Statistical Analysis Plan

Study Title:
Augmenting Hospitalization for Serious Mental Illness: Cognitive Bias Modification

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NCT#: NCT03509181

VI. BIOSTATISTICAL ANALYSES

Phase 1: Development
Not applicable

Phase 2: Open Trial
The primary aims of this treatment development project are to develop: a) HabitWorks, b) procedures for hospital augmentation and bridge to outpatient care, and c) procedures for a subsequent RCT. First, we will analyze qualitative data obtained from post-treatment interviews and exit questionnaire. The PI will content analyze audio recordings using a rapid coding technique. Audio recordings will then be transcribed verbatim and analyzed with more conventional analytic methods. Using the constant comparison method from grounded theory[113] transcripts will be read for emerging themes. After independently categorizing thematic clusters, the scientific team will create a coding scheme to organize data, prepare a written report detailing the emerging themes, and discuss results with the advisory board.

We will compare outcomes to **a priori target outcomes** (see Table) after each iteration of the open trial. We will calculate descriptive statistics (e.g., mean, frequencies) to evaluate whether the target outcome was met. When the target is not met, this will prompt a discussion with the team and advisory board about potential modifications. We will calculate effect size estimates to characterize pre-post differences (open trial) and the associated 95% CIs, to understand the precision, or lack thereof, of our estimates.

Target Outcomes
Target Engagement: 75% of HabitWorks group moves into normal range[20,23,108] of interpretation bias (Benign endorsement = 70%; Negative endorsement = 30%) on the WSAP and on the Scenario Recognition Task (Similarity rating (1 to 4) for target sentences: benign = 2.3; negative = 1.9).
Treatment Credibility & Expectancy: Average = 5 (moderate credibility or 50% expectancy)
Retention: 75% of participants complete the 3 month-assessment 75% of participants complete HabitWorks daily during acute treatment 50% of participants complete HabitWorks 3x week in transition phase
Satisfaction: Average rating 5 or above (on a 1 to 7 scale) on the Exit Questionnaire
Treatment response: 50% of HabitWorks group responds to treatment ("much or very much improved" on CGIS) and 20% reduction in functional impairment in HabitWorks group with a clinically meaningful between group effect size of *d* = .40

Case series: We will report results from 4 participants from the Phase 2 open trial and the Phase 3 randomized controlled trial in a case series format. We will report data on app usage, clinical outcomes, and app feedback collected throughout the project. In all 4 participant case reports, we will remove any identifiable information, and will report limited demographic information (e.g., age range, gender, race, and ethnicity).

EMA data. We will pilot the use of EMA methods and anticipate following a similar analytic strategy as prior EMA work[112]. In brief, we will examine change in affect using repeated measures ANOVA. We hypothesize that individuals who complete the WSAP just prior to the random EMA PANAS-X assessment will report an increase positive affect and a decrease in negative affect from the prior EMA assessment. We will primarily rely on Latent Growth Models (LGM) due to our interest, and hypotheses, related to HabitWorks administration and change in interpretation events. LGM provides a flexible, powerful, and easily interpreted statistical approach to examine affective and cognitive change modeled around a discrete event. We first construct models for negative and positive affect; these models will initially be specified as parallel growth processes to account for shared variance, but will be tested individually if a parallel growth model cannot be fit. We will estimate intercept (i.e. mean) and slope (i.e. linear

rate of change over time) for each of these constructs using the anchor event (i.e. HabitWorks session) and 1-2 EMA assessments before and after, providing 3-5 time points to model change. Should linear slope poorly describe the data, we will investigate nonlinear slope or specify piecewise, discontinuous, linear growth processes. We first fit unconditional models to determine the optimal change trajectory for each outcome. Once an optimal growth trajectory has been identified, we regress growth parameters (i.e. intercept and slope) on changes in WSAP responses to examine the association of intercept and slope of interpretation bias outcome variables with affect and symptoms.

Power analysis. One goal of the current project is to determine the recruitment rate at our site, and to compare it to the rate needed for an adequately powered RCT (i.e., 4 individuals per month = 200 participants over 50 months (estimated recruitment duration of a subsequently proposed RCT)). Our primary hypothesis for the subsequent RCT is that HabitWorks will be superior to control on our primary outcomes. We determined that a clinically significant difference for a low-intensity, augmentation treatment is an effect size of d = .40, which corresponds to a post-treatment between-group difference of 2.8 points on the WSAS. We conducted preliminary power analyses using these numbers and a 15% dropout rate (based on our pilot studies). We estimated that a sample size of 200 would give us >80% power to detect a group difference of d = .40. This effect appears feasible, given that our pilot RCT resulted in a between-group effect size of d = .63 on a measure of well-being.

Phase 3: Randomized Controlled Trial

We will conduct similar qualitative, descriptive, and EMA analyses as noted in the open trial. We will calculate effect size estimates to characterize between group differences and the associated 95% CIs, to understand the precision, or lack thereof, of our estimates.