GOFRESH

STATISTICAL ANALYSIS PLAN

VERSION 1.0

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1 Introduction

GoFresh is an individual level, randomized feeding trial to determine the effect of 12 weeks of dietitian-assisted DASH-patterned grocery shopping on seated blood pressure in 150-176 adults in the ages of 18-100 years. Participants are randomly assigned to one of 2 groups: (1) Dietitian-assisted, DASH-patterned grocery shopping or (2) Self-directed grocery shopping group. The trial is organized into two phases: the intervention phase (assessed at 3 months) and the observation (maintenance) phase with physical assessments at 6-months and behavioral assessments at 6 and 12 months. The primary trial analysis described in this document focuses on physical assessments at 3 and 6 months. Other outcome assessments performed during the study (i.e., qualitative interviews as well as questions related to quality of life, grocery shopping and dining habits, and perceived stress) are not planned as part of this analysis.

The **primary outcome** is the net effect of DASH groceries with reduced sodium, DASH-patterned groceries versus self-directed grocery shopping on 12-week seated systolic blood pressure (as measured at 3 months, the end of the intervention phase).

1.1 Primary aim

To determine the effects of 12-weeks of dietitian-assisted, home-delivered, virtually-ordered, low sodium, DASH groceries compared with self-directed grocery shopping (DASH education and a $500/month stipend over 3 months) on seated office systolic blood pressure among Black adults.

In this randomized controlled trial (RCT) of at least 150 participants, we will compare the DASH grocery intervention versus the self-directed group over 12 weeks to determine its effect on seated systolic blood pressure.

1.2 Other aims

To estimate the effects of the DASH grocery intervention on the following secondary outcomes:

- Measured at 6 months (observation phase):
  - Seated, office-based, systolic blood pressure (SBP)
- Measured at 3-month and 6-month visits (intervention & observation phase):
  - Seated, office-based, diastolic blood pressure
  - Ambulatory blood pressure monitoring (ABPM): wake-time systolic and diastolic blood pressure
  - Body Mass Index (BMI)
  - 24-hour urine sodium
  - 24-hour urine potassium
  - Hemoglobin A1c

    - Lipids: total cholesterol, high density lipoprotein cholesterol, derived low density lipoprotein cholesterol, and triglycerides
    - Serum potassium
    - Serum creatinine
- Daily intake of fat, fruits, and vegetables
- 24-hour dietary recall

2 Data Source

Data pertaining to the recruitment drive of the GoFresh Trial will be managed in a secure Excel document that will be accessible to team members for tracking recruitment activities. These data include the total number of inquiries (both enrolled and non-enrolled persons).

Data for all screened and randomized participants will be entered by clinic staff into a REDCap dataset (Vanderbilt University, Nashville, Tennessee). REDCap is a secure, password-protected, web-based, research data capture and management application, hosted by the REDCap eData Collection Core of Beth Israel Deaconess Medical Center.

Grocery nutrient information will be derived from the ESHA Research platform (Beaverton, Oregon) and Nutrition Data System for Research (NDSR, University of Minnesota, Minneapolis, Minnesota). Backup files of the database will be generated and stored at regular intervals in a secure, independent location, to permit regeneration of the database in the event that it is destroyed. Data from ambulatory blood pressure monitoring (ABPM) (Sentinel, Spacelabs Healthcare, Snoqualmie, Washington), laboratory results (Quest Diagnostics, Secaucus New Jersey), and the Automated Self-Administered 24-hour Dietary Assessment Tool (ASA24, U.S. Department of Health and Human Services, Washington D.C.) will be regularly uploaded into REDCap to create a centralized analytic dataset.

3 Primary Outcome: Seated Blood Pressure

3.1 Randomization and primary analysis

Participants will be randomized using a permuted block scheme (sizes of 2, 4, or 6) through a randomization feature embedded in REDCap in strata of baseline BP (SBP 120 to <140 mm Hg or 140 to <150 mm Hg). Blood pressure will be used as a stratification variable to ensure that people with varying degrees of hypertension are evenly distributed between interventions.

Randomization assignments will follow a 1:1 ratio such that half of participants will be assigned to order home-delivered, low-sodium, DASH-patterned groceries with the assistance of a registered dietitian over a 12-week period. The other half will be assigned to self-directed grocery shopping. This group will receive a handout about the DASH diet and receive a $500 monthly stipend for 3 months.

3.2 Primary analysis

Our primary comparison is the net effect of randomized assignment (dietitian-assisted vs. self-directed shopping) on office SBP from baseline to 3- (primary) and 6-months post-randomization. Office SBP will be based on the average of three visits at baseline (two screening visits and the randomization visit each with 3 measurements; nine measurements total), two 3-month follow-up visits (each with 3 measurements; six measurements total), and two 6-month follow-up visits (each with 3 measurements; six measurements total). We will first confirm that the residuals of office SBP are normally distributed (if not it will be log-transformed). Modeling will be performed using generalized estimating equation (GEE) models with a treatment-by-visit interaction term. We will perform an intent-to-treat analysis. The visit term will be used to compare changes between 3 months versus baseline, 6 months versus 3 months, and 6 months versus baseline with a product (interaction) term to compare changes across intervention. Models will be adjusted for ZIP code or baseline blood pressure in sensitivity analyses.

Our hypothesis is that 12 weeks of dietitian-assisted, home-delivered, low sodium, DASH groceries will lower office SBP compared to 12-weeks of self-directed grocery shopping. The null hypothesis is that there will be no difference in office SBP between the two intervention arms. The comparison between the two treatment groups will be performed by comparing the regression coefficient for treatment with zero (a two-sided alpha of <0.05 will be considered statistically significant for the primary comparison at 3-months.

For additional pre-specified sensitivity analyses and subgroups to assess effect medication, see below.

3.3 Power and sample size

The primary outcome is change in SBP between the two randomized assignments. Our power calculation is based on the 12-week means and variances from the DASH-Sodium trial,[1] where the 12-week between-group difference in SBP was −8.9 mm Hg. With 75 people in each arm, we will have sufficient power to detect a difference in SBP of −5.8 mm Hg (type 1 error of 0.05, power of 0.85; assuming a standard deviation of 11.85 and 11.4 for control and intervention groups based on the DASH-Sodium trial). We will over-recruit up to at least 176 participants to account for a 15% attrition rate.

With respect to secondary endpoints, we will have sufficient power to detect small differences of 15% or less in the following secondary endpoints: wake-time SBP, BMI, cholesterol, triglycerides, and hemoglobin A1c. Regarding adherence, we will be able to detect changes of 13.0%–29.5% in self-reported fruit and vegetable intake, urine sodium and potassium, and 24-hour recall potassium.[2] These differences are smaller in magnitude than the actual differences observed in prior trials.[3,4]

3.4 Secondary Pre-specified Subpopulations Analysis

We will repeat the primary analysis to evaluate the effect of the intervention within the following subpopulations:

1. Age (≥65 vs < 65 years)
2. Biologic sex (female or male) based on index participant
3. Meal preparer status of the index participant
4. Baseline body mass index (≥30 vs <30 kg/m^2)
5. Baseline hemoglobin A1c (5.7 to <6.5%, <5.7%)
6. Family size (single family versus more than 1 participant)
7. Baseline SBP (following the randomization scheme)

We will fit generalized estimating equations restricted to the strata of interest. Three-way interaction product terms will be used to assess effect modification by baseline characteristic. Note these analyses are contingent on having sufficient number of participants in each strata. The strata involving baseline SBP will be performed regardless of number, following our randomization scheme.

Other stratified or subpopulations analyses based on baseline characteristics may be performed for hypothesis generation beyond the main study.

3.4 Sensitivity analyses

In our primary analysis, we will include all measurements performed within the intended 3-month visit window, including those from participants with medication changes and

those with only one of the intended two sets of triplicate measurements over two visits at 3-months post-randomization. To address these situations, we have pre-specified the following sensitivity analyses.

Medication changes

First, in sensitivity analyses, we will exclude all participants with any antihypertensive medication change during the study period.

Second, we will tabulate and report the number with changes in antihypertension medication by direction of change (increase/start, decrease/stop, no change) according to intervention assignment.

Third, we will add 10 mm Hg (systolic) and 5 mm Hg (diastolic) to their follow-up visit measurement for those who started or intensified hypertension treatments. Conversely, for those with a reduction or cessation in antihypertensive medications we will subtract 10 mm Hg (systolic) and 5 mm Hg (diastolic) from the follow-up visit measurement. This approach has been adopted by others.[5] We will also use the approach described by Law et al, i.e., $\text{adjusted}_{\text{systolic}} = 1.11*[\text{systolic blood pressure}] - 7.00$ and $\text{adjusted}_{\text{diastolic}} = 1.12 *[\text{diastolic blood pressure}] - 5.81$.[6,7]

Fourth, we will calculate the hypertension daily dose, using the approach by Min et al to examine the effect of the intervention on treatment intensity. The hypertension daily dose is a continuous variable, but we anticipate it will require log-transformation.[8]

Protocol deviations in the number of blood pressure measurements

In sensitivity analyses, we will exclude those with protocol deviations in blood pressure measurement, specifically having only 1 of the 2 intended triplicates measures at 3-month follow-up visits.

Protocol deviations in the timing of blood pressure measurements

In sensitivity analyses, we will include those excluded from the primary analysis for having measurements outside the intended visit window (i.e., <105 days of when the intervention started).

Protocol deviations with respect to adherence

In other sensitivity analyses, we will also perform a per protocol analysis whereby we exclude participants, whose adherence to the grocery intervention was <85% based on

dietary compliance records. This will be reported in the Supplement of the primary paper.

4 Other outcomes

4.1 Adherence

Compliance will be quantified by (1) 24-hour urine sodium and potassium (2) 24-hr dietary recall, estimating servings of DASH food groups as well as nutrients consumed, (3) Rapid Block screener for fruit, vegetable, fat, and sodium,[9,10] and (4) DASH Diet Index.[11] The data will be reported by treatment group.

4.2 Secondary Endpoints

We will examine the effect of the DASH-patterned grocery intervention on the following additional outcomes, testing the null hypothesis that there is no difference in the following outcomes between the DASH-patterned groceries and the self-directed intervention. We will examine the distribution of all variables. We will use generalized estimating equations with a robust variance estimator and a normal family identity link for normally distributed outcomes or a binomial distribution, logit link for binary outcomes. A visit term will be used to compare changes between 3 months versus baseline, 6 months versus 3 months, and 6 months versus baseline with a product (interaction) term to compare changes across intervention. Continuous variables with non-normal residuals will be log-transformed with effects reported as a percent change. If residuals are still not normally distributed even after log transformation, we will apply non-parametric approaches.

- **Seated, office-based, diastolic blood pressure**: This will be based on the average of three visits at baseline (two screening visits and the randomization visit each with 3 measurements; nine measurements total), two 3-month follow-up visits (each with 3 measurements; six measurements total), and two 6-month follow-up visits (each with 3 measurements; six measurements total). This is a continuous variable that we anticipate will follow a normal distribution.

- **Ambulatory blood pressure monitoring**: We will determine the mean wake-time systolic and diastolic blood pressure (intervention & observation phases) measured at baseline, 3-months, and 6-months after randomization. This is a continuous variable that we anticipate will follow a normal distribution.

- **Body Mass Index (BMI)**: This is derived from a height measurement at baseline and two weight measurements at baseline, 3-months, and 6-months. This is a

continuous variable that we anticipate will follow a normal distribution.

- **24-hour urine potassium/creatinine and sodium/creatinine ratio**: This is collected after a clinic void over a 24-hour period at baseline, 3-months, and 6-months. These continuous variables are often skewed and may require log-transformation in which case they will be reported as a percent change. We will examine potassium/24hr period and sodium/24hr period as well.

- **Hemoglobin A1c**: Measured in whole blood at baseline, 3-months, and 6-months. This is a continuous variable we anticipate will follow a normal distribution.

- **Lipid concentrations**: Measured in fasted serum specimens collected at baseline, 3-months, and 6-months. This includes total cholesterol, high density lipoprotein cholesterol, derived low density lipoprotein cholesterol, and triglycerides. These are continuous variables. Triglycerides typically require log-transformation. We will examine the distributions of the other lipid types prior to analysis.

- **Serum potassium and creatinine**: Measured in fasted serum at baseline, 3-months, and 6-months as part of a basic metabolic panel. These are continuous variables we anticipate will follow a normal distribution.

- **Daily intake of fat, fruits, and vegetables:** Assessed via questionnaire in-person and via phone call using a validated food screener.[9,10] This is a measure of adherence. We will focus on assessments performed at baseline, 3 months, and 6 months after randomization (12-month assessments will not be the focus of our primary analysis). We anticipate this continuous variable may have a non-normal distribution, requiring log-transformation.

- **24-hour dietary recall:** Assessed via questionnaire measured at baseline, 3-months, and 6-months after randomization. This will be used to determine a DASH Diet Index.[11] We anticipate this will not follow a normal distribution, requiring log-transformation.

5 Missing data

We will employ a number of recommended strategies to prevent missing data:

- A simplified data collection schedule that minimizes participant burden;
- Intention-to-treat analysis that includes following participants according to the data collection schedule regardless of compliance with the study intervention;
- Frequent engagement with the participants through visit reminder calls or notes;
- Contiguous windows of time during which specific follow-up visits are allowed;
- Monetary incentives to encourage enrollment and continued participation;
- Rigorous training of clinic staff emphasizing the importance of
    - Positive and warm interpersonal relationships between the participants and study staff
    - Study commitment during the consent process to ensure that potential participants understand the importance of completing the study
    - Addressing participant concerns to minimize dissatisfaction
    - Collecting data even if a participant discontinues the study treatment
    - Reasons for any drop-outs will be documented.

We will perform the following sensitivity analyses using established methods for addressing missingness in clinical trials: use of out-of-window blood pressure measurements, multiple imputations at the individual level, and best and worst-case scenarios. We will compare the results from these approaches with primary analysis results to assess the primary result's robustness to the effects of missing data. Further, we will compare the baseline characteristics of complete cases and participants with missing measures between the two assignments.

6 Safety outcomes

We will compare self-reported symptoms that are thought to potentially arise from the diet. The symptoms will be summarized by the counts and proportions of participants in each group and overall. The treatment groups will be compared with respect to safety outcomes by using a chi-square test (Fisher exact test when there are cell counts less than 5).

7 References

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