Data Analysis Plan

PUSH Plus Protein Pilot Study for Hip Fracture Patients

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Trial Registration

ClinicalTrials.gov

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Primary Aim

The primary aim is to compare the PUSH Plus Protein study subjects (n=30) to those who received PUSH from CAP (n=105). The primary outcome is the distance walked in six minutes (6MWT). Previous analyses of various physiologic measures in the Baltimore Hip Studies data ("BHS"; data unpublished) have shown a r>0.80 within subject correlation of measures across time. Preliminary data from CAP-MP have shown a within subject correlation of r=0.78 for initial subjects in usual walking speed (n=13).

Secondary Objectives

A longitudinal analysis using Generalized Estimating Equations (GEEs) will be employed. A model of the form Y(t) = a + b1 X + b2 t4 + b3 Xt4 will be used where: Y(t) is the dependent variable Y at time t (which is 0 or 4 months post baseline testing); a is the intercept; X is an indicator variable for treatment group (PUSH vs PUSH+ Protein); t4 is an indicator variable for time at 4 months post baseline testing; Xt4 is an interaction term for treatment and time; and b1 through b3 are empirically derived regression coefficients. An unstructured covariance matrix, an identity link function, and robust standard errors will be used. The effect of intervention on each mechanistic factor will be assessed by estimating the magnitude of the coefficient b3, which is interpreted as mean change in outcome from baseline to 4 months comparing PUSH Plus Protein to PUSH alone. The primary outcome will be the 6-minute walk test (6MWT). Other potential outcomes include: activities of daily living (ADLs), quality of life, lower-extremity physical performance, increase of ≥ 50 meters in distance walked in six minutes, cognitive status, and nutritional status.

Missing Data

By design, there will be no missing data at baseline because only participants with complete baseline data will be randomized. At follow-up, scores for scales that have published rules for handling missing scale items (e.g., the CES-D and the SF-36) will be calculated using those rules. All other scales will be considered missing if any part of the scale is missing. To correct for potential selection bias from missing data, we will perform a weighted estimating equations (WEE) analysis.[169] This method involves two steps. First the probability of being observed (not missing) is calculated as a function of predictors of missingness. Next the relationship of treatment group to outcome is assessed using the inverse probability of being observed as a weight in the GEE model. WEEs are advantageous because a) they are consistent with the ITT principle because participants with missing data are included in the analysis through the estimated weight, and b) unlike other methods for addressing missing data, they can be performed in conjunction with marginal structural modeling by multiplying both weights together.

Sample Size Adequacy

Power analyses were conducted for detectable mean changes from baseline (conservatively) assuming a within subject correlation of r=0.70. For between group differences, assuming 10% loss to follow up from all causes (mortality, attrition, etc.) by 16 weeks post randomization (CAP n=105 in the PUSH arm and this study will have n=30, so effective n=94 compared to n=27 including attrition). The study will have 80% power to detect differences of 0.475 standard deviations assuming two-sided tests and an alpha level of 0.05. These differences are considered small-to-moderate effects using Cohen's criteria for interpretation of effect sizes (where 0.2 is "small" and 0.5 is "medium). Given a 6MWT mean of 186.7 and SD=55.8 in the most recent overall sample from CAP (n=199, DSMB report May 2017), this would translate into

a difference of 22.9. Similar magnitude of effects (SD=0.41) are detectable comparing to other measures available in the CAP study (e.g, SPPB, 3MS, etc.).

For outcomes only available in the CAP-MP study, the comparison sample is 19 subjects in CAP-MP PUSH. Assuming 10% loss to follow up (n=17 in CAP-MP PUSH group vs n=27 in pilot study), the study will have 80% power to detect between group differences of 0.62 standard deviations assuming two-sided tests and an alpha level of 0.05. This is considered a moderate-to-large effect size by Cohen.