Supplement 2

STATISTICAL ANALYSIS PLAN

Kaiser **P**erma**n**ente Evaluation **o**f Medically Tailored Meals in Ad**u**lts with Ch**r**onic Med**i**cal Condition**s** at **H**igh Readmission Risk (***KP NOURISH***)

Study Name:	***KP NOURISH***
Study Phase:	Phase III
Indication:	Heart failure, Type 2 diabetes mellitus, chronic kidney disease
Funder:	Kaiser Permanente's National Shared Agenda Leadership Team, as part of the Bold Moves Food for Life Activation (Kaiser Permanente Community Health)
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1 Study Overview

Title	**K**aiser **P**erma**n**ente Evaluation of Medically tailored Meals in Ad**u**lts with Ch**r**onic Med**i**cal Condition**s** at **H**igh Readmission Risk
Brief Title	***KP NOURISH***
Clinical Phase	Phase III
Investigation Type	Interventional (Pragmatic)
Study Type	Prospective, virtual, remote, Electronic Health Record (EHR)-based, parallel-group, randomized, decentralized pragmatic clinical trial (PCT)
Purpose and Rationale	Adults with chronic conditions account for two-thirds of total U.S. health care expenses. Based on current trends, by 2023, chronic diseases will cost $4.2 trillion annually in treatment and lost economic output in the U.S. Addressing the social determinants of health can be an effective mechanism for reducing health care costs. Specifically, for adults with chronic illness, previous research has found a correlation between the delivery of certain types of social services and reductions in avoidable hospitalizations. Additionally, existing literature suggests that food insecurity or evidence of poor nutrition are common among individuals at the time of hospital discharge, and particularly among older adults and those with multimorbidity. These individuals may also experience other basic resource needs (inadequate or unsafe housing, transportation barriers, social isolation, etc.) that compound their difficulty in obtaining sufficient and/or nutritious food. Home-delivered meals may thus free up financial resources to address other social needs, reduce social isolation, and reduce transportation demands on the individual and their family. This is even more relevant in California given the impact of the ongoing novel coronavirus disease 2019 (Covid-19) pandemic and associated public health responses (e.g., statewide shelter in place orders enacted in early 2020) and supply chain difficulties, which have collectively introduced additional barriers to obtain healthy food, especially among at-risk individuals. Medically tailored meals (MTMs) provided for a limited time after hospital discharge may help achieve several desirable outcomes. Most directly, they may mitigate food insecurity, social isolation and nutritional deficits related to their nutrition-sensitive chronic medical condition. In turn, these effects may help vulnerable patients return to a more optimal nutritional status and clinical recovery more quickly after hospital discharge and improve patient and family satisfaction with care at home. The cost of MTMs may also offset use of acute care services (hospitalizations and emergency department [ED] visits) that could potentially be prevented after discharge from the index hospitalization. Given the increasing consideration among health insurers about providing MTMs as a benefit

	of enrollment, and recent federal Center for Medicare and Medicaid Services' guidance allowing MTMs as a supplemental benefit in selected populations, there is a pressing need to generate robust evidence about the potential efficacy of MTMs to guide health policy and health care delivery system decision-making.
Study Design	This study is a remote, decentralized, randomized PCT. We will compare outcomes in 3 groups of recently hospitalized patients with a targeted, nutrition-sensitive chronic medical condition (i.e., heart failure, diabetes mellitus or chronic kidney disease): participants receiving MTMs alone, participants receiving MTMs with remotely delivered nutritional counseling, and patients receiving usual standard of care. Participants will be recruited from Kaiser Permanente (KP) Santa Rosa, Santa Clara, Oakland, San Francisco, and San Rafael Medical Centers. The Ceres Community Project (Ceres) will provide MTMs service to patients enrolled at KP Santa Rosa and San Rafael Medical Centers and Project Open Hand (POH) will provide MTMs service to patients enrolled at KP Santa Clara, Oakland and San Francisco Medical Centers.
Intervention	MTMs (with or without remotely delivered nutritional counseling) vs. usual care
Inclusion Criteria	1. Men and women age ≥18 years at admission to the index hospitalization 2. Hospitalized at KP Santa Rosa, Santa Clara, Oakland, San Francisco, or San Rafael Medical Centers 3. Kaiser Permanente Northern California (KPNC) membership at admission to the index hospitalization 4. Has a prior history of at least one of the following conditions: a. Heart failure (defined as ≥3 prior outpatient diagnoses or ≥1 inpatient principal discharge diagnosis or heart failure on current hospital problem list with a corresponding inpatient B-type natriuretic peptide value ≥100 pg/mL) b. Diabetes mellitus (defined as ≥1 principal inpatient discharge diagnosis within 5 years or ≥2 outpatient diagnoses, excluding optometry and ophthalmology diagnoses, within 5 years or ≥2 abnormal diabetes-related lab test results on separate days within 3 years or ≥1 prescription of a diabetes medication at any time, and not meeting the following exclusions: any diabetes indicator within 8 months before to 1 month after childbirth or a diabetes therapy prescription of metformin or a thiazolidinedione within 2 years after a diagnosis of a non-diabetes metabolic or fertility issue, with no other indication of diabetes.) c. Chronic kidney disease (defined as ≥2 outpatient estimated glomerular filtration rate [eGFR] values between 30-45 ml/min/1.73 m^2 within the prior 2 years and the most recent value ≥30 ml/min/1.73 m^2) 5. Able to speak English 6. Able to provide verbal informed consent
Exclusion Criteria	1. Inability to receive meals delivered to home residence

	2. Inability to store or heat food 3. Requiring individual meal customization beyond MTMs
Primary Outcome	Occurrence of an acute hospitalization for any reasons within 90-days after discharge from the index hospitalization.
Secondary Outcomes	1. 90-day emergency department visit for any cause 2. 90-day death for any cause 3. Composite of 90-day readmission, emergency department visit, or death for any cause 4. 90-day readmission for heart failure 5. 90-day readmission for diabetes-related complication 6. 60-day readmission for any cause 7. 30-day readmission for any cause
Clinical Impact	KP is partnering with two community-based MTMs vendors to evaluate the effects of MTMs and remotely delivered nutritional counseling on various outcomes of patients with targeted nutrition-sensitive chronic medical conditions being discharged to home from KP Santa Rosa, Santa Clara, Oakland, San Francisco, and San Rafael Medical Centers in a randomized controlled trial (RCT) cohort. Due to the projected rise of Covid-19 in our patient population within KPNC and the urgency for optimizing care for our most at-risk members, there is a national KP effort to implement this study as quickly as possible.

2 Sample Size Calculation

Based on pre-pandemic data from KPNC, the 90-day regional rate of readmission for any reason for adults hospitalized with heart failure is approximately 10-15%. Using this conservative estimate of 10% for the primary outcome of all-cause readmissions among hospitalized adults with heart failure, type 2 diabetes mellitus (hereafter referred to as diabetes) and/or chronic kidney disease who are discharged home, a total sample size of 2000 (1000 assigned to MTMs, 1000 assigned to usual care) and a two-sided α=0.05 will provide 80% power to detect a hazard ratio of 0.68, corresponding to a 32% relative reduction in the risk of readmission for any cause among participants receiving MTMs versus usual care. Assuming a higher 90-day rate of 20% for a composite outcome (i.e., hospitalization, emergency department visit or death from any cause) and a two-sided α=0.05, a sample size of 2000 will have 80% power to detect a hazard ratio of 0.76, corresponding to a 24% relative reduction in the risk of this composite outcome among participants receiving MTMs versus usual care.

Comparisons in utilization and survival outcomes between participants receiving MTMs alone compared with MTMs and remotely delivered nutritional counseling are considered exploratory given the limited power to detect clinically meaningful differences. However, given the anticipated total sample sizes of 2000 (1000 assigned to MTMs, 1000 assigned to usual care) or 1000 (500 assigned to MTMs alone, 500 assigned to MTMs with remotely delivered nutritional counseling) and using a two-sided α=0.05, we will have >80% power to detect even small differences in patient reported outcomes which rely on continuous measures.

3 General analysis considerations

3.1 Analysis populations

Primary analysis population: The primary analysis population will consist of all patients who are randomized and consented to the KP NOURISH study and who survive until hospital discharge, divided into those assigned to MTMs (in addition to Usual Care) and those assigned to receive Usual Care alone. Participants will be analyzed as randomized according to the intention-to-treat principle, regardless of receipt of MTMs.

Heart failure subpopulation: The heart failure subpopulation will include all patients in the primary analysis population with pre-existing heart failure as their qualifying medical condition. This population will be analyzed as randomized (MTMs vs. Usual Care) according to the intention-to-treat principle.

Diabetes subpopulation: The diabetes subpopulation will include all patients in the primary analysis population with pre-existing diabetes mellitus as their qualifying medical condition. This population will be analyzed as randomized (MTMs vs. Usual Care) according to the intention-to-treat principle.

Patient reported outcomes subpopulation: The patient reported outcomes (PRO) subpopulation will include all participants in the primary analysis population with complete baseline and follow-up surveys and excludes participants who died or did not complete the follow-up survey. This population will be analyzed as randomized (MTMs vs. Usual Care) according to the intention to treat principle.

MTMs subpopulation: The MTMs subpopulation will include all patients in the primary analysis population who are randomized to either MTMs alone or MTMs with remotely delivered nutritional counseling. This population will be analyzed as randomized (MTMs alone vs MTMs with remotely delivered nutritional counseling) according to the intention-to-treat principle.

Heart failure MTMs subpopulation: The heart failure MTMs subpopulation will include all patients with pre-existing heart failure as their qualifying medical condition who are randomized to either MTMs alone or MTMs with remotely delivered nutritional counseling. This population will be analyzed as randomized (MTMs alone vs MTMs with remotely delivered nutritional counseling) according to the intention-to-treat principle.

Diabetes MTMs subpopulation: The diabetes MTMs subpopulation will include all patients with pre-existing diabetes as their qualifying medical condition who are randomized to either MTMs alone or MTMs with remotely delivered nutritional counseling. This population will be analyzed as randomized (MTMs alone vs MTMs with remotely delivered nutritional counseling) according to the intention-to-treat principle.

PRO MTMs subpopulation: The PRO MTMs subpopulation will include all participants who are randomized to either MTMs alone or MTMs with remotely delivered nutritional counseling that have complete baseline and follow-up surveys. This population will be analyzed as randomized

(MTMs alone vs MTMs with remotely delivered nutritional counseling) according to the intention to treat principle.

3.2 Follow-up and censoring

Participants will be followed for 90 days after discharge for all utilization outcomes and death and will be censored the end of 90 days, loss of KPNC membership or last known contact if they are lost to follow-up.

3.3 Covariates

Baseline characteristics overall and by treatment arm will be described using the list of covariates in **Table 3-1**. Balance of characteristics will be assessed using standardized differences. Given the potential unknown impact of one or more surges of Covid-19 during the enrollment and follow-up period of the study, an *a priori* decision was made to adjust for indices for acute severity of illness, predicted short-term readmission risk and multimorbidity burden as well as the presence of active Covid-19 during the index hospitalization, along with any observed additional baseline differences in participant characteristics for regression models of efficacy.

Table 3-1. List of candidate covariates.

Category	**Variables**
Demographic characteristics	Age, self-reported gender, self-reported race/ethnicity
Prior medical history	Heart failure, diabetes mellitus, chronic kidney disease, acute myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, mitral or aortic valvular disease, atrial fibrillation or flutter, ventricular tachycardia or fibrillation, ischemic stroke or transient ischemic attack, venous thromboembolism, hypertension, dyslipidemia, current smoker, hospitalized bleed, hyperthyroidism, hypothyroidism, chronic liver disease, chronic lung disease, diagnosed depression, diagnosed dementia
Pre-admission vital signs	Body mass index, systolic blood pressure
Index hospitalization characteristics	length of stay, major discharge diagnosis category (MDC) based on diagnosis-related groups (DRG), laboratory-based acute physiology score version 2.0 (LAPS 2), predicted readmission risk score, comorbidity point score version 2.5 (COPS 2.5), evidence of active Covid-19 infection
Inpatient laboratory values	Hemoglobin, serum creatinine, blood urea nitrogen

3.4 Missing data

The state-of-the-art EHR at KPNC will be used to identify all hospitalizations and emergency department visits, including any that occur at non-network hospitals given that KPNC is fiscally liable for these types of urgent or emergent resource utilization. Deaths are systematically captured through EHR data (including participant proxy reporting) complemented by external state death certificate data and Social Security Administration vital status file information, with >97% estimated capture based on prior studies involving KPNC members. In addition, all participants' medical records will be manually reviewed for the occurrence of death at the end of follow-up if the research team is unable to reach the participant or their listed secondary contact(s). Thus, it is unlikely to be missing data on clinical outcomes or that data availability will be differentially available between those assigned to MTMs or Usual Care. Participants with missing data from follow-up surveys will be excluded from analyses of patient-reported outcomes.

Missing data on covariates will be described in the baseline table and imputed for use in models, as needed. If less than 5% of covariate data are missing across all covariates of interest, then missing data will be imputed using the median value of each covariate in the full sample. If more than 5% of data are collectively missing for covariates of interest, then a multiple imputation approach will be used to impute data across all covariates.

3.5 Interim analysis

There are no planned interim analyses, and adjustments for multiple comparisons will not be performed.

3.6 Software

All analyses will be conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

4 Efficacy analyses

4.1 Primary outcome: Readmission for any cause within 90 days post-discharge

The frequency and risk with associated 95% exact (Clopper-Pearson) binomial confidence intervals (CI) for participants experiencing readmission for any cause within 90 days after discharge from the index hospitalization will be reported by treatment arm. Risk differences will be calculated along with associated Wald 95% CI. Cumulative incidence curves from the cumulative incidence function will be reported descriptively without statistical testing.

The primary measure of association will be the hazard ratio (and associated 95% CI) for MTMs vs Usual Care obtained from a Cox proportional hazards model adjusted for acute severity of illness, predicted short-term readmission risk and multimorbidity burden as well as the presence of active Covid-19 during the index hospitalization, along with any observed additional baseline differences in participant characteristics in the primary analysis population.

The subdistribution hazard ratio (95% CI) for MTMs vs Usual care obtained from Fine and Gray subdistribution hazard models adjusted for acute severity of illness, predicted short-term readmission risk and multimorbidity burden as well as the presence of active Covid-19 during the index hospitalization, along with any observed additional baseline differences in participant characteristics in the primary analysis population will also be reported to examine the effect of MTMs on the cumulative incidence of hospitalizations for any cause accounting for the potential effects of a competing risk of death.

4.2 Secondary clinical outcomes

1. 90-day emergency department visit for any cause
2. 90-day death for any cause
3. Composite of 90-day readmission, emergency department visit, or death for any cause
4. 90-day readmission for heart failure
5. 90-day readmission for diabetes-related complication
6. 60-day readmission for any cause
7. 30-day readmission for any cause

All analyses and reporting for the primary outcome described in Section 4.1 will also be conducted for all secondary clinical outcomes.

Analyses of emergency department visits, death and the composite outcome will be conducted in the primary analysis population. Analysis of hospitalization for heart failure will be conducted in the heart failure subpopulation only. Analysis of hospitalization for a diabetes-related complication will be conducted in the diabetes subpopulation only.

Subdistribution hazard ratios will not be calculated for all-cause death and the composite outcome of utilization and death, given that death is part of those outcomes.

4.3 Secondary patient-reported outcomes

The following scales will be analyzed for the targeted patient-reported outcomes:

1.) Change in perceived social isolation (Likert 1-5 scale: Never, Rarely, Sometimes, Often, Always)
   a. I feel left out.
   b. I feel that people barely know me.
   c. I feel isolated from others.
   d. I feel that people are around me but not with me.
2.) Change in perceived self-efficacy (i.e., “How confident are you that you can stick with healthful foods?” Likert 1-10 scale: ranging from Not Confident to Completely Confident)
   a. Even if you need a long time to develop necessary routines?
   b. Even if you have to try several times to make it work?
   c. Even if you have to rethink your entire way of nutrition?
   d. Even if you have to make a detailed plan?

3.) Change in perceived caring (i.e., “My current meals help to create a caring environment that helps me heal”: Likert 1-5 scale: Strongly Disagree, Disagree, Neither Agree nor Disagree, Agree, Strongly Agree)

All answers to survey questions will be reported at baseline and follow-up in the PRO subpopulation. The change in responses to each survey question will be measured as the difference in score between follow-up and baseline responses. The proportion of participants with a decrease in isolation, increase in self-efficacy, or increase in perceived caring responses from baseline to follow-up will also be reported and compared using chi-squared tests.

A difference-in-differences approach will be used to compare the change in each survey question response by assigned group. The measure of association will be the coefficient (95% CI) for MTMs vs. Usual Care in linear regression models for each change in response adjusted for baseline differences in the PRO subpopulation.

4.4 Secondary comparisons

All outcome comparisons outlined in Sections 4.1 – 4.3 will be repeated in the MTMs, heart failure MTMs, diabetes MTMs, and PRO MTMs subpopulations, as appropriate. Frequencies and risks, risk differences, hazard ratios, subdistribution hazard ratios, and linear regression coefficients will be calculated and reported comparing participants assigned to MTMs alone versus assigned to MTMs with remotely delivered nutritional counseling.