CHANGING HEALTH THROUGH FOOD SUPPORT FOR DIABETES (CHEFS-DM)

PROTOCOL AND STATISTICAL ANALYSIS PLAN

Version 2

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Table of Contents

Section 1: Administrative Information

1) Title and trial registration

a. Changing Health Through Food Support for Diabetes (CHEFS-DM)
b. Trial registration number: NCT04959487

2) Protocol/SAP version number with dates

a. Version 2 –02/05/2025
b. Version 1 – 07/08/2021

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

a. Kartika Palar—CHEFS-DM study MPI. University of California, San Francisco.
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c. Edward A. Frongillo, Jr., PhD—Senior statistician. University of South Carolina, Columbia.
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4) Signatures

a. Multiple-PIs
b. Senior statistician

Section 2: Introduction

1) Background and rationale

Type 2 diabetes mellitus (T2DM) affects 29.1 million persons in the United States (US),[1] disproportionately impacting low-income communities.[2] Forty million people in the US are also food insecure.[3] Food insecurity – defined as limited or uncertain access to safe, nutritious food– is strongly associated with T2DM[4] acquisition, and among people with T2DM, poor glycemic control.[5,6] In 2017, 49 million Americans were food-insecure.[3]

Food insecurity contributes to increased T2DM-related morbidity and mortality through nutritional (poor diet quality, obesity), mental health (stress, depression), and behavioral pathways (non-adherence, missed clinic visits).[7-10] Food-insecure households often cope with inadequate food budgets by purchasing cheap, energy-dense foods,[11,12] which are typically suboptimal for glycemic control.[13,14] They often also live in neighborhoods with poor access to healthy foods (ex: fruits & vegetables).[15] Together, these factors contribute to poor diet quality among food-insecure individuals, leading to worse outcomes for T2DM and other chronic illnesses. Existing nutrition safety-net resources are inadequate to address the health effects of food insecurity. Half of all CalFresh enrollees (California's "Food Stamps") continue to be food insecure, and 40% of food-insecure households receive no government aid at all.[16] While 13% of Americans rely on community food programs, these programs seldom provide medically tailored diets. Policy makers increasingly recognize the premise that "Food is Medicine" (FIM), i.e., medically tailored food for chronically ill, food-insecure people, can play a critical role in achieving optimal health outcomes. As the evidence mounts that FIM may also save significant healthcare dollars,[17,18] a growing number of programs seek to incorporate medically tailored food support into the healthcare system.[19] Yet the evidence for the efficacy of FIM programs is nascent and significant gaps remain. There is an urgent need to develop, implement, and evaluate novel strategies to reach food-insecure individuals with T2DM to improve diabetes outcomes and reduce disparities.

Partnering with Project Open Hand (POH), a non-profit organization, that provides food support to San Francisco's and Oakland's most vulnerable residents with chronic illness, a pragmatic randomized controlled trial (RCT) of Changing Health through Food Support for Diabetes (CHEFS-DM) will be conducted. The study consists in a 6-month intervention providing supplemental food support meeting ~75% of daily energy requirements via a DM-tailored diet, and DM-focused nutritional education provided by POH registered dieticians (two sessions of individual counseling and four session of in-group diabetes-tailored nutrition education sessions). This RCT follows a pilot study in which the intervention was feasible, acceptable, and associated

with improvements in food security, diet quality, health behaviors, mental health, and trends towards improvements in acute care use, and clinical indicators.[20,21]

2) Objectives

Aim 1: To determine the impact of CHEFS-DM on glycemic control and other cardiometabolic outcomes. The hypothesis is that CHEFS-DM will improve hemoglobin A1c (primary outcome), dyslipidemia, and health-related quality of life (HRQoL); blood pressure (BP) and acute care utilization; and improve diabetes medication adherence (secondary outcomes). Participants will be randomized to intervention versus control.. Data collection will include surveys, anthropometry, 24-hour dietary recalls, BP measures, medical record review, and blood draws. Characteristics of those most likely to benefit from CHEFS-DM will be described (e.g., poor T2DM control, gender).

Aim 2: To determine the impact of CHEFS-DM on intermediate outcomes that may mediate any impact of CHEFS-DM on T2DM health. Using our novel conceptual model, the hypothesis is that that CHEFS-DM will improve food insecurity (proximal intermediate outcome) which in turn will lead to improvements in nutritional (e.g., improved diet, body mass index), mental health (e.g., less diabetes distress, depression), and behavioral (e.g. improved medication adherence, diabetes self-management, and clinic attendance) paths (distal intermediate outcomes). Together these will improve T2DM control, cardiometabolic health, and HRQoL. Identifying the predominant causal paths will enable to further tailor the program to enhance impact during future implementation.

Aim 3. To determine the cost-effectiveness and sustainability of CHEFS-DM and obtain information to inform scale-up. a) The cost per quality-adjusted life year gained will be calculated; b) Whether any improvements in the intervention arm were sustained over 12 months of follow-up will be assessed; and c) A process evaluation will be performed, collecting qualitative and quantitative data with study participants and staff to determine what worked and did not work to guide future intervention scale-up efforts. The hypothesis is that the intervention may be cost-effective and possibly cost saving, and that health benefits will be sustained at 12 months.

Section 3: Study Methods

1) Trial design

A pragmatic RCT will be conducted to test the efficacy of CHEFS-DM, a six-month multicomponent food and nutrition intervention among low-income adults with T2DM, on diabetes health. Participants will be randomized 1:1 to the intervention, using a parallel design.

2) **Intervention description**

Diabetes-tailored food support. The intervention group will receive six months of supplemental food support meeting on average 75% of their daily energy requirements in the form of a T2DM-tailored diet. POH staff will administer the intervention. Food support will consist of a mix of meals tailored for T2DM, and T2DM-healthy groceries, consistent with the American Diabetes Association (ADA) guidelines. Meals will be tailored to many common food preferences of the clients (e.g., vegetarian, pescatarian, no fish, low salt). Meals may be picked up at one of two fixed POH locations, at a POH mobile site (i.e., van that provides POH resources to neighborhoods without easy access to their locations with 3 locations in San Francisco and 1 location in Alameda County), or home-delivered for non-mobile individuals. POH will offer the option of food delivery to all participants during the coronavirus pandemic as needed to comply with changing COVID guidelines and as requested by participants because of the coronavirus pandemic. Mobile site hours may be limited due to the COVID pandemic.

Nutritional counseling and education. A registered dietitian from POH will meet with intervention participants individually two times (at baseline and month 5-6) for a 1-hour nutritional counseling support session. In addition, a registered dietitian from POH will conduct group-based nutrition education over four 1-hour-long sessions. The group-based session nutrition education will be consistent with published diabetes self-management education principles utilizing strategies shown effective in lower-income, lower-literacy populations. Nutrition education topics will include how to utilize and prepare POH food, understanding the role of diet and nutrition in T2DM health and management, strategies to shop for and prepare diabetes-healthy meals, reading nutrition labels, support and self- efficacy around maintaining a diabetes-healthy diet, reducing sedentary activity, and increasing physical activity including

aerobic exercise and strength training. POH will implement use of technology such as Zoom to conduct group class sessions as needed during the COVID-19 pandemic to be compliant with UCSF guidelines. Class sessions will be held in person, as originally planned, when it is safe and acceptable to do so, and remote options will continue to be available after the COVID-19 pandemic to improve accessibility.
Control condition. Control participants will receive the standard of care as offered by clinical partners to al T2DM participants, including referral to nutritional counseling, T2DM support groups, and participation to local diabetes self-management programs. Control participants are also often provided referral information for locally available food support services in the region that provide diabetes-appropriate foods. After 6-months, the control arm will have the opportunity to receive diabetes-tailored food support from POH along with nutritional counseling, regardless of whether they meet regular POH eligibility criteria. The services that the control group will after the six-month period will be similar to what the intervention group receives during the intensive CHEFS-DM intervention - 6-months of food sufficient to meet 67% of their daily requirements, video recordings of the 4 CHEFS- DM intervention nutrition education classes and access to a POH RD at their request.
Given that POH could not easily absorb a large number of additional new clients in a relatively short time frame, the wait time is also in line with programmatic considerations.

5) Data collection

Follow-up will be broken up into two phases. From baseline to six months, the CHEFS-DM intervention will be implemented, and researchers will follow both intervention and control arm participants (n=281 (actual)). After the end of the six-month follow-up, the intervention arm will transition to receiving standard POH services (comprising 33% to 67% of daily energy requirements depending on health status), and will be followed for an additional six months, to assess the extent to which any health benefits are sustained at 12 months (n=156). Hence, control arm will be followed for 6 months and participate in two assessments, and the intervention arm will be followed for 12 months and participate in three assessments.

At baseline and 6 months for all participants and at 12 months for intervention arm, the following data will be collected:

a) Structured interviews (baseline, 6 and 12 months). Trained UCSF research assistants (RAs), including Spanish/English bilingual RAs, will administer the structured interview either in person or over the phone and/or zoom, depending on public health protocols and acceptability of in-person visits to participants due to COVID-19. When visits are conducted in-person, interviews will take place in private offices at POH, in a private room at a partner clinic (if available), in a private location at a community space (e.g. library, community center), or at a private location of the participants choosing (e. g. home visit).

The content of the interviews will cover:

- Socio-demographic information.
- Food insecurity and diet quality
- Physical activity
- Mental health (e.g., depressive symptoms, diabetes distress and social support, self- efficacy for following T2DM recommendations).
- Adherence to T2DM medications.
- Health care utilization (e.g., missed clinic visits, acute care use (hospitalizations and emergency department visits).
- Health-related quality of life.
- Medication inventory (for cardiometabolic conditions only).
- Diabetes co-morbidities (e.g. nephropathy, retinopathy).
- Economic information (e.g. economic impacts of COVID-19, household expenditures on food).
- In addition, at 6-month follow-up, the structured interview will also include questions to assess participant costs related to the intervention (e.g. transportation), food utilization (e.g. sharing, waste), barriers to intervention use, and program satisfaction among intervention participants, and use of free food resources (not including POH) among control and intervention participants.

b) Anthropometric assessments (baseline and 6 months). Anthropometry will be assessed by trained UCSF RAs at the same time as the structured interview, except when interviews are conducted by phone due to COVID. During COVID, UCSF staff may schedule anthropometric assessments separately from structured interviews to reduce exposure between staff and participants and will follow COVID safety guidelines for research (e.g. using personal protective equipment). UCSF RAs trained by clinicians in anthropometry will

obtain three repeated measurements of weight (kg), height (cm), and waist and hip

circumferences (cm). Tanita WB-800H portable digital scales will be used to measure the weight, SECA-213 stadiometer will be used to measure the height. For wheelchair-bound individuals RA will conduct anthropometry at a clinic with a wheelchair-accessible scale and stadiometer. At baseline and six months, all participants will undergo anthropometry

c) Blood pressure assessments (baseline and 6 months). Blood pressure (BP) will be assessed by trained UCSF RAs at the same time as the anthropometry. BP will be measured using the Omron HEM 907XL IntelliSense Professional Digital Blood Pressure Monitor. Three blood pressure measurements will be taken after three to five minutes of inactivity and averaged to obtain a more accurate measure. At baseline and six months, all participants will undergo blood pressure measurements; at twelve months, blood pressure will be assessed in the intervention arm only.

d) Blood draws (baseline, 6, and 12 months): Participants will undergo a blood draw (testing a lipid panel, and HemoglobinA1c) at one of 28 Quest Diagnostics labs in San Francisco or Alameda counties Phlebotomy will be performed using universal precautions. Date and time of phlebotomy, and specimen number will be recorded in a participant log. Specimens will be aliquoted and stored at –70°C using standard universal precautions. Data will be received from Quest Diagnostics in the form of a spreadsheet which can be easily merged with other study data by participant ID or will be accessed by UCSF staff using the secure Quest Diagnostics HIPPA-compliant online portal. At baseline and six months, all participants will undergo the blood draw; at twelve months, the blood draw will be implemented in the intervention arm only.

e) 24-hour Dietary Recall (baseline and 6 months). Dietary intake will be assessed via 24-hour dietary recalls by UCSF RA trained by registered dietitians using the National Cancer Institute's Automated Self- Administered 24-hour Dietary Recall (ASA24). Participants will complete two unannounced recalls (one weekday and one weekend day) during a one-week period. In total, participants will complete four recalls: 2 at baseline and 2 at 6-month follow- up. RA's will inform the participant of which week the calls will be attempted. Previous work

has indicated that lower income or older adults may need additional assistance with completing the ASA24, therefore the questions will be administered over the phone or in person (if COVID permits), using strategies to ensure the collection of dietary data is accurate and does not burden the participant. The 24-hour dietary recall will be conducted at baseline and six-month follow up.

f) Medical record review (baseline, 6, and 12 months). Medical records will be used

during recruitment to confirm T2DM diagnosis, to confirm participant HbA1c, preferentially greater than or equal to 6.5%, and to determine whether a patient has controlled or uncontrolled T2DM using latest HbA1C test result. Medical record review is also being used to collect follow-up HbA1c data if completing a blood draw is not possible during follow-up, if medical record A1c is available within the assessment time frame, and with the consent of the participant.

g) Qualitative interviews. In-depth, semi-structured interviews of 60-90 minutes will be conducted by UCSF RAs with up to 40 participants, including both completers and non- completers of the intervention. Most of these interviews will occur after the 6-month intensive phase of the intervention, with approximately 10 interviews at the end of 12 months. UCSF RAs will also interview up to 20 key informants including POH staff, study personnel, and clinicians from safety net clinics. Interviews will focus on mechanisms underlying program impacts, including possible nutritional, behavioral and mental health pathways. Other topics that will be asked during the interview are related to factors affecting program adherence and satisfaction, strengths and limitations of the CHEFS-DM intervention, barriers and facilitators to program participation, and suggestions for scale-up. The 12-month interviews will provide insight on experiences with transitioning to POH regular programming, and issues related to sustainability of any perceived impacts. Interviews will be conducted in English or Spanish by bilingual UCSF RAs, audio-recorded, and transcribed in the original language. The interviews will be conducted either over the phone and/or zoom or in-person, if able to do so per COVID-19 guidelines and based on the acceptability of meeting in-person among participants.

h) Administrative records from POH. POH will provide the following information:
   - Intervention costs incurred by POH. POH will provide administrative records of program expenditures to track all intervention costs, excluding research costs. These costs come from goods (the food and packaging), personnel, and fixed infrastructure and overhead.
   - Records of pick-up and/or receipt of delivered food. POH will provide administrative records of weekly pick-up and/or delivered food for each participant.

4) Randomization

281 participants were randomized 1:1 to the intervention and control arms,

stratified by county (San Francisco vs. Alameda County) and poor diabetes control (A1c < 9%, vs. ≥ 9%). Details of the randomization and stratification method is stored securely in REDCap. Randomization based on a computer-generated assignment will occur after the participant has provided informed consent and completed baseline assessments.

5) Sample size

The sample size was determined based on power calculations on our primary outcome (HbA1c) and estimated attrition based on our previous studies in this population. Power calculations were based on standard deviations (SD) for changes in baseline to follow-up from our prior pilot study and assumed 80% power for a one-sided test at alpha of 0.05 corresponding to our hypothesis that the intervention would improve glycemic control and other outcomes. With the outcome of change in percent HbA1c from baseline to follow-up, using a SD of the change of 1.3937 for a minimum important difference of 0.5 in the change, the sample size needed is n=196 (n=98 in each of the two study arms). This sample size also provides 80% power for differences between arms in change in change in diabetes distress of 0.256 points, change in food insecurity of 1.3 points, and proportion at follow-up of 0.16 (e.g., 0.36 vs. 0.20) or greater for any binary outcome such hospitalization or emergency department visit. Anticipating attrition of 20%, the total sample size needed at recruitment would be at least 245. To be conservative, we enrolled 281 participants to account for the possibility of higher attrition than anticipated.

6) Framework

The superiority hypothesis testing framework will be used, testing whether exposure to the intervention results in better outcomes than exposure to the control arm. Comparisons will be presented as differences between arms in changes in outcomes from baseline to endline.

7) 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

8) **Timing of final analyses**

Analysis is planned to begin in March 2025 upon completion of all field data collection in February 2025, when the 6-month follow-up of all participants is done. Analysis to evaluate the durability of the intervention will be commence after the end of 12-months of follow-up of the intervention arm (July 2025).

7) **Timing of outcome assessments**

Research staff will administer surveys, dietary recall, anthropometric evaluations, and blood draw at baseline and at 6 months in both study groups. Additional evaluations will be done only in the intervention arm at 12 months. Data will be collected within a window period around each data collection time point of up to 2 months.

Section 4: Statistical Principles

1) Confidence intervals and P Values

a. **Level of statistical significance.** No significance testing will be conducted unless required by a journal. We will report 95% confidence intervals and exact p-values (or $p<0.001$).
b. **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.
c. **Confidence intervals to be reported.** 95% confidence intervals will be reported alongside exact p-values.

2) **Adherence and protocol deviations**

a. Definition of exposure to the intervention and how this is assessed including extent of exposure:

Adherence to the intervention will be assessed through the following mechanisms:

i. Counseling: Attends at least the first individual counseling session (out of 2)
ii. Group education: Attends at least 50% of group education sessions (2 out of 4).
iii. Food: Receive at least 60% of weekly food allotment.

b. Description of how adherence to the intervention will be presented – We will Adherence to the intervention will be presented through a brief description in

the narrative summarizing the percent of weekly engagement with food deliveries/pickups,
% of food allotments received, and % of food reported eaten, as well as % of counseling sessions and education sessions attended.

c. **Protocol deviation.** The following are pre-defined minor protocol violations:

    i. Participants that for any reason are not seen within the visit window (up to two months later).

    ii. Investigators miss giving a questionnaire or a section of the questionnaire to the participant, including the dietary recall questionnaire.

    iii. Investigators miss recording or performing any anthropometric / blood pressure evaluations or blood draw or done outside of visit window.

The following are pre-defined major protocol violations:

i. Participants that are mistakenly enrolled in the study without meeting the inclusion criteria.

ii. Participants in the control arm receiving meals or groceries from Project Open Hand during the active intervention period (baseline to 6 months).

iii. Participants for whom informed consent was not obtained prior to any study- specific tests/procedures.

iv. Lapse in study approval

The number (and percentage) of participants with major and minor protocol deviations will be summarized by arm with details of type of deviation provided. The participants that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3) Analysis populations.

a. **Intention-to-treat.** The primary analysis will be intent to treat (ITT). The ITT analysis will include all participants in both arms who were enrolled and completed all baseline assessments, regardless of if they received the

intervention or not.

b. **Per protocol.** A secondary analysis will be per-protocol, including control participants with baseline and follow-up evaluations who did not have any major protocol violations, and intervention participants with baseline and follow-up evaluations who adhered to the intervention (i.e., attended at least the first individual counselling session, 2 out of 4 group education sessions, and received at least 60% of weekly food allotment), and no major protocol violations.

Section 5: Trial Population

1) **Screening Data**

a. Participants will be recruited primarily from safety-net clinics serving low-income individuals in geographic areas of San Francisco and Alameda County.

b. Participants will be recruited through community clinics in one of following ways: 1) Providers and staff at the clinic will refer adults with T2DM confirmed with medical or laboratory records to the CHEFS-DM study using an outreach script provided by research staff; 2) Recruitment flyers will be posted in clinics and waiting areas and at various community sites such as senior centers; individuals with T2DM can then contact the study coordinator directly through the contact information listed on the flyers; 3) research staff will be available in clinic to discuss the study opportunity with patients and conduct eligibility screening. . Research staff will then conduct phone outreach to assess for eligibility and interest in participating.

UCSF will screen patients either over the phone or in-person for eligibility based on study inclusion and exclusion criteria using the study recruitment script and by reviewing the diabetes diagnosis, HbA1c test date and result provided by a study clinic or managed health care plan partner, and by noting whether the individual is a current or past Project Open Hand client.

A summary will be provided indicating the number of participants screened, number of participants eligible, number of participants not eligible and reason for non-eligibility, number of participants enrolled, number of participants not enrolled and the reason for non-enrollment, and the number of participants randomized. This summary will be provided overall, and by location (i.e., San Francisco or Alameda county).

2) **Eligibility** – summary of eligibility

criteria Inclusion Criteria:

1. Confirmed diagnosis of T2DM confirmed by medical or laboratory records. For T2DM, the criteria (from the American Diabetes Association) are glycated hemoglobin (HbA1c) ≥6.5%, or fasting plasma glucose of ≥126, or a 2-hour plasma glucose level of 200 or higher during a 75 g oral glucose tolerance test, or a random plasma glucose of 200 or higher in patients with symptoms of hyperglycemia.
2. Age ≥18 years.
3. Screening positive for food insecurity (at least one positive question) in the previous 6 months assessed using the 6-item version of the US Household Food Security Survey Module (US Department of Agriculture) or has household income <200% of the federal poverty level.
4. English or Spanish language fluency.
5. Adequate cognitive and hearing capacity to consent and complete study measures.
6. Reside in Alameda County or San Francisco County.

Exclusion Criteria:

1. Type-1 diabetes mellitus
2. Individuals with disorders known to affect the accuracy of the HbA1c measure (e.g., end stage renal disease and individuals with known hemoglobinopathies).
3. Inability to attend the educational workshops.
4. Inability to schedule baseline assessments and/or blood draw after repeated requests.
5. Pregnant individuals, or individuals planning to get pregnant within 6 months, or are lactating, or are postpartum less than 6 months.
6. Current POH clients, past POH clients who stopped services less than 6 months prior, or past or present participants in other POH medically tailored meals studies.
7. Does not have access to food storage, including a refrigerator and freezer to safely keep food.
8. Does not have access to facilities to reheat and prepare meals using

Project Open Hand food.

9. Anticipates moving out of study area of Alameda and San Francisco Counties in the next 6 months.
10. Receives more than 1 meal per day from a free food support resource or agency.
11. Allergic to or will not eat eggs, soy, wheat, nuts, seeds or seed oils, or other foods commonly included among ingredients in POH meals.
12. Allergic to dairy products, or unable to tolerate any dairy products including milk, yogurt, and cheese.
13. Individual does not eat any or all of POH's meat meal options and will not eat the vegetarian POH meal option.

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

a. Assessed for eligibility at screening
    i. Eligible at screening
    ii. Non eligible at screening, and reasons why were not eligible

b. Eligible and randomized
    i. Eligible and randomized
    ii. Eligible but non-randomized, and reason

c. Lost to follow up at six months, and reason

d. Lost to follow up at twelve months (intervention arm), and reason

e. Discontinued the intervention, and reason

f. Randomized and included in primary analysis

g. Randomized and excluded from the primary analysis, (if any), and reason.

4) **Withdrawal/follow-up**

Reasons and details of withdrawal at 6 months for both arms, and at 12 months for intervention arm will be reported. This information will be summarized in the CONSORT flow diagram. In addition, the numbers of losses to follow up will be summarized by treatment arm.

5) **Baseline patient characteristics**.

a. **List of baseline characteristics to be summarized.** Sociodemographic and clinical characteristics at baseline overall and by study arm will be described.

These characteristics includes age, sex, household size, educational attainment, income, housing situation, relationship status, language(s) spoken, household food insecurity, employment status, health-related quality of life, health care utilization, mental health (depressive symptoms score, diabetes distress scale, behavioral (diabetes medication adherence, diabetes self-management, clinic attendance, diet quality, substance use), and clinical outcomes at baseline (HbA1c, blood pressure, BMI, cholesterol).

b. **Details of how baseline characteristics will be descriptively summarized**. Categorical variables will be presented as numbers and percentages. Continuous variables will be summarized by mean and SD for variables with normal distribution, and by median and IQR if data are skewed. Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be performed for baseline characteristics.

Section 6: Analysis

1) **Outcome definitions**

Primary Outcome Measures:

1. Hemoglobin A1c. At baseline and six months, all participants will undergo the blood draw; at twelve months, the blood draw will be implemented in the intervention arm only. The change on HbA1c from baseline to six months by study arm will be reported.
2. Food security. Food insecurity will be measured with the adult version of the USDA Household Food Security Survey Module (HFSSM), validated in many populations. The score ranges from 0 to 10 . Higher scores indicates higher severity of food insecurity. The change in the food insecurity scores from baseline to six months by study arms will be reported.

Secondary Outcome Measures:

1. Glucose control. The change in the proportion of participants with glucose control, defined as HbA1c <9%, from baseline to six months by study arms will be reported.
2. Low food security. Food security as a binary response will be assessed, identifying a participant having low or very low food security or food security (food security or marginal food secure) by study arm.

3. Systolic and diastolic blood pressure. Changes in the average of three repeated measurements of systolic and diastolic blood pressure (mmHg) from baseline to six months by study arm will be reported.
4. 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. The change in medication adherence (percentage points) from baseline to six months between intervention and control arms will be reported.
5. Acute care utilization. Information on acute care utilization (emergency department and urgent care) by self-report and/or medical record review will be collected. The proportion of participants that used acute health care from baseline to six months by study arm will be reported.
6. Hospitalization. Information on hospital admissions will be collected by self-report and/or medical record review. The proportion of participants with at least one event of hospitalization will be reported by study arm.
7. Missed outpatient visits. Information on missed outpatient visits will be collected by self-report and/or medical record review. The proportion of participants that missed at least one outpatient visits from baseline to six months will be reported.
8. Health-related quality of life (HRQL). The standardized 12-item short form health survey will be used to measure the HRQL. The SF-12v2 provides a summary score for physical and mental health. The transformed *T* score has a mean=50 and SD=10, in which higher values means better health. The change in SF-12 *T* scores from baseline to six months by study arm will be reported
9. Body Mass Index (BMI). The average of three repeated measurements of weight and height will be obtained at baseline and at six months. The BMI will be calculated (weight (kg)/ (height (m)^2). Changes in in BMI values (kg/ m^2) from baseline to six months by study arm will be reported.
10. Diet quality. Dietary information using an automated self- administered 24-hour dietary recall instrument from the National Cancer Institute's (ASA24) will be collected. The HEI-2015 is a measure of diet quality which evaluates how well the food consumed aligns with the Dietary guidelines for American population. The HEI-2015 score ranges from 0-100 in which a higher

    score indicates better diet quality. The adequacy component of the HEI ranges from 0-60 and the moderation component ranges from 0-40 (both with higher score indicating better diet quality). Changes in the adequacy and moderation HEI-2015 scores from baseline to

six months by study arm will be reported.

11. 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 six months among by study arms will be reported.
12. Diabetes distress scale. The diabetes distress scale (DDS) has 17 items measuring frustration, anger, and discouragement associated with managing complex diabetes healthcare directives. The DDS score ranges from 1 to 6, with higher scores indicating higher levels of distress. The change in diabetes distress scores from baseline to six months by study arms will be reported.
13. Diabetes self-efficacy. The 8-item Perceived Diabetes Self-Management (PDSM) scale, which assesses confidence in one's ability to manage numerous self-care behaviors, including diet and glucose management will be used. The PDSM scores ranges from 8 to 40, with higher scores indicating more confidence in self-managing their diabetes. The changes in the PDSM scores from baseline to six months by study arm will be reported.

2) **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, the Rubin causal model (e.g., propensity scores, double- robust estimation) will be used to obtain the desired marginal effect estimates under the counterfactual assumption of balanced arm. Although the computerized data collection protocol and the presence of an interviewer should minimize missing data, 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. Validity and reliability of scale constructs via confirmatory factor analysis and internal consistency will be verified.

Analyses for Aim 1 (Diabetes and other clinical health outcomes): The intervention is intended to improve clinical outcomes suggested by our intervention model. Specifically, the hypothesis is that the CHEFS-DM intervention will lead to improved (i.e., lower) mean HbA1c (primary outcome). For the primary analysis,

an intent-to-treat analysis of covariance will be done using the Stata regress and/or sem procedure with the primary outcome being changes from baseline to six months. The data for this analysis will be constructed in wide form, i.e., with an individual being a row in the data and the columns being the variables from both baseline and six months. The model will regress the change in an outcome variable on the baseline value of that outcome and arm (intervention or control). The model will be estimated by least-squares when using the regress procedure. Additional analyses will be done to a) 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); and b) adjust for medication use. If covariates have missing data, the sem procedure will be used with full information maximum likelihood to incorporate all covariate data under the assumption that missingness is at random.

For a secondary analysis, an intent-to-treat analysis will be performed using the Stata mixed procedure assessing whether the intervention resulted in differentially improved changes from baseline to six months in the primary outcome. The model will specify mixed (i.e., fixed and random) effects, be estimated by maximum likelihood, use all the longitudinal data, and account for variability among and within and individuals using an exchangeable covariance structure. The fixed effects specified will be arm (intervention or control), visit (baseline or six months), and their interaction as a product term. The random effect will be individuals. The model is equivalent to a repeated-measures or differences-indifferences model. A fully fixed- effects model (with individuals as a fixed rather than random effect) will be examined as a robustness check.

Similar analyses will be done for the secondary outcomes using linear or logistic models as appropriate. For primary and secondary outcomes, Box-Cox transformations will be used to correct for skewness if needed.

b. **Analyses for Aim 2 (intermediate outcomes and mediation):**
The hypothesis is that the intervention will improve food insecurity (proximal intermediate outcome) and in turn nutrition (e.g., improved diet quality, BMI), mental health (e.g., less diabetes distress, depression) and health behaviors (e.g., medication adherence, diabetes self-management, clinic attendance) (distal intermediate outcomes) as suggested by our conceptual framework.

As described in Aim 1, analyses will be done for the intermediate outcomes using an analysis of covariance with linear or logistic models as appropriate. Statistical mediation from the intervention to the primary and secondary outcomes by the intermediate outcomes will be assessed first with the Stata sem procedure using traditional path analytic methods, testing for possible interactions between exposure (i.e., arm) and mediators, and then with Mplus using the causal inference method of Valeri and Vanderweele, which yields optimal estimates of indirect effects in the presence of non-continuous outcomes, interactions, and clustered data.

c. **Analyses for Aim 3 (cost-effectiveness analysis and process evaluation).** To understand the relative value of CHEFS-DM in comparison to other health interventions, the incremental CE ratio (ICER) will be computed, defined by the difference in the per-capita intervention cost divided by the difference in the average intervention effectiveness. The cost-effectiveness ratio is given by ICER= (μT-μC)/ (δT-δC), where μT is the per-capita cost of the treatment, μC is the per- capita cost of the control, δT is the health status of the treatment, and δC is the same measure for participants in the control group. To account for uncertainties in costs or effectiveness, estimates across a range of assumptions regarding future costs and health effects will be computed. Confidence intervals for the ICER measures will be calculated using bootstrap methods. In terms of timeframe, the cost savings and health improvements at 6 and 12 months through direct measurement will be estimated. Additional analyses will be considered extrapolating cost savings to future periods under different assumptions of how long those changes last and impacts informed by the literature (e.g. the reduction in DM complications attributable to improved glycemic control).

Regarding process evaluation, a concurrent triangulation mixed methods process evaluation will be performed. Quantitative process evaluation data (structured interview and administrative data) and qualitative data (interviews and weekly team meetings) will be analyzed separately and then compared to cross-validate findings and generate lessons learned. Qualitative data analysis will be performed using content coding procedures to identify key themes using Dedoose software. Emergent themes will be identified and coded inductively. Coding consensus will be considered when transcripts achieve ≥90 percent coder agreement.

3) Sensitivity analysis

a. No sensitivity analyses will be done beyond those described above.

4) Subgroup analysis

a. 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 East Bay versus San Francisco, sex, race/ethnicity, food insecurity, poor T2DM control (A1c≥ 9), and insulin use.

5) Missing data

The study will use several strategies to account for and address missing data. Missing data will be categorized into missed individual questions and missed visits.

a. Missed individual questions: If needed, multiple imputation will be used to address incomplete data under the weak assumption that incomplete data arise from a conditionally missing-at random mechanism (MAR) rather than the missing-completely-at-random process assumed by ad hoc methods such as listwise deletion. 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.
b. Missed visits: When a participant misses a visit, this will be noted in the study register, and no data will be imputed for this participant for that visit.

6) **Additional analyses**

a) **Durability of health benefits:** To assess whether any improvements in primary, secondary, and intermediate outcomes were sustained in the intervention arm, researchers will estimate effects of the intervention on outcomes measured at 12 months. We will specifically assess the durability of HbA1c values and of the food security score from six months to twelve months in the intervention arm. For the intervention arm only, mixed models specifying two visit fixed effects will be used, one for differences between baseline and six months and one specifying differences between six and 12 months. The random effect will be individuals.

7) **Harms** Research will be conducted according to Good Clinical Practice guidelines, the

U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards), and the Declaration of Helsinki.

a) **Data safety:** Participant confidentiality will be prioritized following strict guidelines on privacy. For the proposed study, all data will be collected in private and be handled as confidentially as possible within the law. For interviews, anthropometric and blood pressure assessments, 24-hour dietary recall, and medical record and laboratory data collected as part of the study, participants will be assigned a unique study identification number, and the participant's name or other public identifiers (e.g., phone number, address) will not be included with any data. All consent and other material with personal identifiers (e.g., recruitment and follow-up tracking documents) will be kept separately from all data sources. The project manager will keep consent materials in a locked cabinet in a locked office and/or in a password protected file on an encrypted computer. Research assistants and support staff will be trained on procedures for maintaining privacy and will sign a pledge of confidentiality. All electronic records (computer, online, audio-recorder) will be password protected and encrypted to prohibit illicit access. When these procedures are followed, it is highly unlikely that any information revealed by participants during the study will be disclosed to the analyst or anyone outside the research team.

b) **Adverse events**. The co-PIs will report all serious events and problems having to do with participant safety to UCSF's Human Research Protection Program within ten working days. All serious adverse events and events associated with the study participation will be reported in writing. Drs. Weiser and Palar will annually provide a discussion of any problems noticed during the previous year of the study to the UCSF Human Research Protection Program during the annual review. Participants will be provided with information on how to contact the study staff to report serious adverse events and adverse events associated with study participation. Field staff will be trained to collect information about serious adverse events that will be sent to the study principal investigators. All serious adverse events related to the study, will be reported by arm. No formal statistical analysis will be done.

8) Statistical software

The following software systems will be used in the analysis: 1) SAS 9.4; 2) Stata SE version 14 [College Station, TX: StataCorp LP]; Stat Transfer 14. 3) Mplus V 8.6. 4) R version 4.4.1 (2024-06-14 ucrt)

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Section 7: Changes from previous Protocol/SAP version

Protocol/SAP Version 2 changes: This version of the Protocol/SAP includes several changes to the trial approved by NIH (January 2024) and the UCSF IRB since the initial Protocol/SAP (Version 1) was registered.

- Sample size change: Our original proposed sample size was n=440 (n=220 in each arm). Given challenges with recruitment during and after the COVID pandemic, we re-calculated the sample size using updated power calculations with early data from the trial for the standard deviation in HbA1c and assuming 80% power for a one-sided test at alpha of 0.05 rather than 90%. Our new minimum sample size was calculated as n=246 (n=123 in each arm). As recruitment has ended as of June 2024, the final actual sample size is n=281 (n=156 in intervention and n=125 in control).
- Reduced measures: To reduce participant and staff burden, we reduced the number of measures and procedures. The changes included:
    - Removed fasting requirement and therefore fasting glucose and fasting lipids (still measuring non-fasting lipids)
    - Removed the following scales or measures at all time points:
        - Anxiety
        - Physical activity
        - Social support
        - Select items on economic status
        - Waist and hip circumference
    - Reduced the following scales or measures at all time points:
        - Reduced food security scale to retain adult items only
    - Removed the following measures at 12 months only
        - Weight
        - Blood pressure
- Medical record review: Allowed using an A1c from the medical record *if* blood draw was not possible at follow-up, if medical record A1c is available within the assessment time frame, and with the consent of the participant. We are not collecting medical record information on healthcare utilization and medications as this was not possible given the final sample was recruited from across the community and a wide array of healthcare settings/systems with variable payers.
- Statistical model: Our primary analysis will employ analysis of covariance rather than mixed effects (mixed effects will be employed as a secondary analysis).

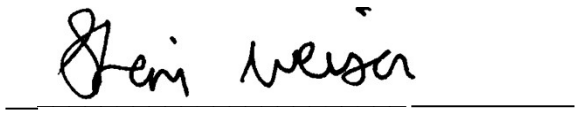
Signature Page

Declaration

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

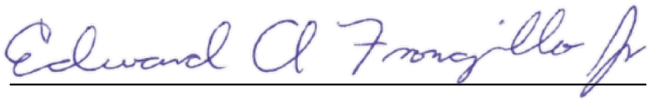
February 5, 2025

Kartika Palar, Principal Investigator Date



February 5, 2025

Sheri D. Weiser, Principal Investigator Date



February 5, 2025

Edward A. Frongillo, Senior Statistician Date