ANDES STATISTICAL ANALYSIS PLAN

Study Title: Addressing Hypertension and Diabetes through Community-Engaged Systems in Puno, Peru (ANDES)

Multiple Principal Investigators:

Stella Hartinger (contact), PhD, Universidad Peruana Cayetano Heredia, Lima, Peru

Victor Dávila-Román, MD, Washington University in St. Louis, MO, USA

Elvin Geng, MD, MPH, Washington University in St. Louis, MO, USA

William Checkley, MD, PhD, Johns Hopkins University, Baltimore, MD, USA

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1. Sample Size Considerations

   To detect a difference in systolic blood pressure of 2.5 mmHg between intervention and control arms using a two-sided test at the 0.05 level of significance and with 90% power and a standard deviation of 12 mmHg, we would need 485 participants per arm. Assuming a conservative lost-to-follow-up of 10% at 12 months, we would need to randomize 1068 participants in total (534 participants per arm).

2. Statistical Interim Analyses and Stopping Guidance

   No interim analysis will be conducted.

3. Timing of Analysis

   Analyses will be conducted once data collection is completed during the final year of the grant.

4. STATISTICAL PRINCIPLES

   4.1 Confidence Intervals and P-Values

   Analyses of the primary and secondary outcomes will utilize two-sided tests at an α-level of 0.05. We will use 95% confidence interval for the purposes of estimating the magnitude of effects.

   4.2 Adherence and Protocol Deviations

   The study intervention will test the effect of assignment of a health agent on blood pressure among individuals with hypertension. Protocol deviations occur when the study treatment is not offered. We anticipate protocol deviations occurring in two ways: 1) health agent is not assigned within a week of randomization; therefore, a health agent did not attempt to schedule a visit within a week of randomization; or 2) health agent is assigned but did not make any attempt to contact the patient within 72 hours of assignment. Of note, down-stream events, including the success of health agent actual contact with the patient and activities delivered by the health agent, in so far as they deviate from ideal, do not represent violations of protocol, but rather are study endpoints in this implementation science study.

   4.3 Outcome Variables and Analysis Populations

   The primary outcome measure is systolic blood pressure measured at 12 months. Secondary outcome measures include diastolic blood pressure at 12 months, systolic and diastolic blood pressure at 18 months, the proportion of subjects with blood pressure ≥140/90 mm Hg at 12 and 18 months, and the proportion of subjects with HbA1c ≥7% at 12 and 18 months. The primary analysis will be a modified intention-to-treat analysis that includes all subjects who have at least one valid post baseline systolic blood pressure measurement. Implementation science outcomes include measures of fidelity (time to first encounter with a CHW and the number of encounters with a CHW), acceptability, accessibility, and trust.

5. DATA ANALYSIS

   5.1 Analysis of Primary outcome

   The primary analysis will be a mixed model repeated measures analysis of variance, with the contrast comparing the change from baseline to 12 months in systolic blood pressure in the two study groups

being the primary comparison. This analysis will not be adjusted for covariates. Subsequent secondary analyses will be adjusted for covariates that include age, sex and socioeconomic status.

As we have noted, the above analyses will be conducted using a modified intention-to-treat sample. While the standard intention-to-treat principle requires that all randomized participants be included in the final analysis according to their originally assigned treatment group (regardless of adherence, withdrawal, and loss to follow-up), our modified approach will exclude subjects who drop out of the study without providing any follow-up data. While we appreciate the imperfections of this approach, we prefer it because the pure intention-to-treat analysis requires the imputation of long-term blood pressure data in subjects who have provided no early follow-up data to guide the imputation process. Two important points about this are as follows.

- First, if missing data rates are substantial, we will perform sensitivity analyses that use multiple imputation to facilitate the inclusion of all subjects in a pure intention-to-treat analysis.
- Second and most important, we anticipate that these sensitivity analyses will be unnecessary because of an anticipated very low dropout rate. Our power computations assumed a 10% dropout rate, although we expect the true rate to be lower in practice. If that is indeed the case, it is highly unlikely that imputation would alter the results of our primary analysis. If the dropout rate is higher than anticipated, we will perform sensitivity analysis using multiple imputation.

A central feature of any longitudinal analysis is the selection of the best covariance structure. Our selection process will reflect several considerations including information criteria; the pattern of change in the correlation between observations as the time between measurements increases; and *a priori* preference for structures that, all other things being equal, minimize the number of parameters that must be estimated. We will begin our search for the appropriate structure using both the correlation matrix and graphical presentations. After evaluating correlation patterns to potentially narrow the options, we will use the Akaike Information Criterion and the Bayesian Information Criterion.

5.2 Analyses of Secondary Outcomes

Secondary outcomes as defined in section 4.3 include both continuous and dichotomous measures. The continuous outcome measures will be analyzed using the mixed model approach described above, with the specific contrast of interest being defined by the time point at which the secondary outcome is measured. When we evaluate sustainment of effect, we will examine contrasts comparing changes from baseline to 12 months and 12 to 18 months. Our focus will be on the confidence bounds around the between-group differences in these changes, with the expectation that the 0–18 month contrast will show a sustained intervention effect and that the 12-18 month contrast will be close to zero, reflecting no additional divergence following the end of the intervention at 12months.

The dichotomous measure of uncontrolled blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) and of uncontrolled HbA1c (HbA1c ≥7%) will be evaluated using logistic regression. In addition to the unadjusted analyses, we will also evaluate logistic regression models that adjust for the same covariates that are used in analyzing the primary endpoint.

5.3. Analysis of Implementation Outcomes

Implementation science outcomes include measures of fidelity, accessibility, acceptability, and trust.

Descriptive statistics will be calculated for home visitation where we will estimate the fraction of intended encounters that are completed, with attendant confidence intervals. We will use regression models to identify factors associated with completed visits using covariates such as geographic, socio-demographic, and clinical features of the patient. We will undertake similar analyses of acceptability, in

which we will analyze trust on a validated scale, first descriptively and then to identify factors associated with greater trust using regression models.

Between-group comparisons of implementation outcomes will also be pursued. Differences in the frequency of regular healthcare visits over the past year will be assessed using a chi-square test or Fisher's exact test when appropriate, followed by ordinal logistic regression models adjusting for subject-related covariates if the proportional odds assumption is met. Logistic regression that is applied only to subjects who do not have a diagnosis of hypertension at baseline will be used to make between-group comparisons of the percent of subjects who are diagnosed with hypertension post baseline.

5.4 Assessing the Appropriateness of Analytical Strategies

We will routinely give careful attention to the appropriateness of the analyses we perform. For example, t-tests comparing baseline values will be performed only after assessing equal variance and normality assumptions, with data transformations being pursued if assumptions are violated and Wilcoxon's test being a nonparametric alternative if an appropriate transformation cannot be found. Similar attention will be given to the appropriateness of mixed model analyses where the distributional properties of variables will be evaluated, residual plots will be examined, and influence diagnostics will be assessed to evaluate the impact of potential outliers. The Hosmer-Lemeshow goodness-of-fit test will be performed to ensure the fit of our logistic regression analyses, with data transformation being pursued if the fit is uncertain.