Dietary Prevention of Heart Failure in Hypertensive Metabolic Syndrome

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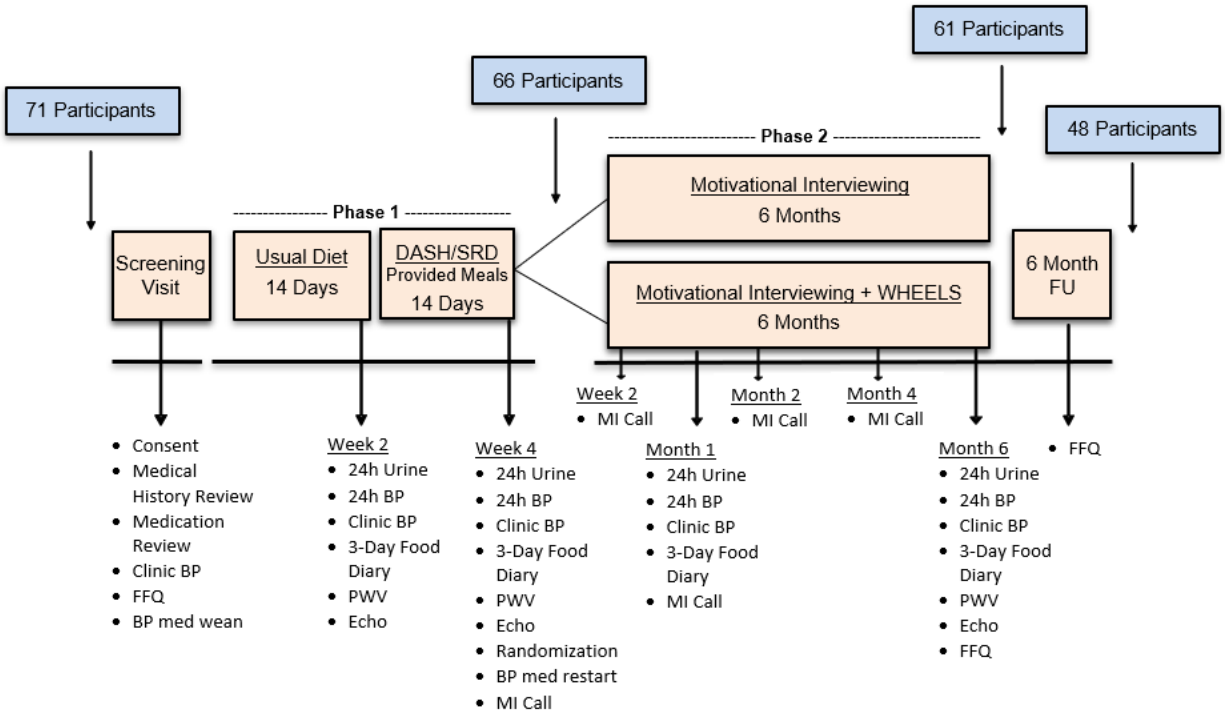
Statistical Plan

The study was conducted in two phases. *Phase 1* evaluated the salt-sensitivity of blood pressure, with 2 weeks of ad-lib diet followed by 2 weeks of provided sodium-restricted Dietary Approaches to Stop Hypertension (DASH/SRD) meals, with outcomes assessed at 2 and 4 weeks of study participation. *Phase 2* evaluated the efficacy of motivational interviewing-based dietary counseling, with or without the Women's and men's Hypertension Experiences and Emerging LifestyleS (WHEELS) mobile application, with outcomes assessed from baseline to the end of the study. The study schematic is shown below, along with data collection and the flow of participants that were still actively participating at key timepoints.



The primary outcome of *Phase 1* was the change in carotid-femoral pulse wave velocity (PWV), with secondary outcome of the change in left ventricular global longitudinal strain by echocardiography, between week 2 and week 4 of study participation. Since *Phase 1* of the study occurred prior to randomization, the comparator groups are salt-sensitive and non salt-sensitive individuals, with blood pressure salt-sensitivity defined as a reduction in mean arterial pressure by 24-hour ambulatory monitoring in week 4 (DASH/SRD diet period) compared to week 2 (ad-lib diet period). *Phase 1* outcomes were analyzed using linear regression adjusted for baseline value.

Sample size was based on a 2-sequence, 2-period, 2-treatment crossover design for continuous endpoints (using paired t test for mean differences). We assumed a within-subject correlation of 0.70 for PWV measurements, based on our preliminary data and the literature and assumed a 10% dropout rate during *Phase 1* of our study. Under these assumptions and using a two-sided type I error rate of 5%, 100 subjects, 50 allocated to the DASH/SRD-control diet sequence and 50 allocated to the controlDASH/SRD diet sequence, provides >80% power to detect an effect

size (mean treatment difference/standard deviation) of 0.22 and >90% power to detect an effect size of 0.26. This sample size provides >80% power to detect an effect size of 0.5 in cfPWV change between salt-sensitive vs. salt-resistant subjects. This is a between-groups comparison based on a two-sample t test and two-sided Type I error of 5%.

The remainder of the outcomes are *Phase 2*-related, i.e. intended to determine longer-term effects of dietary change between the WHEELS and non-WHEELS groups, with both receiving motivational interviewing-based dietary counseling. The primary outcome of *Phase 2* was the change in left ventricular mass index (LVMI, using the Devereaux and Dubois formulas for left ventricular mass and body surface area, respectively) by echocardiography, with secondary outcome of change in PWV, between baseline and end of study participation. These outcomes were assessed using linear regression adjusted for baseline value. Key additional pre-specified outcomes were the change in DASH/SRD adherence measured both by 3-day food diary and Food Frequency Questionnaire (FFQ) and the change in clinic systolic and diastolic blood pressure (BP), between baseline and end of study participation. These were measured using generalized estimating equations to account for repeated within-subject measures over time (baseline/2 weeks and at 1 and 6 months of *Phase 2*) and interaction with WHEELS treatment group assignment. Other pre-specified outcomes were changes in serum triglycerides and urine sodium:potassium ratio between baseline to the end of study, evaluated using 2-sample t-testing.

The sample size for *Phase 2* was set by the participants completing *Phase 1* and influenced by drop-out during the 6 months of the interventions to promote DASH/SRD adoption. We assumed that an additional 10% of subjects will drop out during *Phase 2*, resulting in 90 subjects with evaluable data. The sample size was estimated based on anticipated effects on DASH/SRD adherence, the presumed primary driver of cardiovascular and BP changes in the study. Based on national survey data and our preliminary work, we expected the mean baseline DASH/SRD adherence score by 3-day food diary to be 2.5±1.5 points (scale, 0-9). A sample size of 90 provides >80% power to detect an intra-group change of 0.6 between baseline and the end of study, based on paired t-testing two-sided Type I error of 5%. This sample size provides >80% power to detect a differential between group change in dietary score of 0.9, based on a two-sample t test and two-sided Type I error of 5%.