Statistical Analysis Plan

FULL TITLE	A multifaceted adaptive mobile application to promote self-management and improve outcomes in heart failure: ManageHF
SAP VERSION	V1.0
SAP VERSION DATE	August 23, 2023
STUDY STATISTICIAN	Amy Krambrink
PROTOCOL VERSION	V3.1 Dated September 27, 2022
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Statistical Analysis Plan Signatures

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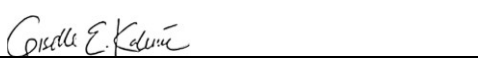
Signature: 

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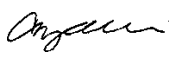
Signature: 

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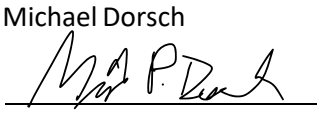
Signature: 

Date: 8/24/2023

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3 Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
OSMB	Observational Study Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

4 Introduction

4.1 Preface

This statistical analysis plan (SAP) describes the statistical methods and analyses for the ManageHF study. This document should be read in tandem with the ManageHF protocol version 3.1, dated September 27, 2022.

The Manage HF study (NCT04755816) 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).

4.2 Scope of the analyses

The purpose of this document is to describe the statistical analyses to be conducted to meet the primary and secondary objectives of the ManageHF study. Ancillary analyses are not covered in this document.

5 Study Objectives and Endpoints

5.1 Study Objectives

5.1.1 Primary Objectives

To determine the impact of two unique adaptive mobile application interventions on death, HF readmissions, and health-related quality of life (HRQOL) in HF patients.

5.1.2 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.

5.2 Endpoints

5.2.1 Primary Endpoint

1. 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).

5.2.2 Secondary Endpoints Endpoint

1. Time to all-cause mortality
2. Time to first HF readmission
3. Change in MLHFQ over 12 weeks

6 Study Methods

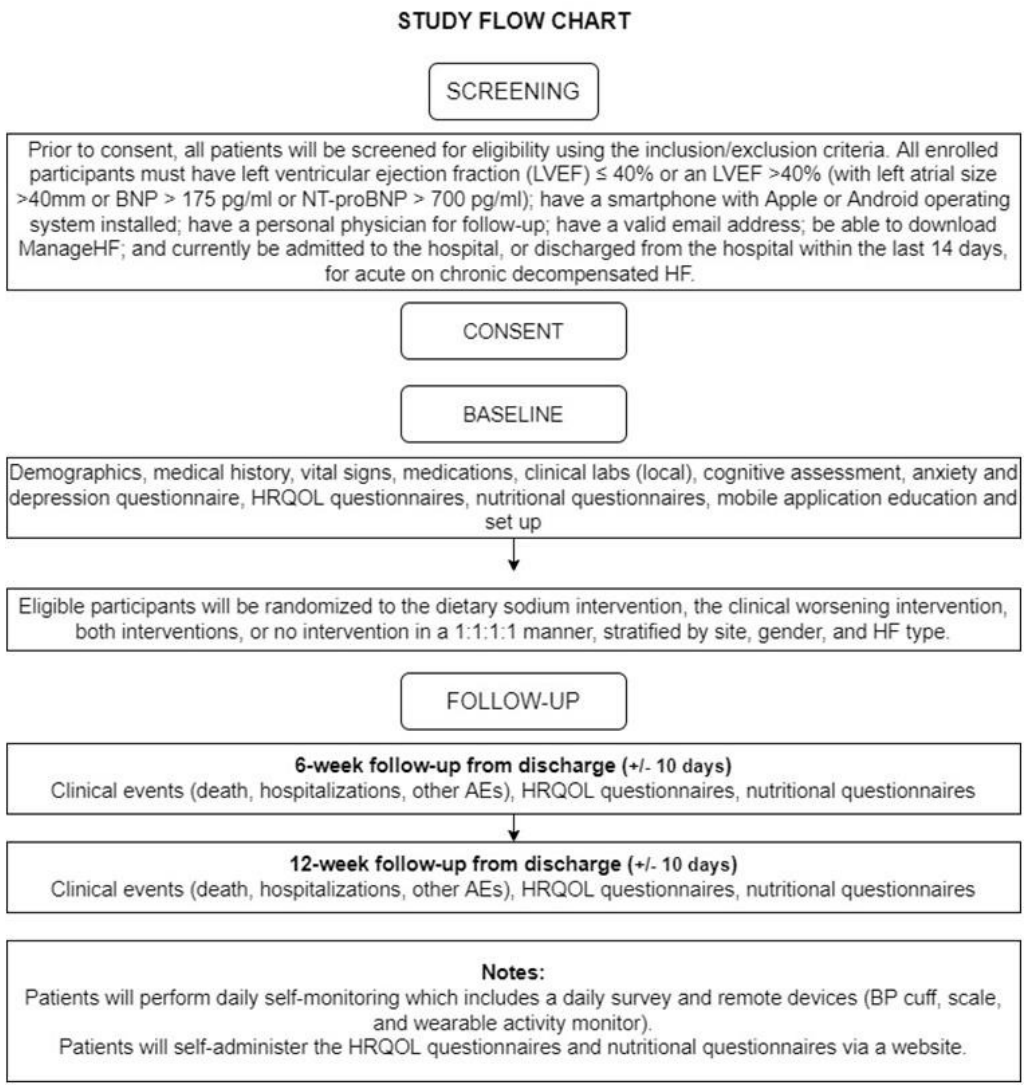
6.1 General Study Design and Plan

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.



6.2 Inclusion-Exclusion Criteria and General Study Population

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

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.

6.3 Randomization and Blinding for Bias Reduction

Participants were 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 were assigned a unique randomization number. Eligible participants were 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 prepared the randomization schedule, using computer-generated permuted block randomization with the random block size(s) known only by the DCC. The randomization schedule was provided to software developers who built the mobile apps. Participants who withdraw from the study prior to completion of the treatment period will not be replaced.

This study is 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 Assessments

The schedule of activities (SOA) details the study procedures:

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.

7 Sample Size

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[1, 2] 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.

8 General Analysis Considerations

8.1 Timing of Analyses

The final analyses of the ManageHF study were to be performed after all enrolled participants have completed study follow-up. The ManageHF study was prematurely terminated by the Data Safety and Data Monitoring (DSMB) Committee owing to insufficient enrollment.

8.2 Analysis Populations

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.

8.3 Primary Endpoint Definition

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. We do not expect an intervention effect on death but are including the event because of its importance using this methodology.

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.

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 the table below, starting with scenario 1.

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.

8.4 Stratification Factors

An exploration of stratification factors was planned in the protocol: site, sex, race, and HF type (HFpEF versus HFrEF). Additionally, the protocol indicated an exploration of whether there is a signal for an interaction effect for the use of both mobile applications. These analyses will not be completed given the early termination of the study and the final available number of participants (see Section 14 below).

8.5 Multi-center Studies

This is a multi-center study. Site effects will not be investigated given the early termination of the study and the final available number of participants (see Section 14 below).

8.6 Missing Data

Assessment of the extent of missing data and its mechanism will be explored for the primary endpoints using the ITT analysis set. Graphical and numerical descriptive methods will be used to summarize the primary outcome over time, by intervention group and overall. We will begin by assuming missing at random and employ multiple imputation methods to handle missing data at the discretion of the study statistician.

8.7 Data Monitoring and Interim Analyses

No formal interim analyses are planned for this study. The study is overseen by a Data and Safety Monitoring Board (DSMB) that reviewed the pooled and by-treatment subject disposition, study conduct, and safety data approximately every 6 months.

8.8 Multiple Testing

Statistical testing is conducted at the 0.05 significance level using two-tailed tests; two-sided p-values are reported unless otherwise stated.

9 Summary of Study Data

Continuous variables will be summarized using descriptive statistics including n, mean, median, standard deviation, range (e.g., minimum, and maximum). Categorical variables will be summarized using counts and percentages. Summaries will be provided by treatment group and overall.

9.1 Subject Disposition

Participant disposition will be summarized descriptively. The number and percentage of participants randomized, completed, and withdrawing, along with reasons for withdrawal, will be tabulated and summarized in a consolidated standards of reporting trials (CONSORT) diagram, both overall and by treatment group. The number of participants in each analysis population will be reported. Other disposition and study conduct information, including major protocol violations will be summarized. Duration of the study follow-up will be summarized overall and by treatment group.

9.2 Derived variables

Derived variables include:

1. Treatment groups
    1. Dietary intervention (Yes/No)
    2. Clinical Worsening (Yes/No)
2. Win Ratio - 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.
3. Change in MLHFQ over 12 weeks.

9.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Protocol deviations are provided in a table listing the frequency of each protocol deviation category.

9.4 Demographic and Baseline Variables

All the following demographic and baseline variables will be summarized overall and by treatment group.

Demographic characteristics will be summarized: age (years); age (18-35, 36-50, 51-65, 66 to 80, >80 years, missing); sex at birth (male, female, not reported); ethnicity (Hispanic or Latino, not Hispanic or Latino, unknown or not reported); race (white, black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Multi Race, Unknown or Not Reported).

Baseline characteristics will be summarized: heart failure type (reduced ejection fraction, preserved ejection fraction); NYHA (category 1, category 2, category 3, category 4, missing); baseline MLHFQ score; baseline sodium screener (mg/da); heart rate; systolic blood pressure.

9.5 Compliance with Standard of Care

After the 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.

10 Analyses

10.1 Statistical Hypotheses

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.

10.2 Primary Analysis of Primary Endpoint

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. 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 win ratio will be summarized overall and by each treatment group (dietary intervention group yes/no, clinical worsening intervention group yes/no). The test for intervention effect is a nonparametric rank sum test.

10.3 Primary Analysis of Secondary Endpoints

Secondary endpoints will be summarized overall and by treatment groups: time to all-cause mortality, time to first heart failure readmission, and change in MLHFQ over 12 weeks.

Simple Cox proportional hazard models will be used to assess time to all-cause mortality and time to first heart failure readmission as a function of treatment group assignments. Hazard ratios and 95% confidence intervals will be reported. Kaplan-Meier curves will be used to visually assess time to all-cause mortality and time to first heart failure readmission by treatment group assignments.

Simple linear regression models will be used to assess the outcome of change in MLHFQ over 12 weeks. Beta coefficients and 95% confidence intervals will be reported. Estimated marginal means for each treatment group will be computed with 95% confidence intervals. The outcome of change in MLHFQ over 12 weeks will be visually assessed with side-by-side box plots (by each treatment group status).

11 Safety Analyses

The number 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 pose a 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.

11.1 Definition of Adverse Events

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).

11.2 Definition Serious Adverse Events and other Significant Adverse Events

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.
- Pregnancies are not reported as serious adverse events.

11.3 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)

11.4 Prior and Concurrent Medications

All prescription and over-the-counter medications and therapies, used by the participant, were recorded at the baseline evaluation and during the course of the study.

12 Other Analyses

No other analyses have been defined.

13 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, IQR or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

14 Summary of Differences between Protocol and SAP

The changes from the protocol-specified definitions of aims, outcomes and statistical analytic approaches are outlined below. These changes are documented herein and represent changes made prior to the database lock.

1. **Premature end of the study**

The study was prematurely ended by the DSMB on February 9, 2023.

2. **Secondary outcomes**

Additional secondary outcomes were listed in the protocol but will not be analyzed as part of this statistical analysis plan:

1. HF hospitalization within 30 days of discharge
2. Days alive and out of hospital over 12 weeks
3. Change in estimated sodium intake over 12 weeks
4. Percent time in a clinically worse state over 12 weeks

3. **Statistical Analyses**

Many of the statistical analyses described in the protocol are not reflected in this SAP and will not be performed due to the premature end of the study. For the primary analysis, stratification factors will not be explored as planned in the protocol. For the secondary analyses, the same stratification factors will also not be explored, and multivariable models will not adjust for the stratification factors as planned in the protocol. A planned subgroup analysis examining the intervention effects by cognition and depression status will not be conducted. The mediation analyses planned in the protocol (analyses of secondary endpoints: proximal outcomes) will not be conducted. The exploratory analysis using application data for prediction modelling planned in the protocol will also not be conducted.

15 Changes to the SAP Between Versions

Not applicable

16 References

1. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *European Heart Journal* 2012:176–82. https://doi.org/10.1093/eurheartj/ehr352.

2. Kotalik A, Eaton A, Lian Q, Serrano C, Connett J, Neaton JD. A win ratio approach to the re-analysis of Multiple Risk Factor Intervention Trial. *Clin Trials* 2019;**16**:626–34.

17 Listing of Tables, Listings, and Figures

See the separate document, “ManageHF TLFs V1.docx”.