ClinicalTrials.gov Cover Page – Statistical Analysis Plan

Title: Talk Therapy by Phone to Promote Treatment for Alcohol Problems
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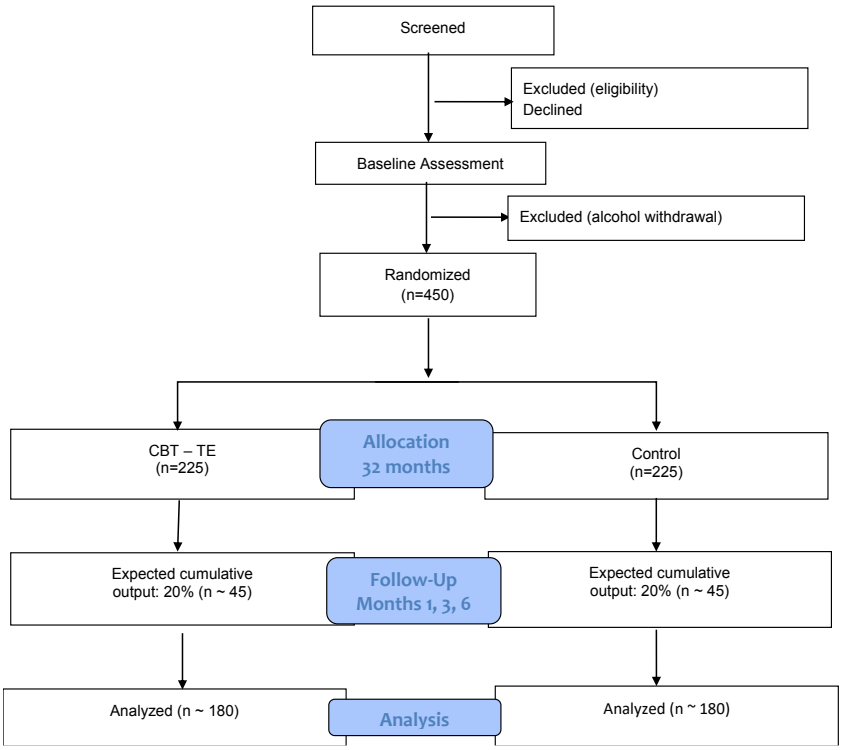
Statistical Design and Power

Sample size calculation: Power Analysis: Our estimates of statistical power and required sample size were informed by the prior study by Stecker and colleagues (8). In this study, the control group rate of treatment use was 12%, and the treatment group rate was 31%, representing a 2.58 times increase. Given that this study was the first test of the intervention in a sample with elevated alcohol use, we chose a more conservative effect size of a 2.0 times increase in treatment use to account for the potential uncertainty in the generalized effect size and to buffer against the potential for regression to the mean across conditions. Using this effect size and base rate of treatment use, a sample of 450 participants (~225 in each condition) would provide power of 0.89 at a two-tailed alpha level of 0.05. This sample size allows for a loss of up to 20% of participants at follow-up while maintaining power at 0.81, and serves as a further buffer against the downward bias associated with intention-to-treat principles. In the table, we have provided power estimates using both these conservative settings (i.e., smaller than expected effects with high attrition) and more likely scenarios. We were further conservative in our approach by utilizing a two-tailed alpha level, as there is little reason to anticipate an iatrogenic effect in the current study. Use of a one-tailed alpha (i.e., testing if treatment use is higher in the intervention condition than in the control rather than simply whether they are different), provides power of 0.80 to find an effect as small as 1.75 times difference, with power of 0.73 retained if 20% attrition were observed.

Statistical Power assuming a baseline sample of 450 participants, 12% treatment use in the control condition, and two-tailed α level of 0.05		
Treatment Use % in the Intervention Condition	Attrition Proportion	Statistical Power
24% (2.00X increase)	10%	0.86
27% (2.25X increase)	10%	0.96
30% (2.50X increase)	10%	0.99
24% (2.00X increase)	20%	0.81
27% (2.25X increase)	20%	0.94
30% (2.50X increase)	20%	0.98

The baseline sample size of 450 affords us the ability to detect bivariate associations between treatment use and alcohol consumption outcomes at the 6-month follow-up as small as 0.14 with power of 0.85 (0.15 with power of 0.85 and 10% participant attrition; 0.16 with power of 0.85 and 20% participant attrition). We used MacCallum, Browne, and Cai's (110) method for deriving power estimates for the fit of nested SEMs (111), which, in this case, involves comparing freely estimated models to those without certain paths (i.e., models without residual direct effects of treatment condition on alcohol consumption outcomes, which imply full mediation). Following common cut points for model fit (112), we assumed a RMSEA of 0.05 for the well-fitting model and 0.10 for a poor fitting model. With a sample size of 450 and our variables of interest, we have power of approximately 0.87 to detect significant changes in fit associated with eliminating paths from the model.

Randomization procedures. Baseline assessments are performed by the University of Rochester Medical Center (URMC) based study team. After the baseline assessment, subjects will be randomly assigned with equal allocation to Cognitive Behavioral Therapy for Treatment Engagement (CBT-TE) or the control condition. The randomization plan will be generated by Dr. Abar, co-I and study statistician, using an established SAS macro. Only Dr. Abar will have access to the treatment assignment prior to a subject being randomized, eliminating the possibility of selection bias. The randomization will be implemented via a REDCap module. The randomization plan will also include blocking to ensure that an equal number of subjects have been assigned to the two treatment groups after a certain number of subjects have been enrolled (block size). Only Dr. Abar will be aware of the block size used.



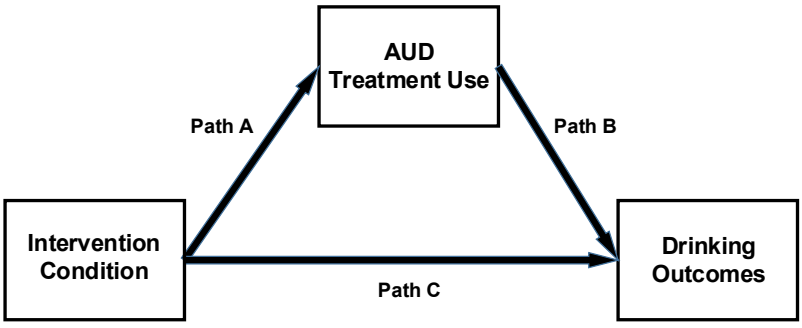
Following baseline assessment, the URMC based research staff member who performed the assessment will inform the subject that he/she will be contacted and informed of his/her study assignment within one business day by a member of the Medical University of South Carolina (MUSC) based study team. Upon ending the call, the URMC based research staff member will inform the MUSC team that a new subject has been enrolled and requires randomization and follow-up within one business day, with the subject number provided. The MUSC based research assistant will access the subject's assessment information and contact information through REDCap with a username and password, and subsequently access the module to receive the subject's treatment assignment. Within one business day, the MUSC research assistant will contact the subject and inform them of their treatment assignment (CBT-TE or control), following a script for informing subjects of their condition. For control subjects, the research assistant may perform the control intervention (i.e., read the subject an NIAAA pamphlet) immediately if the subject wishes, or schedule the control session. Subjects assigned to the CBT-TE therapy condition will be provided an appointment with a therapist within one week. The strategy to have the randomization assignment accessed by the MUSC based team, and communicated to subjects by the MUSC based team, allows the URMC based research staff to remain blinded to treatment assignment. This strategy is facilitated by the unique roles played by URMC (data management, recruitment, baseline assessment, follow-ups) and MUSC (provision of CBT-TE and control interventions). Accordingly, the same URMC research staff member who performed the initial assessment will be able to perform follow-ups, advantageous to maintaining rapport with subjects. Subjects will be instructed not to communicate their treatment group during follow-up assessments.

Statistical Analyses: Overview: We will use structural equation models (SEM) in Mplus 7.11 (99) to accomplish our specific aims. SEM is a flexible analytic method that enables us to examine the main effects of the intervention on alcohol treatment use (**Aim 1**) and alcohol use outcomes (**Aim 2**), as well as mediation pathways to alcohol use outcomes through treatment use (**Aim 3**).

Key measures: The primary measures are: 1) assignment to CBT-TE (intervention) or attention control condition (control); 2) any use of AUD treatment measured at 1- and 3-month follow-up assessments (present, absent); and 3) intensity of alcohol consumption (mean number of standard drinks per drinking day, DDD) and frequency of alcohol consumption (percent days abstinent, PDA), assessed at 6-month follow-up.

Preliminary analyses: Baseline demographics will be examined using descriptive statistics prior to the primary and secondary analyses. Treatment conditions will be compared on baseline demographic and behavioral data using χ^2 tests of independence and independent-samples *t*-tests (or non-parametric analog) as randomization checks. The following characteristics that groups significantly differ on ($p < 0.05$) at baseline will be included as covariates in later analyses: age, sex, and AUD symptom count. The alcohol consumption variables (i.e., DDD, PDA) including assessments obtained at baseline will be included in all models.

Primary analyses: The Figure presents the general framework for the analytic plan to accomplish our aims using the Baron and Kenny (100) nomenclature for associations among variables of interest.



In Aim 1, the AUD treatment use variables assessed at 1- and 3-month follow-ups will be regressed upon intervention condition (Path A). SEM in Mplus is flexible to the inclusion of a variety of outcome distributions including dichotomous variables like whether or not a participant received AUD treatment. The model used to address Aim 1 will be saturated (i.e., all possible associations among variables are modeled), such that model fit will be irrelevant and we will instead focus on statistical significance of path coefficients and corresponding effect size estimates (101). Relevant exogenous covariates will be incorporated into these analyses, and will not impact the saturation of the model. It is upon Aim 1 that the overall study has been powered (see sample size calculation above).

In Aim 2, alcohol consumption outcomes (i.e., DDD, PDA) at a 6-month follow-up will be regressed upon intervention condition in a saturated SEM (Path C). Outcome values will be examined prior to performing this analysis in order to identify the most appropriate distribution for modeling and/or the need to transform alcohol consumption variables.

In Aim 3, mediation of the intervention effect on alcohol consumption outcomes by AUD treatment use will be evaluated using the Sobel test utility in Mplus (Path A x Path B). This utility in Mplus is able to evaluate the statistical significance of multiple indirect pathways (e.g., assignment to CBT-TE or control condition → use of AUD treatment assessed at 1- and 3-month follow-up → DDD assessed at 6-month follow-up; assignment to CBT-TE or control condition → use of AUD treatment assessed at 1- and 3- month follow-up → PDA assessed at 6-month follow-up) simultaneously (102-103). The SEM models also allow for comparisons with and without residual direct effects (i.e., effect of intervention condition on drinking outcomes when accounting for the mediating role of AUD treatment engagement) to determine an observed mediation effect is partial or complete. A significant indirect effect and an observed decrement in model fit with the removal of the residual direct effect is indicative of a partially mediated effect, whereas a significant indirect effect and a non-significant change in model fit is indicative of a fully mediated effect. The fit of competing models will be evaluated using model χ^2, the Comparative Fit Index, and the Root Mean Square Error of Approximation (104-105), with greater changes indicative of poorer fit for the new model (corresponding to the interpretation of a partial mediation).

Secondary analyses: We previously discussed the rationale for secondary analyses focused on select subject characteristics (sex, alcohol-related severity) and treatment considerations (type of care, short-term retention in care). An SEM framework affords the opportunity to conduct secondary analyses on data including (A) moderated mediation analyses of the associations between variables of interest by salient demographic- (e.g., sex) and clinical characteristics (e.g., alcohol-related severity) using multiple groups modeling (106) and/or multiplicative interaction terms (e.g., centered X1, centered X2, and X1 by X2) and (B) latent variable modeling such as latent class analysis to examine subgroups of participants for whom the intervention might be most effective (107). Although the study was not powered specifically to perform these types of sub-group analyses, the sample size will allow us to explore select differences in treatment response as suggested by the literature including comparisons by sex (39-40) and alcohol-related severity (41-42). We will define alcohol-related severity using AUD symptom count, obtained at baseline assessment. We will also explore if the mediating effect of alcohol-related care differs by the type of care received as defined using a 3-group categorization (43), consistent with moderated mediation. In sensitivity analyses, we will repeat the primary analyses using short-term retention in care or "engagement" (45-46) as the measure of alcohol-related care (Aim 1) and as the mediator of alcohol use outcomes (Aim 3).

Missing data: Missing data will be addressed in two ways. First, all models performed in a structural equation modeling framework will use a full information maximum likelihood (FIML) estimator robust to non-normality to account for missing data over time (108). These methods yield unbiased estimates and appropriate standard errors without sacrificing cases (thus maximizing statistical power) when data are missing completely at random or predicted by other variables in a given model but independent of the values of the outcome itself (i.e., missing at random). Statistical comparisons on baseline data (e.g., treatment condition, participant sex, alcohol-related severity) will be made between cases retained and those lost at follow-up to determine differential attrition and which covariates require inclusion in the models to meet the missing at random assumption. Mplus has a variety of FIML estimators for use with different outcome distributions and model specifications. Second, following much of the literature examining RCTs, we will apply intention-to-treat principles to data missing at follow-up (109). Specifically, we will ascribe undesirable values to all missing data points (e.g., assume no treatment use has occurred). Estimates from each method for handling missing data are valuable, as the FIML approach will provide a reasonable estimate of the true intervention effect whereas the intention-to-treat approach will provide lower bounds of the efficacy of the intervention.