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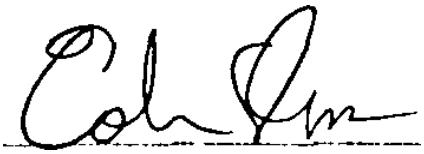
Re: Cover Letter for Clinical Trials.gov NCT 02035202 (Depp)

This Cover Letter accompanies Statistical Analysis Plan for this trial NCT012035202 which completed.

Sincerely,



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Hypothesis Testing: Hypothesis 1 (Primary Outcome): Compared to EMA and Standard Care, the CBT2go intervention will be associated with greater improvement in global psychopathology. Dependent Variable: BPRS Total Score. Independent Variables: Condition and Time (0,6,12,24 Weeks)

Statistical Analysis: This hypothesis will be tested using GAMMs. Condition will be entered into the model as a fixed-effect predictor along with time on study and their interaction. Scores will be entered along with any demographic variables identified as covariates. If the smoothed interaction of treatment condition and time is significant at the .05 level (as determined by an F test of the relevant coefficients in the model) we will test for all pairwise differences with Westfall-Young adjusted p values.

Power Analysis: The lack of prior RCTs of mobile interventions in BD or SZ makes it challenging to determine the effect size with which to power the study. The underlying assumption of our RCT is that effect sizes will be comparable to that seen in in-person CBT; Accordingly, we conservatively powered the study based results of recent meta-analyses of CBT in SZ and BD in a total of 46 RCTs[8,9], which revealed a median effect size of 0.4 (small to moderate) in favor of CBT with active comparators. Sample size estimates were based on the Hedeker, et al.[130] method for various covariance structures for mixed effects models. For the proposed study, we assumed an autoregressive covariance structure, with conservative correlation between sequential assessments set at 0.5. Using this methodology, assuming an alpha level of 0.05, we have a minimum 80% power to detect a medium effect size with 20% attrition at 12 weeks (based on pilot data) when there are 85 subjects per each condition for a total of 255 subjects.

Hypothesis 2 (Secondary Outcomes): Compared to EMA-only and Standard Care, the CBT2go intervention will be associated with greater improvement in EMA and standard lab-based measures of medication adherence, social functioning, and hospitalization and emergency service utilization. Dependent Variables: EMA-outcomes; Medication adherence Composite; SFS Score; PSR Toolkit Composite and Hospitalizations/ER visits. Independent Variables: Condition and Time (0,6,12,24 Weeks).

Statistical Analysis: As above, this hypothesis will be tested using GAMMs. Condition will be entered into the model as a fixed-effect predictor along with time on study and their interaction, and we will test for all pairwise differences (e.g., CBT2go vs. Standard Care) with Westfall-Young adjusted p values. EMA outcomes (which include up to 252 observations per person) will be assessed with Hierarchical GLM analyses with a multinomial sampling model with a logit link functioning, with time (days in study) as a predictor and Condition (CBT2go vs. EMA-only) as a predictor of intercept and growth parameters of the model.

Power Analysis: Our secondary outcomes have the same assumptions as those in Hypothesis 1 and thus are independently powered to detect a medium effect size for each measure. The power to detect differences by condition with EMA analyses should be equal or greater by virtue of number of observations.

Hypotheses 3 and 4 (Moderators and Mediators): Neurocognitive ability will account for more variation in device compliance and treatment response than diagnostic group; Improvement in cognitive insight and reduction in dysfunctional beliefs will mediate treatment response. Dependent Variable: Outcome (Slope of change in BPRS between Baseline and Week 24) Independent Variables: Moderators: Cognitive ability (MCCB); Diagnosis (BD vs. SZ); Mediators: Insight (BCIS) and Dysfunctional Attitudes (DAS).

Statistical Analysis: The primary moderation and mediation analysis will be based on the recommendations of Kraemer et al.[131] MacArthur Network. Moderation (Diagnosis, MCCB) will be confirmed by the presence of a significant interaction effect (Diagnosis x Condition) on trajectories using GAMMs, and that the diagnosis interaction effect will no longer attain significance with cognitive ability entered into the model. For mediation, we will assess for: (1) non-zero relationship between the mediator and Condition and (2) non-zero relationship between the mediator and outcome. We will implement the test for mediation by (1) fitting mixed models testing for treatment differences in BCIS and DAS trajectories by week 6; (2) fitting mixed models testing for BCIS and DAS differences in trajectories of BPRS from week 6 to 12; (3) testing whether the product of coefficients from these two models assessing change in mediators and outcomes is significantly different from zero using the bootstrap test of Preacher et al. (2004)[132].

Power Analysis: Based on the Fritz and McKinnon's estimates for sample size[133,134] to detect mediation, and conservatively using change scores to compute power, we have at least 80% power to detect mediation with the hypothesized effect size.