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Brief Title: Reducing Cardiometabolic Risk and Promoting Functional Health in Older Adults With Obesity and Prediabetes (Sustain-DPP)
Statistical Analysis Plan as of 1/12/24

Statistical Analysis Plan

All analyses will be conducted in consultation with Dr. Lan Yu, and KwonHo Jeong, the study biostatisticians, using SAS 9.4 (SAS Institute, Inc., Cary NC). Descriptive analyses and graphic displays will be used to identify outliers, missing data, and patterns of attrition. Demographic variables and baseline measures will be contrasted between the Active Comparator: DPP Plus 30-minute Calls (DPP Plus) and the Placebo Comparator: DPP Minimal 15-minute Calls (DPP Minimal) conditions. In all outcome analyses we will use an intent-to-treat (ITT) approach in which participants remain in the study arm to which they are randomized regardless of attrition. The primary analytic strategy will be a linear or generalized mixed-effect models approach in which treatment group, time, and time by group interaction are treated as fixed effects, and subject is treated as a random effect to account for individual subject variability. Hypothesis tests will be two-sided, and significance will be set at the 0.05 level. Mixed models are applicable to longitudinal datasets that contain missing observations, with the assumption that the data are missing at random. Our prior intervention studies suggest that we can anticipate 90% retention at 6 months and greater than 80% retention over the 18-month extended intervention period (at 24 months) with no differential attrition between arms. Those who drop out or are lost to follow-up will be compared to those who have completed intervention for research assessments using standard parametric and non-parametric methods, as appropriate. We will examine the patterns of missingness and, if necessary, account for missingness in outcome analysis (e.g., the covariate approach). Regression modeling will be conducted to adjust for covariates such as race, sex, age, socio-demographic factors and other designated baseline clinical variables.

Research Questions

Analysis Plan for Hypotheses 1 and 2: We will apply mixed effect models to evaluate differential changes in weight measures at 6, 12, 18, and 24 months from baseline, with fixed terms of group (DPP Plus vs. DPP Minimal), time as a factor (6,12,18, and 24 months), and the group by time interaction. We will employ the following steps as the pre-randomization balancing logic: (1) group subjects by weight loss status (≤ 3.5 vs. > 3.5 percent at 6-months) and age (≤ 70 vs. > 70 years at baseline), (2) group subjects by sex (male vs. female) and race (Black/African American or Black/Mixed/Other vs. White/Caucasian), (3) group subjects using all 4 factors (based on 2x2 frequency table) and (4) randomly assign the subjects in the same cell into 2 conditions (DPP Plus vs. DPP Minimal). Subject will be included as a random term. To test the differential treatment effect, we will evaluate the coefficients that are associated with the group and the group by time interaction by using an F test. Planned contrasts will be set up from the mixed models to compare the improvement in weight from baseline to Months 12, 18 and 24 between the two conditions (DPP Plus vs. DPP Minimal). A generalized mixed-effect model will be fit to the binary outcome of achieving ≥ 5% weight loss at 6, 12, 18, and 24 months, with the logit link, which includes similar fixed and random terms as above. Average percent weight loss and the proportions achieving ≥ 5% weight loss will be compared between the two groups at 12, 18 and 24 months. We will perform similar analyses for fasting glucose, HbA1c, and insulin (and other biometric measures), physical activity/function, and secondary outcomes at subsequent assessment points.

The planned contrasts will be set up to compare differential changes from baseline to Months 12, 18, and 24. Benjamini-Hochberg's method will be used to control for the overall type I error for multiple secondary outcomes. More intensive modeling will be performed accounting for factors that are known to affect the outcomes as well as those that have been found to differ between treatment conditions at baseline and at Month 6 (the timepoint at which participants are stratified by < or ≥ 3.5% weight loss and other factors and randomly assigned to the two 18-month conditions). We will also perform analyses in which we restrict our linear and generalized

mixed-effect analyses to those who did not reach ≥ 5% weight loss at 6 months and set up the contrasts to compare DPP Plus with DPP Minimal, on average, and the proportion reaching ≥ 5% at 12 months and 18 months from baseline.

Exploratory Aim: Examine available Medicare data for those insured by a large regional payer to assess group and time from baseline differences in medical utilization metrics (e.g., type of outpatient, inpatient, or emergency visits) and participation in activity programs, for a proportion of the sample. We will extract Medicare data on numbers of outpatient, inpatient and emergency visits, and number of subjects participating in activity programs, and compare the numbers between the two conditions using linear and generalized regression models. We will explore the potential moderation effects of sex and race. We will include the interaction of sex by group or race by group in the aforementioned mixed-effect models, as well as the three-way interaction of sex, group and time or race, group and time, if the group by time interaction is significant in the original model.

Power and Sample Size Considerations. We powered this study on the main comparisons between the Active Comparator: DPP Plus 30-minute Calls (DPP Plus) and the Placebo Comparator: DPP Minimal 15-minute Calls (DPP Minimal) on average weight loss at 12 months from baseline. With 180 subjects per arm and projected 90% attritions at Months 12, we would have 80% power to detect effect sizes of 0.31, using two-sided t tests at the 0.05 level. Our prior Pitt Retiree study observed approximately 7.5 % weight reduction at 12 months among those subjects who received active intervention for 12 months, and 5.5% reduction at 12 months among those in the placebo comparator group. Assuming similar effects and similar standard deviation of 5.8% as observed in the Pitt Retiree study, we expect to see a standardized group difference ranging 0.34 at Months 12 between DPP Plus and DPP Minimal. We anticipate that our projected sample size will enable us to detect group differences with power greater than 0.8 for our primary weight outcome.