A Patient-Centered Strategy for Improving Diabetes Prevention in Urban American Indians

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Statistical Analysis Plan

October 9, 2019

CHANGES FROM ORIGINAL PROTOCOL

1. The second investigational site was changed from Indian Health Center of Santa Clara Valley to the Timpany Center at the San Jose State University Research Foundation.

2. Blood samples were obtained by fingerstick method rather blood draw.

METHODS

The primary model for participant *j* at time *k* nested in cohort *i*

$$Outcome_{ijk} = \beta_0 + \beta_{0i} + \beta_{0ij} + \beta_1 Intervention_j + \beta_2 Month6_{jk} + \beta_3 Month12_{jk} + \beta_4 Month18_{jk} + \beta_5 Intervention_j * Month6_{jk} + \beta_6 Intervention_j * Month12_{jk} + \beta_7 Intervention_j * Month18_{jk} + \beta_8 Gender_j + \varepsilon_{ijk}$$

will be used to test the co-primary hypotheses that BMI will decrease and quality of life will increase in the enhanced DPP arm relative to the standard DPP arm upon completion of the study. The linear regression model includes a random intercept β_{0i} to account for within cohort correlation, a random intercept β_{0ij} to account for within participant correlation, and adjusts for gender ($Gender_j$), the stratification factor for randomization. $Intervention_j$ indicates that participant *j* is in the enhanced DPP arm and $Month6_{jk}$, $Month12_{jk}$, and $Month18_{jk}$ indicate whether observation *k* from subject *j* is at month 6, 12, or 18, respectively. To test whether the change in the primary outcome from baseline at 12 months differs between the standard and enhanced arms, we will test the null hypothesis that $\beta_6 = 0$ using the Wald test. Each outcome will be tested at a two-sided **α** = 0.05 for an overall **α** = 0.10.

The primary analyses will follow the intent-to-treat principle and will use all available data. We will describe any missing data and will conduct sensitivity analyses to evaluate the impact of the missing data on our conclusions. Sensitivity analyses considered to evaluate the robustness of our findings to the presence of missing data will include multiple imputation methods and worst-case imputation where missing values are filled with an extreme value (eg 5% greater than value observed at baseline), which can be used to determine how extreme the unobserved missing values would need to be in order to change the conclusion of the trial. [51,52] Secondary analyses will replace the primary outcome in the model above with secondary outcomes.

Additional secondary analyses will consider pre-specified moderators and mediators (depressive symptoms, coping skills, and social support/community cohesion) of the primary outcomes. We will investigate the moderators and mediators using mixed effects linear regression by including an interaction term of treatment and the hypothesized moderator and centering the independent variables.[53,54]

SAMPLE SIZE AND DATA INTERPRETATION

Our study was designed to provide sufficient statistical power to test the study's co-primary hypothesis that the enhanced DPP will result in greater weight loss and quality of life improvement compared to the standard DPP. In determining the sample size we considered the definition of clinically significant weight loss, the standard deviation of weight change in past clinical trials of lifestyle interventions, and acceptable levels of Type I and Type II errors. Our power estimates are based on simplified assumptions and the actual power may be different because of the correlated errors induced by the cohort effect and the repeated measures over time. In the original DPP trial, the average weight loss in the intensive intervention arm was 6.9% ± 4.5% after 6 months of follow up and 4.9% ± 7.4% at the end of the trial (mean follow-up of 3.2 years).[55] This percent weight loss is similar to other studies and greater than that observed in the SDPI evaluation where Jiang et al reported a percent weight loss of 4.4% following the 16-week program.[10] Based on this literature, we expect a mean percent weight loss of 4.0% in the standard DPP and 6.5% in the enhanced DPP. To be conservative, we powered the study to be able to detect a difference of 2.0%. Dividing a 2.0% difference (6.0%-4.0%) by the DPP SD (4.5%) yields an effect size of approximately 0.45. A sample of 81 participants per arm will be required to compare the standard and enhanced arms for an effect size of 0.45 at a two-sided α=0.05 with 80% power. We estimate 20% will be missing BMI at follow-up and have therefore inflated the initial sample size to 102 participants per arm. As the secondary analyses are exploratory, no adjustment for multiple testing will be made for secondary analyses. The secondary analyses are not intended to produce clinically actionable results, but rather to supplement conclusions based on the primary analysis and to inform future research. They will be interpreted properly within that context, considering the totality of evidence available.