models that can predict episodes of clinical worsening.	Clinical worsening as defined by the mobile app	A machine learning model from the physical activity and heart rate monitor, scale, and blood pressure cuff could identify clinical worsening more accurately than our rule-based model.

4 Study Design

4.1 Overall Design

This phase III trial will determine the effectiveness of two interventions within a mobile application and builds on the research team's previous work. The two mobile interventions are the clinical worsening intervention and the sodium intake intervention. Our central hypothesis is that a patient-centered mobile application with contextual just-in-time adaptive interventions (JITAIs) about self-management during a clinical worsening and dietary sodium will improve the health status of HF patients.

This study is a 12-week prospective randomized controlled double-blind 2x2 trial. See section 1.2 for an overview of the schema. The 2x2 factorial arms of the study are: 1) Both the sodium intervention and the clinical worsening intervention, 2) the sodium intervention only, 3) the clinical worsening intervention only, and 4) no intervention. Eligible participants will be randomized to the dietary sodium intervention, the clinical worsening intervention, both interventions, or no intervention in a 1:1:1:1 manner, stratified by site, gender, and HF type (HFpEF versus HFrEF). The DCC unblinded statistician will

prepare the randomization schedule, using computer-generated block randomization with the random block size(s) known only by the DCC. See Section 9.3.2 for more stratification details.

This multicenter clinical trial will be managed by the University of Michigan through the clinical coordinating center(CCC) and the data coordinating center. The CCC will be led by chief principal investigator, Michael Dorsch, and the data coordinating center will be led by the Statistical Analysis of Biomedical and Educational Research (SABER) unit. Nine sites, including the lead site, have been selected because of their extensive experience either in the NHLBI Heart Failure Research Network or completion of several randomized clinical trials at the site.

4.2 Scientific Rationale for Study Design

Factorial Design

Two of the most common clinical problems that lead to a HF hospitalization are lack of recognizing worsening HF and dietary sodium nonadherence. Over the past four years, the research team has developed interventions for each of these clinical problems. As our preliminary data suggests, each intervention may be effective, but larger studies are needed to confirm their efficacy. Although dietary sodium interventions have been studied in HF, this specific dietary sodium intervention has not been studied in HF. These facts have led us to the proposed 2x2 factorial design of this clinical trial. A factorial design allows comparing the interventions main effects, additive effects and mediators in a more efficient manner without requiring large numbers of participants in the study. This is different from a standard randomized clinical trial that compares the interventions to each other and allows us to determine what interventions should ultimately be included in a next generation mobile application.

Control Group

Once enrolled, all participants receive the mobile application (which includes the two interventions), a physical activity monitor with heart rate sensing capabilities, a blood pressure monitoring device, and a scale. Each participant will then be randomized to one of 4 treatment groups: 1) the app with neither intervention activated, 2) the app with dietary intervention and clinical worsening intervention activated, 3) the app with clinical worsening intervention activated and the dietary intervention not activated, and 4) the app with dietary intervention activated and the clinical worsening app not activated. All patients will receive the health monitoring devices and perform the daily questionnaire. This is done to assure that the interventions are the reasons for any outcome differences, rather than the questionnaire and health monitoring devices. Some studies have shown that remote monitoring may not effect outcomes[28], but we aimed to remove all question in the design of the control group.

4.3 Justification for Dose

The “doses” or intensity of the interventions in this study have been investigated in preliminary work in focus groups, surveys, and clinical trials. In general, patients felt that the number of push notifications was appropriate for the dietary sodium intervention, so we based the max number of push notifications

per day for both interventions off that premise. When a participant is randomized to both interventions, the user can receive several messages throughout the day, overburdening the participant and causing user fatigue. In order to reduce message burden, we maximize the number of messages a user can receive in one day for both interventions.

HF patients are at greatest risk for hospital readmission and death for 7-weeks post-discharge and then the risk plateaus.[25] To account for the increased risk for 7 weeks post-hospitalization, participants will be followed for 12 weeks to capture data both during the highest risk phase and as patients enter a lower risk period.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled event shown in the Schedule of Activities (SoA), Section 1.3

In our examination of each intervention, we have a single primary endpoint and are not conducting interim analyses to stop for benefit or futility.

5 Study Population

5.1 Inclusion Criteria

All eligibility criteria must be met in order to participate in this study:

1. Age 18 years and older at screening
2. Currently admitted or discharged from the hospital within the last 14 days with a diagnosis of acute or acute on chronic decompensated HF.
3. Based on one of the EF criteria (LVEF within 12 months of randomization. BNP or NT-proBNP criteria within 30 days prior to randomization):
    - Left ventricular ejection fraction (LVEF) ≤ 40%.
    - LVEF >40% and BNP > 175 pg/ml or NT-proBNP > 700 pg/ml. Thresholds for NT-proBNP and BNP for LVEF > 40% will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 kg/m2.*
4. Have a personal physician for follow-up
5. A smartphone with a compatible Apple or Android operating system installed and able to download and use ManageHF including accepting all permissions
6. A valid email address
7. Fluent in spoken and written English

8. Signed written informed consent. (Note that each participant must be able to consent for themselves.)

*BNP threshold for eligibility

BMI	BNP LVEF >40	NT-ProBNP LVEF >40
25	175	700
26	168	672
27	161	644
28	154	616
29	147	588
30	140	560
31	133	532
32	126	504
33	119	476
34	112	448
35	105	420
36	98	392
37	91	364
38	84	336
39	77	308
40	70	280
41	63	252
42	56	224
43	49	196
44	42	168
45	35	140
46	28	112
47	21	84
48	14	56
49	7	28

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Contraindication to recommending a sodium restriction diet
2. Scheduled intervention for primary valvular heart disease will occur during the study period

3. Cardiac resynchronization therapy (CRT) within 3 months prior to screening or current plan to implant CRT device during the study period.
4. Dialysis
5. Previous cardiac transplantation or implantation of a ventricular assistance device or similar device.
6. Listed status 1, 2 or 3 for heart transplant
7. Implantation of a ventricular assistance device is expected within 3 months after randomization
8. Non-cardiac illness with expected survival of less than 3 months
9. Discharge to a setting other than home
10. Requirement for chronic inotropic therapy (e.g. milrinone, dobutamine)
11. Inability to use Withings devices due to equipment limitations or contraindications
12. Currently pregnant or intend to become pregnant during the study period.

5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants whose sodium intake is less than 1,500 mg per day as measured by the Block Sodium Screener will be considered screen fails.

If a participant is randomized during a re-hospitalization they will be considered a screen failure.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be re-screened if they are readmitted at a later point in time.

5.4 Strategies for Recruitment and Retention

Potential participants will be identified from current HF admissions at the enrolling site. During the enrollment period an online dashboard of participants enrolled in the clinical trial will be available to the CCC. This dashboard will demonstrate all milestones that need to be met by each study participant and compare local retention with de-identified overall metrics from the other sites. This information will be reviewed at the meetings with each site to identify retention successes/concerns and determine strategies to improve retention. Successful site retention strategies will be shared with all sites through online communication and conference calls. Concerns from sites will also be communicated with all sites

to determine solutions for low retention. In addition, the study closeout payment to each site will be linked to the completion of all patient data entered in the dashboard.

Study participants will also be targeted to improve retention. Study site staff will stress the importance of adherence during the informed consent interview and throughout the study. After initial enrollment, participants receive a welcome email with baseline assessments. Outcomes from the clinical trial are completed remotely and do not require the participants to travel to a study site after study initiation. Online assessments are sent via email and text message. Reminder emails and text messages are sent from the system if participants do not complete them. As the study enrolls, we will continuously review feedback to determine if there are other participant-specific items to implement that can improve retention.

To improve recruitment and retention, participants will receive up to $200 for participating in the study. Participants will receive $50 for completing the enrollment visit, $50 for completing all Week 6 study activities, and $100 for completing all Week 12 study activities. Participants will be paid at the end of their participation in the research study. Additionally, participants keep the study devices (blood pressure monitor, scale, and smartwatch) at the end of their participation in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The mobile application, developed at the University of Michigan, includes two JITAIs that are turned on or off based on the randomization assignment for the clinical trial. The clinical worsening intervention promotes self-monitoring and self-management with a health status indicator that is linked to adaptive, personalized and contextual push notifications to promote a behavioral change (see figure 2). The dietary sodium intervention facilitates lower sodium choices at home, restaurants, and grocery stores using tailored and contextual push notifications.

Both JITAIs use NumberEight, an internet-based service, that use sensors (Wi-Fi, Bluetooth, accelerometer, gyroscope, magnetometer, GPS) on the participant's device to predict their location. User's identifying information is anonymized in NumberEight. The mobile sensor data and NumberEight profiles are not attached to the personalized identifiers (e.g. phone number, email). Data are stored as long as the user is using NumberEight. Study staff will not have access to participants' location during the study period.

Clinical worsening intervention: The intervention adapts to the participant's reported symptoms and provides feedback with a global health status indicator (HSI). The mobile application includes 8 questions which are completed by all (see table 1). After the questions are answered, participants

randomized to the clinical worsening intervention arm will be shown the HSI screen. Access to the HSI screen is restricted to participants in the clinical worsening intervention arms. The HSI screen presents a graphic (figure 2). The HIS graphic is a speedometer-like pictograph that goes from green (good health status) to yellow (fair health status) to red (poor health status). The movement from green to yellow to red is based on the answers to each daily questionnaire. The health status indicator includes text explaining the green, yellow or red status and what they can do for self-management. Additionally, users will receive two push notifications per day in the yellow and three push notifications per day in the red until they are back in the green. The notifications will link to in-app educational content, if appropriate for the notification.

Table 1. Active Remote Monitoring: Daily questions within the App

Question score	0	1	2	3	4
Sense of fullness during a meal earlier than usual	Never	Rarely	Sometimes	Most of the time	Always
Loss of appetite	Never	Rarely	Sometimes	Most of the time	Always
Pain or discomfort in abdomen	Never	Rarely	Sometimes	Most of the time	Always
Shortness of breath	None	Walking up a flight of stairs	Walking 100 yards	Showering or bathing	When sitting down
Energy level	Very good	Good	Fair	Poor	Very poor
Level of swelling	None	Ankles and feet	Up to the level of the shins	Up to the level of the thighs	Up to the level of the abdomen or back
Shortness of breath while laying down flat	Never	Rarely	Sometimes	Most of the time	Always
Shortness of breath when bending over at the waist	Never	Rarely	Sometimes	Most of the time	Always

Personalization: We have developed a baseline survey, adapted from the Self-Care in Heart Failure Index (SCHFI) questionnaire parts B, C and D. The survey includes 2 questions: 1. Listed below are behaviors that people with heart failure use to control their symptoms. When you have symptoms, how likely do these behaviors help you feel better? (5-point scale); 2. In general, how confident are you that you can: (list behaviors and 5-point scale). The questions will include behaviors that are linked to message categories from patient and nurse focus groups (weight management, fluid restriction, symptom recognition, and medications). Messages are prioritized in the categories that have previously helped them feel better. Questions are used to frame the message to be congruent with the user's confidence. A user that is less confident performing a behavior will receive a more motivational message than someone very confident. Also, we use the participant's name, emojis and time of day to provide messages that engage participants. The clinical worsening intervention selects three times a day to send a message (when a user wakes, 6 hours after a user wakes and before a user goes to bed). These times are different every day and predicted by NumberEight. Messages at bedtime will be used for reflection on the behavior for the current day and planning for the following day.

Dietary Sodium intervention: The dietary intervention provides just-in-time contextual information using NumberEight's location services to determine when a participant is at home, arrives at a grocery store or arrives at a restaurant. NumberEight uses artificial intelligence algorithms that analyze the changes in mobile phone sensors, including Wi-Fi, Bluetooth, accelerometer, gyroscope, magnetometer, and GPS. The artificial intelligence algorithm understands the user's pattern of phone sensor use, recognizes his or her present context and predicts future activity. For example, when a user gets in their car in the morning and drives to work, they exit their home Wi-Fi network and connect to their car Bluetooth. Patterns like this happen continuously and are analyzed in the background. NumberEight does not collect any identifiers on the users, other than a unique identifier that links to the user in the App. These predictions, generated by NumberEight, then alert the mobile application that the user is at home, a grocery store or restaurant.

Nutritionix is a company that aggregates nutrition data for over 690,000 grocery store items and 149,000 restaurant menu items of over 790 national chains. It also provides the Universal Product Code (UPC) for the grocery items to enable the scanning of products with labels and the ability to receive standard nutritional facts for common foods without a label. The Nutritionix data is used to gain access to the most up-to-date food information at the time the user is interacting with the app. The essential advantage of using Nutritionix is the ability to tailor what data elements are presented and show items based on sodium content.

Once the app knows the user's context from NumberEight, the user receives a tailored message based on the context (home, grocery store or restaurant). Tapping on a push notification at a grocery store takes the user to a page where they can scan UPC on food packaging or text search at the grocery store. As the participant scans the food item, the UPC will be linked to the nutritional facts for the product. Tapping on a push notification at a restaurant will take the user to a page with dietary information about that specific restaurant based on GPS location. The user can also find the nutritional information in the app at any time, regardless of context or location. This allows participants to also check foods in their homes and receive feedback. The mobile app provides feedback on the sodium content of the food using a traffic light signal red, yellow and green to show participants, at a glance, whether a product is high, medium or low in sodium.

Personalization: Confidence in following a low sodium diet and a sodium intake screener, two simple baseline surveys, personalize the intervention. At baseline, all participants will complete a short survey to identify their top sodium-containing foods and will select lower sodium alternatives to their top sodium-containing foods, and tag locations where they eat those foods. The responses from the survey and lower sodium alternative foods will be used to program the dietary sodium intervention. The confidence in following a low sodium diet questionnaire is used to determine the user's confidence.[29] The result of this survey alters the framing push notification to align with their feelings. The sodium intake screener asks how often and the quantity of the most common high sodium foods (NutritionQuest, LLC). After completion, there is a summary score of sodium intake. The app asks the participant to define 3 alternative lower sodium foods and the location they eat for each of the top 5

sodium-containing foods from this survey. These alternatives and locations are used as reminders in the push notifications and app about lower sodium foods that the participant committed to eating.

6.1.2 Administration

Study teams at the sites will be responsible for identifying eligible participants using the study's inclusion and exclusion criteria (see section 5 for more details). Study teams will approach potential participants and obtain consent prior to enrolling a participant. After enrollment, participants will complete the enrollment activities outlined in the SoA including all baseline questionnaires and surveys, creating accounts with Withings and ManageHF, and downloading the app.

Study coordinators will also conduct a chart review at baseline to gather demographics, medical history, vitals including weight, clinical labs, HF diagnosis, and hospitalizations. As applicable, coordinators will also record adverse events of special interest (AESI), protocol deviations, and concomitant medications at baseline. Please see section 8.3 for more information about adverse event reporting. In addition to baseline data, coordinators will collect hospitalizations, AESI, serious adverse events, concomitant medications, and protocol deviations at 6 weeks and 12 weeks.

After the baseline MLHFQ is completed, the coordinating center will randomize enrolled participants per the study manual of procedures (MOP). Each participant will be randomized to each of the interventions in the trial (clinical worsening and dietary interventions). The participant, clinician, and investigators will be blinded to the intervention assignment. All enrolled participants will perform daily self-monitoring. Participants answer a short 8 question survey assessing their HF symptoms every day within the mobile application (table 1). Participants also perform self-monitoring by continuously wearing an activity monitor with heart rate monitor, taking blood pressure measurements, and performing a weigh-in using the study provided equipment.

When a participant is randomized to both interventions, the user can receive several messages throughout the day, overburdening the participant and causing user fatigue. In order to reduce message burden, we maximize the number of messages a user can receive in one day to three messages for both interventions. We also authenticate that both interventions are presented. For example, if a user receives a morning clinical worsening intervention message and receives two dietary sodium intervention messages, they will not receive another message. The following day, the app prioritizes the clinical worsening intervention to present at least two messages because of the previous day. Ultimately, this averages both interventions to deliver 1.5 messages per day over a week.

6.2 Acquisition and Accountability

The device supplier, Withings, will ship the physical activity monitors, Bluetooth blood pressure monitors and Bluetooth scales directly to the participants' home addresses. Devices will be retained by the participants after their participation is over; as such, no accounting is required for returning devices to the study team.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized after all screening assessments have been completed and the investigator has verified that eligibility criteria have been met. At the time of randomization, participants will be assigned a unique randomization number. Eligible participants will be randomized to the dietary sodium intervention, the clinical worsening intervention, both interventions, or standard care in a 1:1:1:1 manner, stratified by site, gender, and HF type (HFpEF versus HFrEF). The DCC unblinded statistician will prepare the randomization schedule, using computer-generated permuted block randomization with the random block size(s) known only by the DCC. The randomization schedule will be provided to software developers who are building the mobile apps. Participants who withdraw from the study prior to completion of the treatment period will not be replaced.

This study will be double-blinded, with participants, investigators, and study team masked to study assignments. Due to the interventions using push notifications, users will likely be able to guess which intervention group they are in over time. That is the nature of this type of research. Implications of this are unknown given the objective nature of our primary composite endpoint. Some users could report better HRQOL because they are receiving more push notifications. At the week 12 visit, participants will be asked to complete a short exit questionnaire via Redcap asking them to guess their treatment group.

6.4 Study Intervention Compliance

After device set up, participants' use of the mobile app will be tracked within the app, but study staff will not intervene for lack of interaction with the mobile app. Use of the blood pressure monitor, scale, and watch will also not be monitored by the sites and the study team will not intervene for lack of use.

6.5 Concomitant Therapy

Practitioners will treat participants using their own clinical judgment. Chronic inotropic therapy is not allowed.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Discontinuation of the mobile intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from the study at any time. Data collected prior to the withdrawal may be used for analysis and publications. The study site will instruct the participant to delete the study app from their phone and notify the UM project manager via email within 3 business days. Upon participant discontinuation, the study site is also responsible for asking permission to continue to follow the participant's EHR in order to obtain study endpoints. The participant's decision to allow EHR access after active study participation will be documented in REDCap on the Final Status eCRF.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention

The reason for participant discontinuation or withdrawal from the study will be recorded on the Final Status CRF.

Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she does not complete surveys at week 6 and 12 and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to complete the online 6-week and/or 12-week follow-up surveys:

- The site will attempt to contact the participant and counsel the participant on the importance of completing the daily interventions and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable at week 12, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

A medical record review at the 12-week visit will be completed in order to obtain various endpoints.

8 Study Assessments and Procedures

8.1 Efficacy Assessments

Primary Outcome

The primary outcome is a hierarchical composite of time to all-cause death, time to first HF readmission, and change from baseline to week 12 in MLHFQ using the win ratio.

Death (from any cause) occurring during the study period will be reported by each site.

Readmission is defined as admission to an inpatient unit or stay in an emergency department following discharge after the index hospitalization that results in at least a 24-hour stay.[30] Only admissions associated with events that occur on an emergency or unplanned basis will be considered as potential endpoints and then adjudicated. A HF readmission must have clinical manifestation of new dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar rales/crackles, jugular venous distension, renal hypoperfusion with no other apparent cause or radiological evidence of acute HF and additional increased treatment with either intravenous HF medications (diuretics, inotropes, vasodilators) or mechanical or surgical intervention specifically directed at the treatment of HF. Only readmissions during the study period will be assessed.

The MLHFQ tool consists of 21 questions regarding patients' perception of the effects of HF on their daily lives.[29] The questions produce a total score of 0 to 105, with a higher score indicating poorer HRQOL. The MLHFQ will be collected at baseline, 6 and 12 weeks. A score change of 5 or more is considered a clinically significant difference for the hierarchical composite endpoint.

Secondary outcomes

The individual components of the composite primary endpoint will be assessed and defined as above: -- time to all-cause mortality, time to first HF readmission, change from baseline to week 12 in MLHFQ. Self-reported New York Heart Association Classification using a simple 1 question questionnaire will be used as a secondary endpoint at baseline, 6 and 12 weeks.[31] Evidence demonstrates that this simple questionnaire is a predictor of HF admissions, HRQOL and death.

All-cause 30-day hospitalization will be recorded as a dichotomous variable. In addition, percent of days alive and out of hospital will be measured from baseline to week 12.

Nutritional questionnaires will be used to assess the participants nutritional status and sodium intake. The Food Frequency Questionnaire (FFQ) collected at baseline, 6 and 12 weeks will measure sodium intake. The 110-item Block FFQ (NutritionQuest, LLC) will be electronically self-administered or via paper depending on participant preference. The FFQ records commonly consumed food to estimate nutrient and energy intake. Estimated daily intake of sodium will be the main outcome from the FFQ.

Percent time in a clinically worse state (time in yellow/red) over 12 weeks in combination will also be collected. See intervention section 6.1.1 for more detail on yellow and red status for the HSI.

Tertiary outcomes

The Self Mini Nutritional Assessment (MNA) is a six-question validated nutrition assessment tool that can identify geriatric patients who are malnourished or at risk of malnutrition.[32,33] The MNA will be collected at baseline and 12 weeks.

8.2 Safety and Other Assessments

Participants will not undergo any procedures. The following information will be captured at screening/baseline:

- Mini-Mental State Exam (MMSE) – administered by study staff
- Medical chart review for eligibility, medical history and demographics - This must include an echocardiogram previously performed for clinical purposes.
- Vital Signs- including blood pressure, heart rate, respiratory rate, SpO2. Use values closest to discharge
- Laboratory tests- serum sodium, serum potassium, blood urea nitrogen, brain natriuretic peptide (BNP), N-terminal-pro hormone BNP, and serum creatinine performed locally as part of standard of care. Use values reported closest to discharge.
- Hospital Anxiety and Depression Scale -- self-administered via study website
- Baseline questionnaires for mobile app settings - The participant will complete these web-based questionnaires at the time of mobile app set-up.
    - Block Sodium Screener (screening assessment)
    - Adapted SCHFI Questions
    - Self-Care Confidence in Low Sodium Diet questionnaire
- HRQOL Surveys - Participant will complete these web-based questionnaires
- Nutritional Surveys - Participant will complete these web-based questionnaires

The following procedures will be performed daily by participants during Intervention period:

- Daily self-weigh-in - Using study provided scale. Weight will be recorded in app via Bluetooth
- Self-administered survey - 8 questions will be answered each day within the app.
- Daily activity monitoring - The participant will wear a heart rate and activity monitor provided by the study.
- Blood Pressure measurement - The participant will take daily blood pressure measurements using the study provided blood pressure cuff. Measurement will be uploaded to the app via Bluetooth.

While in the hospital, participants will be instructed on how to use the devices and be informed that their readings will not be monitored. The blood pressure monitor does provide easy-to-read color-coded feedback based on recommendations from the American Heart Association; however, it is the participant's responsibility to contact their doctors or seek medical attention for high readings.

The following procedures will be performed at 6 weeks and 12 weeks:

- Follow-up phone call - Study staff will contact the participant to capture clinical events, vital status, medication changes and AESI.
- HRQOL Surveys - Participant will complete these web-based questionnaires
- Nutritional Surveys - Participant will complete these web-based questionnaires

Study coordinators are responsible for monitoring the completion of the surveys. Remote participant follow-up will be performed by the study coordinator to ensure timely completion of the surveys and to gather information hospitalizations at outside institutions, AESI, and other data that may not be available in the electronic health records. Please see the table below for an estimation of time commitment needed by each participant in this study. Note: this does not include the daily requirement of weighing in, checking vitals and taking a short (8 question) survey on the app.

Study Assessment	Screening/ Baseline Visit	6-Week Visit	12-Week Visit
MMSE (Approximately 10 minutes)	✓		
SCHFI (Approximately 5 minutes)	✓		
High 5 alternatives (Approximately 10 minutes)	✓		
HADS (Approximately 5 minutes)	✓		
FFQ (Approximately 45 minutes)	✓	✓	✓
Self-MNA (Approximately 5 minutes)	✓		✓
NYHA (Less than 2 minutes)	✓	✓	✓
MLHFQ (Less than 10 minutes)	✓	✓	✓
Block Sodium Screener (Approximately 5 minutes)	✓	✓	✓
Follow-up Phone Call (Approximately 15 minutes)		✓	✓
App Summary Survey (Approximately 5 minutes)			✓
Approximate time to complete all activities	92 minutes	77 minutes	87 minutes

The main safety objectives in ManageHF are to characterize the risk profiles of the two management strategies and to monitor for unanticipated risks to study participants. In this study, all medications prescribed as a part of standard of care for the management of HF have well defined safety profiles. For this trial, reporting is primarily governed by the Common Rule (45 CFR Part 46, Subpart A), Investigational Device Exemptions (Part 812), as well as ICH Guidelines, IRBs and local regulations.

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding events into the appropriate module of the eCRF within data capture system. Investigators are

to report serious adverse events in accordance with their local IRB requirements. Investigators should follow usual clinical practices at their institution for reporting to regulatory authorities serious, unexpected events related to standard of care medications and devices.

Research staff may review participants' medical records for up to 5 years after their participation to study long-term health outcomes.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)"http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of the investigator it results in any of the following outcomes (21 CFR 312.32(a)):

- Results in death;
- Is life-threatening, i.e. places a participant at immediate risk of death from the event as it occurred;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; OR
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

8.3.3 Events of Special Interest

AEs of Special Interest (AESI) for the ManageHF trial, which may or may not meet serious criteria, include any of the following:

- Symptomatic hypotension
- Symptomatic bradycardia
- Hyperkalemia (Potassium > 6.0 mEq/dl or requiring change in therapy)

- Worsening renal function (increase in creatinine by 0.5 mg/dl from last visit or requiring change in therapy)

8.3.4 Classification of an Adverse Event

AESI will be graded for severity and relationship to the intervention by the investigator according to the guidelines to be specified below.

8.3.4.1 Severity of Event

The following guidelines will be used to grade severity of AESI:

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

8.3.4.2 Relationship to Study Intervention

All AESI must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

AESI will be collected from the time of discharge for participants consented inpatient and from time of consent for participants consented outpatient. AESI will be collected until a participant completes study participation. AESI and serious adverse events may be discovered through any of these methods:

- Observing the subject.

- Interviewing the subject [e.g., using a checklist, structured questioning].

- Receiving an unsolicited report from the subject.

Throughout the study, the investigator will record AESI and serious adverse events on the appropriate eCRF regardless of the relationship to study intervention. Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation.

8.3.6 Adverse Event Reporting

Only Adverse Events that meet SAE criteria and AESI will be reported in the ManageHF database.

SAEs and AESI that occur from (1) the time of discharge for those consented inpatient or (2) the time of consent for those consented outpatient through completion of the final study visit will be reported in the ManageHF database in the following manner:

- AEs of Interest that do not meet SAE criteria will be recorded on the eCRF.
- SAEs that require hospitalization will be reported on the eCRF noting the reason for the hospitalization.
- Secondary SAEs that may occur while a subject is hospitalized due to a different reason will be reported on the eCRF.
- Deaths will be reported on the eCRF.
- If the subject was hospitalized for the event that led to death, the event will need to be reported on the eCRF.

The Investigator will follow all SAEs and AEs of Interest until resolution, stabilization or the event is otherwise explained.

8.3.7 Serious Adverse Event Reporting

SAEs are reportable from the time of discharge or consent (based on hospitalization status) until a subject completes study participation or until he/she prematurely withdraws or is withdrawn from the

study. All SAEs should be reported within 24 hours of site awareness. As additional details become available, the AE/SAE eCRF will be updated and submitted.

When an SAE report is sent it will include the PI assessment of the adverse event and assignment of a relationship to any specific aspect of the study. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided.

In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the DCC or its designated representative. The investigator's assessment of causality must be provided. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's causality assessment is "unknown but not related to study intervention", this should be clearly documented on study records. In addition, if the investigator determines the adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate.

Expedited Safety Reporting

The investigator shall report any suspected adverse reaction that is both serious and unexpected (i.e., serious and unexpected suspected adverse reaction [SUSAR]). The investigator shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study intervention and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with exposure to the intervention;

2. One or more occurrences of an event that is not commonly associated with exposure to the intervention, but is otherwise uncommon in the population exposed to the intervention;

3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of the intervention) that indicates those events occur more frequently in the intervention group than in a concurrent or historical control group.

SAEs that are related and unexpected will be reported to the DSMB by the protocol chairs and the DCC within 15 calendar days of their notification of the event. If a death or life-threatening event occurs that is believed by the site investigator to be related to the study intervention, notification to the DSMB by the protocol chairs and the DCC will occur within 7 calendar days after their initial notification of the event. Copies of the Expedited Safety Report will also be provided to the site investigators.

8.3.8 Reporting Events to Participants

Not applicable

8.3.9 Reporting of Pregnancy

Pregnancies are not reported as serious adverse events.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing institutional review board (IRB) and to the data coordinating center (DCC)/lead principal investigator (PI). The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 2 weeks or 10 business days of the investigator becoming aware of the problem.

8.4.3 Reporting Unanticipated Problems to Participants

Not applicable.

9 Statistical Considerations

9.1 Sample Size Determination

Each intervention (clinical worsening intervention and dietary sodium application) will be treated as a standalone study in this 2x2 factorial trial, so there is no need to adjust the Type I error in our sample size calculation. The primary endpoint is a composite of time to event of all-cause death, time to event of HF rehospitalization, and change in HRQOL from baseline to 12 weeks. A win ratio[34] will be estimated to compare the number of participants receiving the interventions who remain event free longer and have more favorable quality of life change than those not receiving the intervention. A win ratio of 1.0 indicates that both comparison groups have equivalent outcomes in terms of events and quality of life, while a win ratio > 1.0 indicates the intervention group has a favorable profile compared to the control group and < 1.0 indicates the intervention group has a unfavorable profile compared to the control group.

We hypothesize that the win ratio for the hierarchical endpoint in our pilot study will be 1.33 in favor of the clinical worsening intervention group, meaning that people receiving the intervention will be 33% more likely to experience favorable outcomes compared to the group not given the intervention. Assuming 10% dropout, 500 randomized participants (250 per main intervention arm) provides 80% power to show a win ratio of 1.30 (56.6% winners in the intervention group excluding ties) assuming a two-sided 5% type-one error rate).[34–36] Figure 3 shows the sample size calculation for different win ratios at 80% power. After dropout, 225 participants per arm will have completed the study, producing 50,400 (225 x 224) permutations of paired comparisons. Identical reasoning is applied to the power and sample size necessary for the analysis of the dietary intervention.

A mediation analysis using structural equation modeling will be used to determine the proximal effect of the mobile phone apps results (M), “clinical worsening” and “dietary sodium intake”. Assuming 10% dropout, and an alpha of 0.05, this study’s 500 participants will provide at least 80% power to detect either a small standard effect size (0.14) on the association between each intervention and the proximal outcomes, and a medium effect size (0.39) on the association between proximal and distal outcomes, or a medium effect of each intervention on proximal results and a small effect on the association between proximal and distal outcomes.[37]

There is insufficient power to detect an interaction effect of both interventions relative to the control. However, this effect will be estimated as an exploratory analysis.

9.2 Populations for Analyses

All randomized participants will be included in the intent-to-treat (ITT) population, which is the analysis set used in all treatment comparisons of primary and secondary outcomes. All randomized participants who received an intervention (safety population) will be included in safety analyses.

9.3 Statistical Analyses

9.3.1 General Approach

The number of expected participants, the expected effect size, the power and the statistical methods for the clinical trial adequately address the factorial design study's hypotheses. As each primary analysis will be for an independent hypothesis concerning each individual intervention, there will be no multiplicity for corresponding statistical tests, and statistical tests with a two-sided p-value <0.05 will be considered statistically significant. Secondary and tertiary analyses are considered hypothesis-generating and will also not incorporate any adjustments for multiplicity. Analyses will be performed using SAS software (SAS Institute, Inc., Cary, NC) or R freeware. [38] A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed; it will be finalized prior to the database lock.

9.3.2 ANALYSES OF PRIMARY AND SECONDARY ENDPOINTS

There are two primary hypotheses for the 2x2 factorial study that investigate the main effects of each of the 2 interventions:

1. The use of the clinical worsening intervention will reduce deaths and HF readmissions and improve health-related quality of life compared to not using the intervention.
2. The use of the dietary sodium intervention will reduce deaths and HF readmissions and improve health-related quality of life compared to not using the intervention.

Note that all analyses will be conducted separately for each mobile app intervention.

The primary outcome is a composite of death, HF readmission, and change in quality of life using the win ratio method, which incorporates a hierarchy of clinical prioritization on event occurrence. We do not expect an intervention effect on death but are including the event because of its importance using this methodology. Following the unmatched pairs win ratio method of Finkelstein and Schoenfeld,[34–36] each participant receiving intervention will be compared to each participant not receiving intervention, resulting in N_i x N_{ni} pairwise comparisons, where N_i is the sample size for the intervention arm, and N_{ni} is the sample size for the non-intervention arm. For each comparison, "winners" will be determined according to Table 2, starting with scenario 1.

Table 2

Scenario	Time to all-cause death	Time to HF readmission	Change in MLHFQ	Win/loss
1	Low			Loss
	High			Win
2	Tie or both alive	Low		Loss
		High		Win
3	Tie or both alive	Tie or both not hospitalized	Comparator	Loss
			12-week change >=5 points better than comparator	Win
4	Tie or both alive	Tie or both not hospitalized	Comparator	Tied
			12-week change within 5 points of comparator's 12-week change	Tied

Within each pairing, the participant with the longest survival time is counted as the "winner" of that pairing. The win ratio is the number winners divided by the number of losers associated with the intervention. The estimate of the win ratio will be calculated, and its 95% confidence interval will be calculated using bootstrap methods. The test for intervention effect is a nonparametric rank sum test. In the event there is more than a 10% loss-to-follow-up, sensitivity analyses based on multiple imputation of the primary outcome will be conducted. However, if some lost or withdrawn participants were readmitted to hospital, a determination may still be possible for the win ratio statistic.

For secondary endpoints, individual components of the composite outcome will be examined, using survival methods for time-to-event outcomes, and linear mixed effects models or piecewise linear regression for longitudinal continuous outcomes (e.g., MLHFQ). The proportion of participants experiencing 30-day readmissions will be analyzed using logistic regression. Number and percent of days alive and out of hospital (DAOH) will be analyzed using linear regression.[39] Repeated measures proportional odds logistic regression[40] will be used to compare NYHA classifications (ordinal measurements).[27] If the proportionality assumption does not hold, the outcome will be dichotomized and a generalized linear mixed model will be used.

For the primary analysis, the following stratification factors will be explored: site, sex, race, and HF type (HFpEF versus HFrEF). For the secondary analyses, the same stratification factors will be explored, and multivariable models will be fit adjusted for the same variables. A subgroup analysis will be conducted to examine intervention effects by cognition and depression status. In addition, we will explore whether there is a signal for an interaction effect for the use of both mobile applications.

9.3.3 ANALYSES OF SECONDARY ENDPOINTS: PROXIMAL OUTCOMES

For Aim 2, we hypothesize that that each intervention, "clinical worsening – time in yellow and red" for the clinical worsening intervention and "measurement of dietary sodium intake" for the dietary sodium intervention is an intermediate outcome, with a significant association with the intervention, and significant association with a composite endpoint of death, hospitalization and 12-week MLHFQ decline.

Mediation analysis will be used to discern the strength of these measurements as proximal outcomes.[37,41] Structural equation modelling will be used to estimate the effect of each interventions proximal results (M), on the relationship between the mobile app interventions (X) on the distal outcomes (Y) of adverse heart failure outcomes and quality of life. In particular, we will estimate the effect of "clinical worsening – time in yellow and red" (M) on the relationship between the clinical worsening intervention (X) and clinical and quality of life outcomes (Y), and the effect of "measurement of dietary sodium intake" (M) on the relationship between the dietary sodium intervention (X) and the clinical and quality of life outcomes (Y). The structural equation model will consist of a statement on the association between the intervention (X) on the proximal outcome (M), and a statement on the association between (X) and (M) on (Y), assuming error terms are uncorrelated. Structural equation modelling will be used rather than widely used standard regression techniques such as those proposed in Baron and Kenny Causal Steps because it provides more power to detect an effect, and because it acknowledges the role of the proximal outcome as both an effect of the intervention and a cause of the distal outcome.[42,43] Both clinical outcomes and quality of life outcomes will be used to explore the assessment of the proximal outcomes as mediators.

As secondary analyses, we will conduct the same mediation analysis using the individual components of the composite endpoint. As exploratory analysis, we will conduct all the above analyses stratifying by race and gender.

9.3.4 PREDICTION MODELING BASED ON APPLICATION DATA (EXPLORATORY ANALYSIS)

A retrospective analysis of the data collected from the 500-participant clinical trial. Each participant day will be represented by a high-dimensional feature vector summarizing the current day and previous day (data preprocessing). In addition, each day will have a binary label indicating whether or not the participant felt clinically worse compared to the previous day. We formulate the problem as a binary classification task, in which we aim to map data in the feature space to a binary label. We will explore both population-level and participant-specific models. When training models for the entire populations, we will split the data at the participant-level into training and test sets. Using the training set, we will perform model selection for both linear (e.g., L2-regularized logistic regression) and non-linear models (e.g., XGBoost). We will evaluate the model's ability to predict clinical worsening on the held-out test set in terms of model accuracy. When training participant-specific models, we will temporally split the data for an individual participant, training on data collected during the first period and testing on the

remaining held-out data. In addition to the model building and evaluation, we will use permutation importance to identify which variables are most predictive of a clinical worsening episode. Permutation importance is used since it is model agnostic, easily understandable and works with black-boxes.

9.3.5 Safety Analyses

The number of and proportion of participants with SAEs, (including segregation of those involving deaths), treatment-emergent AEs, and discontinuation of study intervention due to AEs will be presented, overall, and by randomization group (both intervention, diet intervention only, clinical worsening intervention only, neither intervention). These presentations will be descriptive, with no formal inferential methods used. The JITAIs are not expected to have great risk to participant safety. Thus, no specific rules for halting study enrollment or study interventions for safety are specified.

In accordance with clinicaltrial.gov reporting requirements, the following tables are required and will be provided:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with the number and frequency of such events by arm or comparison group of the clinical study.
- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with the number and frequency of such events by arm or comparison group of the clinical study. (See Adverse Events definition below).
- Other (Not Including Serious) Adverse Events: A table of anticipated events of special interest (not included in the serious adverse event table) with the number and frequency of such events by arm or comparison group of the clinical study.

9.3.6 Baseline Descriptive Statistics

The two treatment groups for each intervention will be compared descriptively with respect to demographic and baseline variables (e.g., age, race, heart failure type). No hypothesis tests will be used to compare the treatment groups.

9.3.7 Planned Interim Analyses

No interim analyses for futility nor benefit will be conducted. The final analyses of the clinical trial will be performed after the last subject last visit.

9.3.8 Tabulation of Individual Participant Data

SAEs, deaths, AEs resulting in discontinuation of study intervention, and AEs will be tabulated for participants who experience these events.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

IRB approved consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individuals agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. A study team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants will be given the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the protocol is amended and requires a change in the consent form, determination of whether a participant is re-consented will be based on IRB discretion.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or the IRB.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Michigan. This will include the participant's contact and identifying information. The study data entry and study management systems used by clinical sites and by the University of Michigan research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Michigan.

To protect participant confidentiality, mobile application data stored on participants' devices is automatically encrypted before it is written to disk using 256-bit Advanced Encryption Standard (AES). AES encryption used for Android devices has an AES secret key that is encrypted with RSA and the RSA key is stored in KeyStore. Keychain is used for encryption on iOS devices. All mobile application data will

be stored on HIPAA-compliant servers to protect from loss of data or in case of the loss of the device. Participant data is transferred via secure sockets layer (SSL) and stored on a secure HIPAA-compliant server with encryption of all identifiable data. If there was a loss of information in transfer from mobile application to server, SSL ensures the data is encrypted and SSL is the industry standard. If data is stolen from our server, encryption of identifiable data ensures that the information cannot be linked to the individual in our study.

We are also using an internet service, NumberEight, for location services. NumberEight uses sensors (Wi-Fi, Bluetooth, accelerometer, gyroscope, magnetometer, GPS) on the participant's device to predict their location. User's data is stored as long as the user is in the NumberEight system. User's identifying information is anonymized in the system. The mobile sensor data and NumberEight profiles are not attached to the personalized identifiers (e.g. phone number). While participants will identify locations they commonly eat or purchase food and pin them on the map, study staff will not have access to participants' location during the study.

The self-monitoring devices (blood pressure cuff, scale, and activity tracker with heart rate monitor) are supplied by Withings. In order to ship the devices directly to the participants' homes and activate the devices, the University of Michigan and Withings will need the participants' name and address.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality are automatically issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the University of Michigan. After the study is completed, the de-identified, archived data will be transmitted to and stored in a repository, for use by other researchers including those outside of the study. Permission to transmit data to the repository will be included in the informed consent.

10.1.5 Key Roles and Study Governance

Principal Investigator	**Co-Medical Monitor**	**Co-Medical Monitor**
Michael Dorsch, PharmD, MS	Scott Hummel, MD	Todd Koelling, MD
University of Michigan	University of Michigan	University of Michigan
North University Bldg Rm 2560E	1500 E Medical Center Dr #6303	1500 E Medical Center Dr SPC 5856
Ann Arbor, MI 48109-2054	Ann Arbor, MI 48109	Ann Arbor, MI 48109

734-647-1452	734-998-7991	888-287-1082
mdorsch@umich.edu	scothumm@med.umich.edu	tkoellin@med.umich.edu

10.1.6 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including members with expertise in heart failure medicine, statistics, epidemiology, and/or research ethics. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the National Institute on Aging (NIA), DCC and the PI.

The DSMB will act in an advisory capacity to the study team and NIA to monitor patient safety, data quality and to evaluate the ability of the trial to achieve its research goals. The DSMB serves in an advisory capacity to the sponsor (study PIs and NIA). They will review the study protocol, monitor all aspects of the study (e.g., recruitment, adverse events, protocol adherence, data quality, attrition, demographic and baseline characteristics) and recommend protocol modifications, including early study termination. All proposed changes to the study protocol will be reviewed by the DSMB.

Reports will be prepared by the DCC every 6 months and will be sent to the DSMB. These will minimally include recruitment, adherence, attrition, adverse events, data quality (e.g., missed visits, late visits), and descriptive characteristics of the study sample. The DSMB will routinely meet yearly via teleconference/webinar to review the cumulative data. An executive secretary will be present for all DSMB meetings. The sponsor or the chairman of the DSMB in consultation with the sponsor may convene additional meetings. Based on the data presented, the DSMB will make recommendations including continuation or termination of the study.

A formal report containing the recommendations for continuation or modifications of the study, prepared by the DSMB executive secretary with concurrence from the DSMB, will be sent to the sponsor within 4 weeks. The DCC will forward the DSMB report or a summary of the DSMB recommendations to the clinical study site PI(s). It is the responsibility of the PI(s) to distribute this report to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

10.1.7 Clinical Monitoring

Remote site visits will be conducted by the DCC.

More detailed information about clinical monitoring can be found in the Clinical Monitoring Plan.

10.1.8 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol and ICH GCP.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

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

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

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a data capture system provided by the University of Michigan. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Participant self-administered questionnaires at baseline, week 6 and week 12 will be captured directly into Redcap through a participant portal. Due to the length of the FFQ, paper copies may be available for participants who prefer to complete a paper and pencil version. Daily self-monitoring performed by the participants (weight, blood pressure, activity monitor) will be transmitted to the study app. The daily 8 question survey assessing participants' HF symptoms every day will be administered within the mobile application

10.1.9.2 Study Records Retention

Each clinical study site will maintain the paper data for the study for at least 5 years after the study ends, or per local or federal requirements.

10.1.10 Protocol Deviations

All local sites are required to report all protocol deviations that significantly impact the integrity of the study or subject safety in Redcap. All reports must be made within 10 business days through Advarra's IRB platform. Any event that requires immediate action will be brought to the attention of the IRB Chair. All protocol-wide decisions will be coordinated with the lead site. All other events will be coordinated with the submitting party. Events that meet the criteria of serious and/or continuing noncompliance will be communicated to the submitting party and the lead site by Advarra. Advarra will ensure prompt reporting to the applicable Federal Agency. The lead site will have access to all reported events of noncompliance across each local site.

10.1.11 Publication and Data Sharing Policy

The PI will share unique research resources developed by the proposed study in accordance with NIH and policies at each clinical study site. As NIH policy requires that unique research resources be made available to the scientific community after the conclusion of a study, the DCC will plan to release databases and adequate descriptors to allow other investigators to determine relevance of the materials. In accordance with NIH NOT-OD-16-149 and DHHS rule 81 FR 64922, we plan to register our trial with and report our results to clinicaltrials.gov as well as present our findings through convention dissemination routes like publications and presentations at specialty societies.

Resource sharing may include sharing of study documents (e.g., recruitment materials, protocols, SOPs, informed consents, and CRFs that may be useful as starting points for other studies) as well as sharing of data and other participant information. Study participants will be informed about sharing of their information and possible risks of breach of confidentiality and will consent to sharing of their information in order to participate. Identification of individuals even in limited access datasets may be possible. Therefore, care will be taken in drafting consent language that describes sharing and in creating sharing plans and datasets.

Our aim will be to prepare data for deposit into the National Institute on Aging supported National Archive of Computerized Data on Aging (NACDA) data repository, located within the Inter-university Consortium for Political and Social Research (ICPSR) (https://www.icpsr.umich.edu). ICPSR is an international consortium of more than 750 academic institutions and research organizations that advances social and behavioral research, acting as a global leader in data stewardship. Researchers at institutions with a Federal Wide Assurance will be able to gain access to repository data by submitting a data access request in accordance with applicable policies. In order to prepare for the eventual archiving and sharing of data:

a. We will use consent forms that allow broad data sharing within the research community.

b. We will create global unique identifiers (GUIDS) for all research participants in the study.

c. We will use the NIH Common Data Elements (CDE) (or Clinical Data Acquisition Standards Harmonization (CDASH, part of the Clinical Data Interchange Standards Consortium or CDISC) and incorporate appropriate measures to serve as the source for data elements included in our CRFs. This will standardize the definitions and data collection, thereby improving data quality, while also making the data more readily accessible for data sharing and incorporation in meta-analyses. Examples of such forms include demographic, adverse events, and protocol deviation forms. We will also explore other disease-specific CDEs with National Institute on Aging.

We understand that because of the nature of our clinical trial (PI masked to results until interim and final analyses), it is unlikely the data will be released to the research community until after the award is complete; however, the DCC will prepare the de-identified data during year 5 after the database lock. As per National Institute on Aging policy, these datasets will be reviewed prior to release and shared through the NACDA data repository, no later than 3 years after the end of the study or 2 years after the main paper reporting the results of the trial, whichever comes first. The de-identified analytic data will be prepared as SAS transport files or ASCII comma-delimited files with accompanying codebooks that describe the data and data structure. The redaction will employ best practices and will be consistent with National Institute on Aging data sharing policies.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

None

10.3 Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AHRQ	Agency for Healthcare Research and Quality
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CCC	Clinical Coordinating Center
CDASH	Clinical Data Acquisition Standards Harmonization
CDE	NIH Common Data Elements

CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
DAOH	Days Alive and Out of Hospital
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FFQ	Block Food Frequency Questionnaire
GCP	Good Clinical Practice
GOURMET-HF	Geriatric OUt-of-hospital Randomized MEal Trial in Heart Failure
GUIDS	Global Unique Identifiers
HADS	Hospital Anxiety and Depression Scale
HF	Heart Failure
HRQOL	Health Related Quality of Life
HSI	health status indicator
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intention-To-Treat
JITAI	Just-In-Time Adaptive Interventions
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MMSE	Mini-Mental State Exam
MNA	Self Mini Nutritional Assessment
MOP	Manual of Procedures
NACDA	National Institute on Aging supported National Archive of Computerized Data on Aging
NIH	National Institutes of Health
NIA	National Institutes of Aging
HSI	health status indicator
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
PHI	Patient Health Information
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SABER	Statistical Analysis of Biomedical and Educational Research
SAP	Statistical Analysis Plan

SCHFI	Self-Care in Heart Failure Index
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Serious and Unexpected Suspected Adverse Reaction
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	**Date**	**Description of Change**	**Brief Rationale**
1.1	2020.12.17	Section 1.3: Moved the timing of the HADS and nutritional assessments from day of discharge to screening/enrollment. Section 8.2 Added the HRQOL and nutritional assessments to the list of items at the screening/ baseline visit.	This will streamline the workflow. Coordinators will be present to answer participants' questions and ensure data collection is completed. This will also decrease the amount of activities the participant needs to complete immediately upon discharge. For internal consistency within the protocol to match the change described above. Section 8.2 now matches the schedule of activities.
1.2	2021.04.09	Added language to describe the smartphone inclusion criteria more clearly (bolded text is new): A smartphone with **a compatible** Apple or Android operating system installed and able to download and use ManageHF **including accepting all permissions**	To ensure the app works as intended, the smartphone must run a compatible operating system and all permissions must be accepted.
1.2	2021.12.03	Updated the study workflow to reflect the new visit windows.	The study workflow has been updated to reflect the changes included in this amendment.
1.3	2021.12.03	Screening, recruitment, enrollment, and the baseline	Recruitment and enrollment have been slower than

		visit can now occur up to 7 days post-discharge. The visit windows for weeks 6 & 12 have been extended to +/-10 days. The 1-question NHYA survey is not required for randomization Process for randomizing participants who are re-hospitalized has been spelled out.	anticipated. The sites have indicated they are experiencing challenges approaching participants before discharge. It is expected that extending the enrollment and baseline visits to up to 7 days post-discharge will improve enrollment by giving the participants and coordinators additional time to complete all enrollment activities. Due to low survey completion at weeks 6 & 12, we are extending the visit windows to give participants more time to complete the survey and give the coordinators more time to follow up. This one question survey is not a primary outcome measure and we do not want to lose participants due to 1 missing question. By allowing enrollment to occur after discharge, there is a higher likelihood a participant could be re-hospitalized prior to randomization.
5.1	2021.12.03	Inclusion criterion #1 – removed “and able to provide consent” Inclusion criterion #2 – changed language to “or discharged from the hospital within the last 7 days with a diagnosis of”	This text was redundant as it is already mentioned in inclusion criterion #8. The language added to inclusion criterion #2 allows participants to be enrolled up to 7 days post-discharge.
5.3	2021.12.03	Added: Participants whose	Low sodium intake is a

		sodium intake is less than 1,500 mg per day as measured by the Block Sodium Screener will be considered screen fails. Added: If a participant is randomized during a re-hospitalization they will be considered a screen failure.	contraindication for this study (exclusion criterion #1) due to the dangers associated with too little sodium. Time to readmission is an outcome measure. Participants who are readmitted prior to randomization would confound the primary outcome measure. They will be recorded as screen failures and can be re-evaluated for eligibility based on their new hospitalization.
6.1.2	2021.12.03	Added an abbreviation for adverse events of special interest (AESI). Changed timing of randomization from upon discharge to 'after the baseline MLHFQ is completed' Removed reference to after discharge.	Abbreviation was added for ease of reading and for consistency with the use of other abbreviations in the document (e.g. SAE). Since participants may be enrolled after discharge, the text was updated to reflect that randomization will occur after the MLHFQ is completed. Removed since participants may be enrolled after discharge.
7.2	2021.12.03	Removed: Adverse events of special interest will be collected from the time of discharge through study completion or study withdrawal/discontinuation.	Section 8 details how AESIs will be captured.
7.3	2021.12.03	Revised text: A participant will be considered lost to follow-up if he or she ~~fails to completely engage (i.e. never uses the study devices or interacts with the mobile app~~ **does not complete surveys at week 6 and 12**~~)~~	Study endpoints use data from weeks 6 and 12. If data is missing from both time points, the participant will be considered lost to follow up.

		~~with the mobile application~~ and is unable to be contacted by the study site staff. Added: "at week 12" to bullet point #3. Added: A medical record review at the 12-week visit will be completed in order to obtain various endpoints.	If a participant is unreachable at week 6, every attempt should be made to contact the participant at week 12 before considering the participant lost to follow up. A medical chart review will be conducted at week 12 to gather any available endpoints.
8.1	2021.12.03	Added a paper copy option for the FFQ.	Due to the length of the FFQ, the sites have indicated some of their participants would prefer to complete the survey via paper instead of electronically.
8.2	2021.12.03	Reordered baseline questionnaires Indicated that the Block Sodium Screener is a screening assessment Summary of assessment table – updated time commitment for the FFQ from 35 minutes to 45 minutes.	Administrative change only to reflect the order of the questionnaires as they appear in the real-world The Block Sodium Screener is used as a screening instrument to rule out participants whose sodium intake is too low and further reduction could cause harm. Based on feedback from the coordinators, the FFQ is taking approximately 45 minutes to complete.
8.3.5	2021.12.03	Revised text (bolded text is added): **AESI** will be collected from the time of discharge **for participants consented inpatient and from time of consent for participants consented outpatient**. **AESI will be**	The clarifying language is necessary to describe the timeframe for collecting AESI based on hospitalization status at time of consent (inpatient vs outpatient).

		collected until a participant completes study participation	
8.3.6	2021.12.03	Revised text (bolded text is added): SAEs and **AESI** that occur from (**1) the time of discharge for those consented inpatient or (2) the time of consent for those consented outpatient** through completion of the final study visit will be reported in the ManageHF database in the following manner	The clarifying language is necessary to describe the timeframe for collecting SAEs and AESI based on hospitalization status at time of consent (inpatient vs outpatient).
8.3.7	2021.12.03	Revised text (bolded text is added): SAEs are reportable from the time of discharge **or consent (based on hospitalization status)** until a subject…	The clarifying language is necessary to describe the timeframe for collecting SAEs based on hospitalization status at enrollment (inpatient vs outpatient).
10.1.9.1	2021.12.03	Added text: Due to the length of the FFQ, paper copies may be available for participants who prefer to complete a paper and pencil version.	Due to the length of the FFQ, the sites have indicated some of their participants would prefer to complete the survey via paper instead of electronically.
10.1.3	2021.12.03	Added bolded text: In order to ship the devices directly to the participant's homes and activate the devices, the University of Michigan and Withings will need the participant**'s** name, address, **and email address.**	Providing Withings with the participant's email address will allow the participant to receive a shipping confirmation email with tracking information.
10.3	2021.12.03	Added: AESI to the abbreviation table.	Added for internal consistency of the document.
1.2, 5.1, 5.2	2022.04.18	Update inclusion and exclusion criteria	Due to lower than expected recruitment, the inclusion and exclusion criteria have been revised to include a broader pool of patients with heart failure.
5.4	2022.04.18	Added compensation with timing and dollar amount.	Participant incentives have been added to improve

		Added texting as a participant contact method.	participant recruitment and retention The DSMB recommended adding texting as participant contact method to improve participant retention.

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12 APPENDICES

APPENDIX A – PATIENT INFORMATION SHEETS

TURNING HEART FAILURE INTO HEART SUCCESS

CardioSmart
American College of Cardiology

LIVING WITH HEART FAILURE IS A JOURNEY. HERE'S WHAT YOU MIGHT EXPECT.

WHAT DOES HEART FAILURE MEAN?

YOUR HEART STILL WORKS.
But it is weaker or stiffer than before.
So your **HEART HAS TROUBLE PUMPING** enough blood to the rest of your body.

IT'S OK TO FEEL:

- **Scared or uncertain**
- As though your world has **turned upside-down**
- **Overwhelmed with questions**

LEARNING TO LIVE WITH HEART FAILURE

PHYSICAL HEALTH

- **Weigh yourself** each morning
- **Take medications** as directed
- **Ditch the salt** (sodium), eat heart healthy
- **Take breaks** and know your limits

YOUR NEW NORMAL

EMOTIONAL HEALTH

- **Find support** from others who have heart failure
- **Stay connected** with what matters most to you
- **Keep in close contact** with your care team

FOR SOME PEOPLE, NORMAL MEANS:

- **Speaking up about how you feel**—you know your body best
- **Celebrating what you CAN do** (versus what you can't)
- **Sticking with your treatment plan**

WHAT DOES **YOUR JOURNEY** LOOK LIKE?

Information provided for educational purposes only. Please consult your health care provider about your specific health needs.

Go to *CardioSmart.org/HeartFailure* to find out how to turn heart failure into heart success.

CardioSmart is supported in part by Novartis. @CardioSmart If you would like to download or order posters on other topics, visit *CardioSmart.org/Posters*

WEARABLE TECHNOLOGY & YOUR HEART HEALTH

CardioSmart
American College of Cardiology

WEARABLE TECHNOLOGY

can help you engage in your health and track certain healthy habits. **BUT IT DOESN'T REPLACE YOUR HEALTH CARE TEAM.**

Learn more about these devices and what they do.

Most accessories and mobile apps are NOT CLEARED AS MEDICAL DEVICES by the U.S. Food and Drug Administration.

HOW PEOPLE USE WEARABLES

- Collect personal health data, see trends over time
- Check blood pressure, blood sugar levels, heart rhythm
- Be more active, take more steps each day
- Set goals and reminders
- Increase motivation, accountability
- Track symptoms

MORE RESEARCH is needed to understand which wearables work and how best to use them.

Talk with your health care professional about:

- Digital devices and health apps you use
- Privacy concerns
- Clinical trials and how you might benefit from them

For more information, visit *CardioSmart.org/Wearables*

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Information provided for educational purposes only. Please talk to your health care professional about your specific health needs. To download or order posters on other topics, visit *CardioSmart.org/Posters*

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