Cardiac Recovery Through Dietary Support (CaRDS)

PROTOCOL AND ANALYSIS PLAN

Version 2

10/10/21

NCT: 03759925 Unique Protocol ID: 16-20742

Principal Investigators:

Rita Ngyen, MD
Kartika Palar, PhD

CaRDS Statistical Analysis Plan (May 2021) Contents

Section 1: Administrative Information

1) Title and trial registration

a. *Cardiac Recovery through Dietary Support (CaRDS) Study*
b. Trial registration number: ClinicalTrials.gov: NCT03759925,
c. UCSF Institutional Review Board number: 16-20742

2) Roles and responsibilities – names, affiliations, and roles of SAP contributors

a. Rita Nguyen, MD – co-Principal Investigator, for CaRDS study. San Francisco Department of Public Health.
b. Kartika Palar, PhD— co-Princiap Investigator for CaRDS study. University of California, San Francisco.
c. Edward A. Frongillo, Jr., PhD—Senior statistical consultant for CaRDS study. University of South Carolina, Columbia.
d. Hannah Kleiner, MPH—Data manager for CarDS study. University of California, San Francisco.
e. Andrea Pedroza-Tobias, PhDc – - Analyst for CaRDS study
f. Aron O'Donnell, BS – Clinical Research Coordinator. University of California, San Francisco
g. Cady Smith, BS, MDc – Clnical Research Coordinator. University of California, San Francisco

Section 2: Introduction

3) Background and rationale [from IRB; 2016**]**

Food insecurity is linked with increased cardiovascular risk, worse control of diabetes, and increased healthcare utilization.[1,2] Food insecure seniors 1.75 more likely to report an experience of coronary heart disease, and 2.2 more likely to experience limitations in their activities of daily living.[3] While lower socioeconomic status is known to correlate with increased rates of heart failure incidence, morbidity and mortality,[4] there are no studies looking at the effects of food insecurity on heart failure outcomes. Prior studies[5] that focused on improving disparities in heart failure outcomes have found that nurse-led case management services have reduced heart failure readmissions and improved heart failure outcomes. A few small studies have also found that dietitian education improves adherence to a heart failure specific diet and heart failure outcomes.[6] These studies support the hypothesis that heart failure outcomes are psychosocially mediated and potentially modifiable by addressing food insecurity.

Little is known about whether the provision of nutritious food can improve health outcomes. Gurvey et al[7] demonstrated that providing three meals per day to clients with nutritionist support was correlated with reduced average monthly hospitalizations by 50% compared to matched controls. Seligman et al. has also found decreased HgbA1c and hospitalizations in patients with diabetes that were connected with food bank-based provision of diabetes-appropriate foods.[8,9] By providing patients a regular supply of healthy food, Seligman, et al. have posited that this not only has direct effects on the patients' diet-sensitive health condition (like diabetes), but also enables patients to shift attention from concern for their next meal towards concern for their chronic health condition.[10] Palar et al. has also demonstrated that the provision of medically appropriate foods can increase medication adherence, increase diabetes control, and decrease healthcare utilization.[11]

Our preliminary findings in the Zuckerberg San Francisco General population have noted that of the 60% of adults admitted for heart failure that are housed, about half express moderate to high levels of food insecurity. The patients face many challenges transitioning back to the community, and challenges with medication access and life chaos (unpublished data) have been noted as contributory to heart failure re- admission rates. Since food access has been known to improve medication adherence and psychosocial stability,[12] this suggests that our intervention may have a direct impact on heart failure outcomes and health care utilization.

4) Objectives

Aim 1: To determine the impact of medically tailored meals, groceries ("the intervention") and nutritional education among patients hospitalized for heart failure exacerbation upon hospital discharge on heart failure clinical outcomes. We hypothesize that the intervention will lead to improved heart failure quality of life (primary outcome) and reduced hospitalizations and emergency department visits, and improved health-related quality of life (secondary outcomes) in the intervention arm compared to the control arm.

Aim 2: To understand the impact of the intervention on intermediate outcomes that may be on the path between the intervention and improved heart failure outcomes. We hypothesize that the

intervention will improve food security, diet quality, depressive symptoms and medication adherence.

Aim 3: Conduct a process evaluation to understand participant experiences in the CaRDS intervention, including experiences of improvement (or lack of improvement) in food security and health over the course of the intervention, how participants utilized the food support, barriers and facilitators to participating in the intervention, and feedback about the intervention to inform future implementation and scale-up.

Section 3: Study Methods

5) Trial design

We conducted a pilot randomized controlled trial (RCT) of an intervention providing five months of medically tailored meals (tapering down the amount of food each month), paired with nutrition education, to patients upon discharge from a safety-net hospital due to congestive heart failure (CHF) exacerbation. Participants were randomized to the intervention (n=106) versus control (n=86) using a parallel design. The goal was to test for feasibility and determine the preliminary impact of the intervention on heart-failure quality-of-life (primary outcome), and on in hospital readmission and emergency department visits (secondary outcomes). We also set out to determine the impact of this intervention on intermediate outcomes important to the health of our population (food security, diet, mental health and medication adherence), which may be on the path from the intervention towards improved heart failure health outcomes. The control arm continued with usual care during the study period and then received the five-month meal program starting the sixth month after discharge from the hospital. Participants were followed with full surveys at baseline, 1 month and 5 months; brief versions of the survey were administered at 2- and 3-months. In addition, we collected medical record data on healthcare utilization outcomes. Alongside the trial, a qualitative study and process evaluation was conducted, which included in-depth interviews with study participants and survey items added to the end-line survey to translate lessons learned to guide a possible scale-up of the intervention.

6) Randomization

Initially, 148 participants were randomized in a 1:1 allocation to the intervention (n=75) and control arms (n=73), stratified by food security (zero affirmative answers vs. at least one affirmative answers on the USDA 12-question food security screener) and healthcare utilization (<3 vs. >=3 hospital admissions at ZSFGH), based on a computer-generated assignment. However, early withdrawals were observed, which was higher in the intervention (n=27) than in the control arm (n=3). Therefore, the randomization of the last 44 participants were allocated in a 2:1 ratio for intervention (n=31) relative to control (n=13) arms to compensate for early withdrawals and have the final study arms balanced.

7) Sample size

Estimates from the literature were used to calculate the sample size needed for this study for the outcomes of changes from month 0 to month 5 in our primary outcome, heart failure quality-oflife. We assumed that the standard deviations (SD) seen in the current study would be similar to that in a similar study conducted in an urban setting in the United States.[13] Sample size calculation were based assuming 80% power for a two-sided test at alpha of 0.05, and SD of 20.0. With the outcome of change in heart failure quality of life score from baseline to 5 months, considering as a minimum clinical difference of 10 points in the heart failure quality of life score, the sample size

needed was 63 individuals in each arm. We assumed a retention in the current study of 80%, thus the sample size needed at recruitment was at least 158 (n=79 in each arm)

8) Framework

The superiority hypothesis testing framework will be used, testing whether exposure to the intervention results in better outcomes than exposure to the control standard of care. Comparisons will be presented as differences between arms in changes in outcomes from baseline to 1 month to capture changes in acute heart failure symptoms and 30-day readmission; and from baseline to 5 months of follow-up to capture longer term and potentially sustained benefits.

9) Statistical interim analyses and stopping guidance

a. Information in interim analyses specifying what interim analyses will be carried out and listing time points
    i. None planned
b. Any planned adjustment of the significance level due to interim analysis i. No
c. Details of guidelines for stopping the trial early
    i. None

10) Timing of final analyses

Final analyses will begin in Fall 2021 upon completion of all field data collection in Fall 2020 and completion of all medical record data collection (Summer 2021).

11) Timing of outcome assessments

Research staff administered full surveys to both arms at baseline, 1 month, and 5 months. Additional brief surveys were collected at months 2 and 3. Medical record data were collected continuously in both arms from 3 months prior to baseline until 9 months after baseline.

Section 4: Statistical Principles

12) **Level of statistical significance**

95% confidence intervals and exact p-values (or p<0.001) will be reported.

13) **Description and rationale for any adjustment for multiplicity and, if so, detailing how the type I error is to be controlled.**

The primary outcomes were established in the protocol, and thus no adjustments will be made for multiplicity.

14) **Confidence intervals**

95% confidence intervals will be reported alongside exact p-values.

15) **Adherence and protocol deviations**

a. Definition of exposure to the intervention and how this is assessed including extent of exposure:
    i. Receipt of medically tailored food support AND
    ii. Receipt of nutrition counseling and/or education
b. Description of how adherence to the intervention will be presented.

Adherence to the intervention will be presented through a narrative summarizing the following points:

i. % of weeks received any food support (out of weeks scheduled to receive food support)
ii. % of food received (out of total food entitlement) (POH data) iii. % of food consumed (out of food received) (survey data)
iv. % of counseling or education sessions received (out of planned sessions) The cut-off points to decide if the patient is adherent to the intervention will be defined during the analysis, based on the participant's exposure to the intervention.

Definition of protocol deviations for the trial. The following protocol deviation occurred during the study and corrective actions were developed:

a. Minor protocol deviation: Participants for study visits were seen outside of the initial protocol specified visit window (+/- 1 month). All efforts were made to reach the participants on time, but the participants were not available or were not able to be located within the window and therefore they were seen outside of the visit window. As a result, the standard operating procedure (SOP) was updated that addresses follow up and retention of participants. The SOP outlines that the research assistants will make calls and conduct home visits in case a participant misses his or her appointment date to ensure that the participants are seen with the appointment window period.

b. Unable to be contacted: 16 intervention participants were randomized but were not able to be contacted by POH to start the intervention and were considered as early withdrawals. Control participants could not be excluded as "early withdrawals" because the next visit would be a month after the baseline. Therefore, researchers modified the protocol and made a phone call to the control participants, right after the randomization, to simulate the call that the intervention participants had by POH to be enrolled in the food and nutrition program. From among control participants called right after randomization in the modified protocol, 2 could not be reached and were considered early withdrawals.

The number of participants with major and minor protocol deviations will be summarized by study arm.

16) **Analysis populations** – definition of analysis populations, e.g. intention to treat, per protocol, complete case, safety

a. Intent to treat - The primary analysis will be intent to treat (ITT). The ITT analysis will include all participants in both arms who were randomized, completed all baseline assessments, and who had at least one follow-up visit. (see CONSORT).
b. Adjusted intention to treat analysis. To adjust for early withdrawals, a propensity score for receiving the intervention will be developed and used to estimate the probability of each participant to receive the intervention. The adjusted ITT analysis will be performed adjusting for the propensity score and for baseline covariates that were different between arms.
c. Per protocol - The per protocol analysis will include all participants in the ITT sample with baseline and follow-up evaluations and who adhered to the food and nutrition intervention. The minimal adherence will be considered as receiving at least 50% of weeks food and groceries, and at least 1 visit with the dietitian. This definition may be

revised depending on the distribution of adherence in the intervention participants. See appendix 1 for details about the food and nutrition education intervention.

d. Complete case— We will not conduct complete case analyses as we will attempt to use all available data from all participants.

Section 5: Trial Population

17) **Screening Data** –

a. Participants were recruited through reviewing patient lists of hospitalizations in collaboration with providers in the Family Medicine and Cardiology Departments at San Francisco General Hospital. At provider meetings, research staff presented study details and eligibility guidelines.
b. Screening was conducted in two stages, during an initial review of medical charts and at a visit with a participant while they were in the hospital prior to discharge. During the medical chart screening, potential participants were screened for congestive heart failure exacerbation diagnosis during their current hospital admission, age 18 years or older, language English or Spanish, less than 6 admissions to ZSFG in the last 12 months, no end stage renal disease diagnosis or known plan to initiate dialysis within 6 months, no severe aortic stenosis diagnosis, no mention of life expectancy less than 1 year, no cognitive impairment, currently housed, discharge plan for patient to discharge home, and currently living in San Francisco. Participants who met all criteria then proceeded to the in-hospital screening, which included confirming potential participants are housed and living in San Francisco, are not receiving more than 7 meal per week of food support, do not have any disqualifying allergies to commonly used foods used at POH, have a refrigerator and freezer to store food and are able to reheat and prepare meals and snacks at home, are able to eat by themselves or have assistance to eat, have cognitive capacity to consent to be in a research study, and are not moving in the next 6 months to a housing situation that does not meet study eligibility criteria.
c. A summary will be provided indicating the number of participants screened, number of participants eligible, non-eligible and reason for non-eligibility, number of participants enrolled, number of participants eligible but not enrolled and reason, and number of participants randomized.

18) **Eligibility** – summary of eligibility criteria

Criteria for inclusion of subjects:

1. Adults hospitalized at ZSFG with acute decompensated heart failure/congestive heart failure exacerbation
2. Adults with their primary residence within San Francisco
3. Age: >18 years old
4. Languages: English or Spanish
5. Housed at a location where they would be able to securely receive, store and reheat food

Criteria for exclusion of subjects

1. Patients with severe or critical aortic stenosis.
2. Patients with six or more hospital admissions within the last twelve months
3. Patients who are being discharged to a living facility that provides meals to residents.

4. Patients who anticipate moving from their current housing situation to one that does not meet our inclusion criteria within six months of enrollment.
5. Patients who are part of meal provision program that provides more than 7 meals a week to the patient.
6. Patients who are unable to feed themselves and do not have adequate support to help them with feeding.
7. Patients with limited physical, cognitive, or behavioral abilities that would interfere with their ability to follow-up with a study as determined by their ability to receive the Project Open Hand services and follow up with survey interviews
8. Patients with anticipated life expectancy of less than a year.
9. Patients who lack capacity to consent to a research study.
10. Patients currently requiring dialysis or determined to need dialysis in the next 6 months.
11. Patients with severe allergies to eggs, soy, wheat, nuts, seeds, seed oils, pineapple, raisins, or certain vegetables such as onions (allergies are considered on a case-by-case basis in consultation with Project Open Hand).

19) **Recruitment** – A CONSORT flow diagram will be used to summarize the number of participants who were:

a. Assessed for eligibility at screening

i. Among people with heart failure, 2996 people were assessed for eligibility

1. 2451 did not meet the inclusion criteria
2. 127 Discharged before doing the baseline evaluations
3. 226 were not interested in participating in the study ii. Eligible and randomized

1. 192 were eligible and randomized

a. 106 allocated in the intervention arm

i. 27 were early withdrawals

b. 86 allocated in the control arm

i. 4 were early withdrawals

See CONSORT diagram for detail on reasons for ineligibility

20) **Withdrawal/follow-up**

Reasons and details of withdrawal and lost to follow up at month 1 and 5 for both arms will be reported and summarized in the CONSORT flow diagram.

a. Level of withdrawal, e.g., from intervention and/or from follow-up

i. Participants were withdrawn from the study due to unavailability to immediately reach out by phone, not meeting the eligibility criteria or deceased immediately following the randomization.

1. 16 (15.1%) of randomized intervention and 2 (2.3%) of randomized control participants were unable to be contacted by phone after the baseline evaluations.
2. 6 (5.7%) participants allocated to the intervention and 2 (2.3%) participants allocated to the control arm were excluded because did not meet eligibility criteria after randomization, and 3 (2.8%) participants in the intervention arm were immediately re-hospitalized.
3. 1 (0.9%) participant in the intervention arm died after being randomized. ii. Lost to follow up (LTFU) occurred through loss of contact with study participants, moving out of the study area, and death. Intervention participants were also considered LTFU if they withdrew consent. Among

those that were randomized and contacted immediately after randomization (n=79 in intervention arm, and n=82 in control arm):

1. At month 1, 75 (94.9%) of intervention participants and 78 (95.1%) of control participants were retained from month 0.
2. At 5 months of follow-up, 60 (75.9%) of intervention participants and 59 (71.9%) of control participants were retained from month 0.

b. Timing of withdrawal/LTFU data

i. Intervention participants left the study prior to their first encounter with Project Open Hand were considered withdrawn, otherwise they were considered LTFU.
ii. Control participants that left the study prior the first call from UCSF staff were considered withdrawn, otherwise they were considered LTFU.
iii. Participants that were excluded immediately after randomization were also considered early withdrawals.

c. Reasons and details of how withdrawal/LTFU data will be presented

i. Withdrawal and LTFU data are presented in the CONSORT diagram, stratified by study arm and visit. These data are included to establish lack of bias in screening and retention between the two arms. (See appendix 2)

21) **Baseline patient characteristics**

We will evaluate several socio-demographic and clinical characteristics at baseline by which we will describe our study sample. These are outlined in Table 1 below and a shell table is provided in the appendix. We will stratify these characteristics by intervention and control arms and report median and the inter-quartile range for continuous variables with skewed data and mean and SD for continuous variables with normal distribution. Categorical variables will be presented as numbers and percentages. No significance testing will be conducted or reported at baseline per CONSORT guidelines.

Table 1: Baseline characteristics of CaRDS participants	
Socio-demographic	Age, current gender, race/ethnicity, household size, relationship status, educational attainment
Economic welfare	Household food insecurity, sources of income, food support sources
Clinical	Heart failure quality of life; general health-related quality of life; medication inventory; blood pressure
Nutrition	Dietary quality; food consumption patterns
Mental Health	Depressive symptoms
Behavioral	Self-reported medication adherence; alcohol use, drug use
Healthcare utilization	Recent hospitalizations, ED visits, doctor visits

Section 6: Analysis

22) **Outcome definitions**

a. Aim 1: Primary Outcomes: Heart failure quality of life: The primary outcome for Aim 1 will be heart failure quality of life, which was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 1 month and 5 months, among all study participants. The Kansas City Cardiomyopathy Questionnaire is a 23-item instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. An overall summary score can be derived from the physical function, symptom (frequency and severity), social function and quality of life domains. A clinical summary score can be obtained from the symptom frequency and burden domains and the physical limitation domain. Scores are transformed to a range of 0-100, in which higher scores reflect better health status.

For analysis of the primary outcomes, we will compare:

i. Change in the overall KCCQ scores from baseline to five months, by study arm. ii. Change in the overall KCCQ scores from baseline to one month, by study arm.

iii. Change in the KCCQ clinical summary score from baseline to five months, by study arm,

iv. Change in the KCCQ clinical summary score from baseline to one month, by study arm,

v. Change in the overall physical domain KCCQ scores from baseline to five months, by study arm. vi. Change in the overall physical domain KCCQ scores from baseline to one month, by study arm.

b. Aim 1: Secondary outcomes:

i. Hospitalization and Emergency Department use: As a secondary Aim 1 outcome, self-reported data as well as abstracted medical record data on hospital readmission and Emergency Department use were collected. From the data we will assess the number of times participants were admitted to the hospital from baseline to 1 month and from baseline to five months and the cumulative probability of being hospitalized by study arm. The following outcomes will be reported:

1. Admissions to Zuckerberg San Francisco General Hospital from baseline to 1 month, as determined by medical records. Number of admissions to Zuckerberg San Francisco General Hospital from baseline to 1 month, by study arm, adjusting for baseline values (-3 to 0 months).
2. Admissions to Zuckerberg San Francisco General Hospital from baseline to 5 months, as determined by medical records. Number of admissions to Zuckerberg San Francisco General Hospital from baseline to 5 months, by study arm, adjusting for baseline values (-3 to 0 months).
3. Admissions to any hospital from baseline to 1 month, as determined by ZSFGH medical records and self-report of admission to hospitals other than ZSFGH. Number of admissions to any hospital from baseline to 1 month, by study arm, adjusting for baseline values (-3 to 0 months).
4. Admissions to any hospital from baseline to 5 month, as determined by ZSFGH medical records and self-report of admission to hospitals other

than ZSFGH. Number of admissions to any hospital from baseline to 5 months, by study arm, adjusting for baseline values (-3 to 0 months).

a. Cumulative probability to be admitted to any hospital from baseline to 5 months by study arm.

5. Emergency room utilization at Zuckerberg San Francisco General Hospital from baseline to 1 month, as determined by medical records. Number of admissions to the emergency room at Zuckerberg San Francisco General Hospital from baseline to 1 month, by study arm, adjusting for baseline values (-3 to 0 months).
6. Emergency room utilization at Zuckerberg San Francisco General Hospital from baseline to 5 months, as determined by medical records. Number of admissions to the emergency room at Zuckerberg San Francisco General Hospital from baseline to 5 months, by study arm, adjusting for baseline values (-3 to 0 months).
7. Emergency room utilization at any hospital from baseline to 1 month, as determined by ZSFGH medical records and self-report of emergency room utilization at hospitals other than ZSFGH. Number of admissions to any emergency room from baseline to 1 month, by study arm, adjusting for baseline values (-3 to 0 months).
8. Emergency room utilization at any hospital from baseline to 5 month, as determined by ZSFGH medical records and self-report of emergency room utilization at hospitals other than ZSFGH. Number of admissions to any emergency room from baseline to 5 months, by study arm, adjusting for baseline values (-3 to 0 months).

ii. Overall health-related quality of life. Self-reported quality of life using the 4-item Healthy Days Core Module of the CDC's Health-Related Quality of Life survey which asks a general assessment of health on a 5-point Likert scale as well as 3 questions quantifying the number of days in the past 30 days participants felt their health was not good.

c. Aim 2 Outcomes. The primary intermediate outcomes are changes between baseline, 1 month and 5 months in food security, diet quality, depressive symptoms, and medication adherence.

i. Food Security: We measured food security status using the 10-item adult version of the USDA Household Food Security Survey Module (HFSSM) Access Scale (HFIAS). This scale has been validated in Spanish and English in the US and is the reference measure for food security in the US [citations]. The ten-item questionnaire covers domains of worry over, sufficiency of, and quality of food accessed by the participant's household. The scores will be analyzed primarily as a continuous variable using a sum of all responses with a possible range of 0 to 18 in households with children, and 0 to 10 in households without children. Higher scores are indicative of less food security. We will examine the following outcomes:

1. Change in food security scores from baseline to 5 months, by study arm.
2. Change in food security scores from baseline to 1 month, by study arm. ii. Change in dietary patterns: Food consumption was collected using food frequency questionnaire that assess the frequency of intake of 32 food items in the prior month. A change in the consumption (servings/day) of food groups from baseline to one month, and from baseline to five months will be assessed. The food groups to evaluate are food high in: Unsaturated Fat (nuts), Saturated Fat, Sodium, Added sugars, Fruits, Vegetables (fresh), Vegetables (canned), Animal-based Protein, Plants-based Protein, Dairy, and Carbs/Starch.

iii. Medication adherence. A Single-Item Rating Visual Analogue Scale (range 0-100) for medication adherence will estimate the percentage of medications taken in the past month and is reliable and valid, including in low-literacy populations. A higher value indicates higher adherence. The change in medication adherence (percentage points) from baseline to one month, and from baseline to five months between intervention and control arms will be reported.

iv. Depressive symptoms. Symptoms corresponding to the Diagnostic and Statistical Manual of Mental Disorders will be measured using the 9-item Patient Health Questionnaire (PHQ-9), a reliable and valid measure of symptom severity. The PHQ-9 score ranges from 0 to 27, with higher scores indicating higher levels of depression. The change in PHQ-9 scores from baseline to one month, and from baseline to five months among by study arms will be reported.

d. Other outcomes.

i. **Sustained health benefits:** To assess whether any improvements outcomes were sustained, researchers will evaluate the hospitalization and emergency department visits, four months after the intervention ended (at 9 months).

1. Admissions to Zuckerberg San Francisco General Hospital from baseline to 9 months, as determined by medical records. Number of admissions to Zuckerberg San Francisco General Hospital from baseline to 9 months, by study arm, adjusting for baseline values (-3 to 0 months).
2. Emergency room utilization at Zuckerberg San Francisco General Hospital from baseline to 9 months, as determined by medical records. Number of admissions to the emergency room at Zuckerberg San Francisco General Hospital from baseline to 9 months, by study arm, adjusting for baseline values (-3 to 0 months).

ii. Process outcomes 24)

23) **Analysis methods:**

a. **Preliminary/Descriptive analyses.** Frequency tables for all variables and measures of central tendency and variability for continuous variables will characterize the sample and be stratified by randomization arm to check for non-equivalence. If the two arms differ at baseline on any covariates, propensity scores approach will be used to obtain the desired marginal effect estimates under the counterfactual assumption of balanced arm.

25) Analysis methods to be used and how the treatment effects will be presented:

a. Aim 1, Hypothesis 1. The intervention will lead to improved heart failure quality-of-life (primary outcome) and reduced acute care utilization (secondary outcomes) in the intervention arm compared to the control arm. Intent-to-treat analyses will assess whether the intervention will result in improved changes in primary and secondary outcomes with mixed effects models. These mixed models are equivalent to repeated measures models. Study arm (intervention or control), visits (baseline, month 1 and month 5), and the interactions between arms and visits will be the fixed effects and individuals will be considered as random effects.

Alternative analyses will be done using analysis of covariance in which the 5 month (and 1 month) outcome measures will be regressed on the corresponding baseline outcome measures and study arm. Analysis of covariance allows relaxing the assumption that the

baseline and follow-up measures have a 1:1 relationship and testing the assumption that the relationship between the baseline and follow-up measures are the same.
Additional analyses will be done to check robustness if the two arms differ at baseline by controlling for the propensity score or the covariates that were important in the propensity score.
For primary and secondary outcomes, Box-Cox transformations will be used to correct for skewness if needed.
To compare the probabilities of hospitalization and emergency room visits by study arm, a log-rank test will be performed, and visualized using Kaplan-Meier curves.

b. Aim 2, Hypothesis, The intervention will improve food security, reduce healthcare utilization, and improve dietary behavior, that in turn will improve mental health (depressive symptoms), and medication adherence. Analysis for intermediate outcomes will be performed using mixed effects models, as described in Aim 1.

c. Any planned sensitivity analyses for each outcome, where applicable: Not applicable.

Any planned subgroup analyses for each outcome including how subgroups are defined:
Additional models and statistical interactions (i.e., product terms) will be performed to identify characteristics of individuals who most benefitted from the intervention, such as biological sex, and food insecurity.

24) Missing data

a. The study team employed several strategies to account for and address missing data during the *CaRDS* trial period. To prevent or reduce missing data, data collection was computerized, and the questions were obtained through a trained interviewer. The analyst will examine patterns of non-response and inspect distributions of mediating and outcome variables to identify outlying or unusual values and assess distributional characteristics. Missing data will be categorized into: 1) missed individual questions, 2) missing forms, and 3) missed visits.
b. Missed individual questions: Multiple imputation will be used to address incomplete data arising from missing forms. The assumption will be that incomplete data arise from a conditionally missing-at random mechanism (MAR. Auxiliary variables will be included to help meet the MAR assumption and sensitivity analyses will be conducted with weighted multiple imputation to assess the MAR assumption. Information on percent of questions missing and imputed will be reported for each variable as appropriate in study manuscripts. Missing items from a scale will be imputing using the other items in the scale.
c. Missed visits: When a participant missed a visit, either home or clinic or both, this was noted in the study register.

25) Additional analyses – None

26) **Harms**

i. Data safety**:**

The study team took several proactive strategies to insure the highest levels of data safety. First, data were collected on password protected tablets or laptops. Data were collected using REDCap and stored on a secure UCSF server. The data was stored in a separate folder than other study materials, and only members of the data team had access to this data. Lastly, any individual who requests study data was required to sign a data agreement which included not sharing the data as well as recommendations for data safety. No identifiers have or will be shared with external investigators.

ii. Details on how adverse events are coded or categorized:

Deaths were reported to UCSF by email within 24 hours after the PIs learned of the occurrence. Other adverse events were not reported.

Individuals were provided with information on how to contact the study staff to report adverse events associated with study participation. No adverse events were reported that were associated with study participation.

27) **Statistical software**

The following software systems will be used in the analysis of *CaRDS* data: 1) Stata SE version 14 [College Station, TX: StataCorp LP]

a. **References**

1 Gundersen C, Ziliak JP. Food Insecurity And Health Outcomes. *Health Aff* 2015; **34**: 1830–9.

2 Golovaty I, Tien PC, Price JC, Sheira L, Seligman H, Weiser SD. Food Insecurity May Be an Independent Risk Factor Associated with Nonalcoholic Fatty Liver Disease among Low-Income Adults in the United States. *J Nutr* 2020; **150**: 91–8.

3 Venci BJ, Lee S-Y. Functional limitation and chronic diseases are associated with food insecurity among U.S. adults. *Ann Epidemiol* 2018; **28**: 182–8.

4 Khariton Y, Nassif ME, Thomas L, *et al.* Health Status Disparities by Sex, Race/Ethnicity, and Socioeconomic Status in Outpatients With Heart Failure. *JACC Hear Fail* 2018; **6**: 465–73.

5 Davis AM, Vinci LM, Chase AR, Huang ES. Cardiovascular Health Disparities. A systematic Review of Health Care interventions. *Med Care Rev* 2007; **64**: 29s-100s.

6 Abshire M, Xu J, Baptiste D, *et al.* Nutritional Interventions in Heart Failure: A Systematic Review of the Literature. *J Card Fail* 2015; **21**: 989–99.

7 Gurvey J, Rand K, Daugherty S, Dinger C, Schmeling J, Laverty N. Examining Health Care Costs Among MANNA Clients and a Comparison Group. *J Prim Care Community Health* 2013; **4**: 311–7.

8 Seligman HK, Lyles C, Marshall MB, *et al.* A Pilot Food Bank Intervention Featuring Diabetes-Appropriate Food Improved Glycemic Control Among Clients In Three States. *Health Aff* 2015; **34**: 1956–63.

9 Seligman HK, Smith M, Rosenmoss S, Marshall MB, Waxman E. Comprehensive Diabetes Self-Management Support From Food Banks: A Randomized Controlled Trial. *Am J Public Health* 2018; **108**: 1227–34.

10 Seligman HK, Schillinger D. Hunger and socioeconomic disparities in chronic disease. *N Engl J Med* 2010; **363**: 6–9.

11 Palar K, Napoles T, Hufstedler LL, *et al.* Comprehensive and Medically Appropriate Food Support Is Associated with Improved HIV and Diabetes Health. *J Urban Heal* 2017; **94**: 87–99.

12 Weiser SD, Sheira LA, Palar K, *et al.* Mechanisms from Food Insecurity to Worse HIV Treatment Outcomes in US Women Living with HIV. *AIDS Patient Care STDS* 2020; **34**: 425–35.

13 Hummel SL, Karmally W, Gillespie BW, *et al.* Home-Delivered Meals Postdischarge From Heart Failure Hospitalization. *Circ Hear Fail* 2018; **11**. DOI:10.1161/CIRCHEARTFAILURE.117.004886.

Signature Page

Declaration

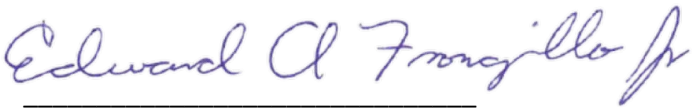
I have reviewed and agree to the Statistical Analysis Pan as presented in this document.

March 23, 2022

Rita Ngyen, Principal Investigator — Date

October 4, 2021

Kartika Palar, Principal Investigator — Date



October 3, 2021

Edward A. Frongillo, Senior Statistician — Date

29) Appendix:

Appendix 1: Description of the intervention components

i. *Medically tailored meals and groceries*:

The five-month intervention followed a tapered model: participants received 100% daily nutrition during the first and second months following discharge from the hospital, 66% daily nutrition during the third month, and 33% daily nutrition during the fourth and fifth months. The intervention was designed to provide easy-to-prepare food during the first 30 days post-discharge and to gradually incorporate items requiring more preparation over the course of the study period. All food was delivered directly to participants' homes, unless they requested pick-up instead. The tapered medically-tailored meal (MTM) plan is summarized in Figure A1.1 and described below:

a. **Month 1** (30 days, twice weekly deliveries): participants received two frozen medically tailored meals per day and supplies for daily breakfasts, including items such as milk, oats, cereal, yogurt, and fruit.
b. **Month 2** (30 days, twice weekly deliveries): participants received one frozen medically tailored meal per day; supplies for daily breakfasts, as described above; and groceries equivalent to one meal per day. Each grocery bag contained 2 protein choices, ½ dozen eggs, 2 dairy choices, 6 raw produce options, 2 bean options, and 3 grain options.
c. **Month 3** (30 days, one weekly delivery): participants received one frozen medically tailored meal per day and groceries equivalent to one meal per day, as described above.
d. **Month 4** (30 days, one weekly delivery): participants made the choice to receive either one frozen medically-tailored meal per day **or** groceries equivalent to one meal per day, as described above.
e. **Month 5** (30 days, one weekly delivery): participants received groceries equivalent to one meal per day, as described above.

Figure A1.1 - Visual Overview of Tapered MTM Intervention

Month 1	Month 2	Month 3	Month 4	Month 5
 Daily breakfast   supplies 14 frozen meals/wk	 Daily breakfast  supplies Groceries  (7 meals/wk)	 Groceries  (7 meals/wk) 7 frozen meals/wk	 Groceries (7 meals/wk)  **OR** 7 frozen meals/wk	 Groceries (7 meals/wk)

	7 frozen meals/wk			

ii. *Nutrition education*: Participants in the intervention arm received monthly nutrition education and counseling with a Registered Dietician (RD). These sessions occurred at a location of participants' choosing (presumably home) for the initial and fifth encounters and over the phone for sessions during the second, third, and fourth months of the study period. During their assessments, RDs collected the following information: three-day food log, weight as reported by participant, quality of life questions, heart failure symptom control questions, and utilization of food resources. The five-month curriculum for RD visits is summarized below in Table A1.1.

Table A1.1 - Overview of RD Nutrition Education Visits

	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5
Time point:	Within 14 days post-discharge from hospital	Between 30-60 days postdischarge	Between 60-90 days postdischarge	Between 90-120 days postdischarge	Between 120-150 days postdischarge
Location:	Participant's Home (or phone if preferred/ during COVID-19)	Phone	Phone	Phone	Participant's Home (or phone if preferred/ during COVID-19)
Visit Goals:	Instruct on how to keep a food log Review food plan for phases 1, 2, and 3 Select preferences for delivered grocery shop Review nutrition for heart failure	Check homework: review food log DASH Diet Meal pattern Instruct on fluid restriction + teach volume concepts Food Referral Chart	Follow up on food referral access- did they connect? Low Sodium diet and label reading	Navigate Eat Fresh (if internet access) or page 60, 61, 62 Recipe reading and use Provide written instruction for cooking and recipes	Shopping Skills Meal planning Cooking skills

Materials/ Recipes Covered:	Introduce education materials to be used over next visits: - Tenderloin Cooking School Book - Folder with handouts	Kitchen Basics- page 10	Spice Not Salt- page 34 Souped-up soup- page 13 ToasterRoasted Vegetables- page 41	Tuna salad with pears- page 36 Red Beans & Rice- page 37	Southwest based potatoes- page 44
Homework:	3 day food log	Try one new recipe from cookbook	Try one new recipe from cookbook	Try one new recipe from cookbook	

CaRDS RCT – CONSORT Flow Diagram

Enrollment

Assessed for eligibility (n=2996)

Excluded (n=2804)
- Not meeting inclusion criteria (n=2451)
- Discharged (n=127)
- Not interested (n=226)

Randomized (n= 192)

Reasons for early withdrawal
- 16 unable to be contacted
- 3 discharged to a facility
- 3 immediately re-hospitalized
- 1 unhoused
- 1 diagnosed with severe subaortic stenosis
- 1 insufficient cognitive capacity
- 1 withdrew consent
- 1 died immediately after randomized

Allocation

Allocated to intervention (n=106)
- 27 early withdrawals
- 79 (75%) participants enrolled

Allocated to control (n=86)
- 4 early withdrawals
- 82 (97%) participants enrolled

Reasons for early withdrawal
- 2 unable to be contacted
- 1 discharged to a facility
- 1 unhoused

Follow-Up

Reason lost to follow up after baseline
- 2 requested to stop receiving the intervention and then were LTFU
- 2 were LTFU

1-Month Visit
- 75 retained at 1-month
- 64 participants completed 1-month visit
- 4 lost to follow up

1-Month Visit
- 78 retained at 1-month
- 62 participants completed 1-month visit
- 4 lost to follow up

Reason lost to follow up after baseline
- 4 died

Reason lost to follow up after 1-month visit
- 4 died
- 1 moved
- 10 LTFU

5-Month Visit
- 60 participants completed 5-month visit
- 1 participant stopped receiving intervention after 1 month, completed 5-month visit
- 15 lost to follow up

5-Month Visit
- 59 participants completed 5-month visit
- 19 lost to follow up

Reason lost to follow up after 1-month visit
- 2 died
- 1 moved
- 16 LTFU