Statistical Analysis Plan

Web-based Addiction Treatment: Cultural Adaptation with American Indians
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Outcome Measures and Covariates

We will recruit 80 outpatient clients of diverse AI/AN tribal affiliation (40 per treatment arm) in Months 5 to 25.

Aim 1 [primary] outcome: 1) Consecutive weeks of abstinence from illicit drugs and alcohol confirmed by weekly urine drug/breath alcohol tests and TLFB self-report (continuous). The primary outcome was selected because it was a strong variable indicating TES effectiveness in a prior trial[30] and it is a consistent outcome measure used in CM and combined CRA/CM studies, allowing comparability across results. It is also clinically meaningful in that consecutive stretches of abstinence are a desirable impact of treatment intervention.

Aim 1 [secondary] outcomes: 1) abstinence in the last 4 weeks of treatment (longitudinal, dichotomous); 2) post-treatment abstinence (proportion days abstinent at 3-month follow-up; continuous); 3) weeks of treatment retention (time to drop-out 0-11 weeks, continuous); 4) coping strategies (mean score, continuous); 5) social functioning (index score, continuous); 6) HIV risk behavior (consistent condom use (dichotomous); intention to use condoms (ordinal)); and 7) treatment acceptability (continuous).

Additional variables: *Covariate, primary and secondary outcomes*: 1) abstinence status at baseline (dichotomous); *Moderators*: 2) demographic characteristics (gender, age, etc.); 3) primary substance (stimulant vs. other; dichotomous); 4) ethnic identity (continuous); 5) enculturation (continuous); and *Mediators*: 6) social connectedness (continuous); 7) alcohol/drug craving (categorical); and 8) coping (continuous). See *Table1*.

Intent to Treat, Dropouts, and Missing Data

The primary analyses will be on the Intent-to-treat (ITT) sample, i.e., all randomized subjects (N=80) according to the treatment arm they were assigned. Primary outcome analysis will begin once all participants have completed the 12-week treatment phase. For clients who do not drop out of treatment completely, missed visits will be assumed non-abstinent except, as consistent with Petry et al.,[159] for allowance of excused absence without penalty if the most proximal visits before and after the missing value are abstinent. For clients who drop from treatment completely, the primary outcome will be the number of consecutive half-weeks abstinent prior to dropout. We will account for dropouts by assigning appropriate weights to partially observed data. We will also perform an extensive sensitivity analysis to examine the influence on the outcomes for those who dropped out of treatment by performing several imputation methods, for instance imputing missing weeks as all abstinent or all non-abstinent.[164-168] Comparison of the inferences from assuming various models for the missingness provides a measure of the validity of the efficacy estimate from the primary model.

Significance Testing and Preliminary Analyses

All tests for main effects will be performed at two-tailed significance α=5%. Before performing specific analyses, we will examine outcome measures and covariates for outliers. The distributions of continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. Distribution of demographic variables will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. Covariates will be examined for association with treatment outcome. Covariates associated with treatment outcome will be adjusted for use in models used to test study hypotheses.

Aim 1: Primary outcome

Statistical Model: (M1) *TES-NAV+TAU will promote greater number of consecutive weeks of drug and alcohol use abstinence compared to the TAU arm during the 12 weeks of treatment.* The positive effect of randomization to the TES-NAV+TAU group compared to TAU group on number of consecutive weeks of drug and alcohol abstinence will be examined and estimated. We will use generalized linear mixed effect models (PROC GLIMMIX in SAS®) with subject as random factor and appropriate link function of the outcome variable (identity for normally or log-normally distributed; log for Poisson or negative binomial distribution) and adjusted for baseline abstinence status: $\boldsymbol{Y_i = \beta_0 + \beta_1 I_i^M + \beta_2 C_i + s_i}$ where Y_i is the continuous outcome measure (number of consecutive weeks of abstinence) for i^{th} subject; I^M is an indicator for the treatment group ($I^M = 1$ for TES-NAV+TAU and $I^M = 0$ for TAU); C is baseline abstinence status; and s_i is a random effect of i^{th} subject.

Power Analysis: There are no previously published trials specifically examining CRA/CM with AI/AN. The primary purpose of the R34 is to conduct a pilot study to estimate effect size of TES-NAV on measures of abstinence and associated outcomes and to assess whether effect sizes are clinically meaningful. This will be done using confidence interval methodology. The resulting 95% confidence intervals provide considerably more information than testing a specific null hypothesis. They give a range of plausible parameter estimates for the differences of population proportion of consecutive weeks of abstinence between TES-NAV+TAU and TAU. Such a range of plausible effect sizes can be used to estimate potential effect size in a larger clinical trial. It is strongly advised to use the least favorable end of the confidence interval for designing larger clinical trials. Because of the novelty of the proposed study, the following power calculations are only in support of the study and for the purpose of sample size calculation. With 40 participants per group, and assuming the TAU arm achieves 2.55 consecutive weeks of abstinence (based on TAU performance in prior effectiveness trial of TES, see Sect.C4.1), we have 80% power, at two-tailed α = .05, to detect an effect size of 1.903/3 = 0.634 (medium size effect). Statistical power of the aims will be increased by accounting for baseline abstinence status.

Table 2. *Power Analysis Aim 1: Mean Difference (wks) TES-NAV+TAU – TAU*

	Standard Deviation (in wks)		
Power	3	3.5	4
80%	1.903	2.220	2.537
70%	1.687	1.969	2.250
60%	1.503	1.754	2.004

Aim 1: Secondary outcomes

Statistical Models: The effect of randomization to the TES-NAV+TAU arm to (M2) increase the proportion abstinent in the last 4 weeks of treatment; (M3) increase the proportion of days abstinent three months post treatment; (M4) increase treatment retention; (M5) increase coping strategies; (M6) improve social functioning; and (M7) increase proportion of consistent condom users will be estimated. Aim 2 outcomes will be analyzed using logistic regression (for dichotomous outcomes) and general linear models or longitudinal general models (for continuous outcomes), with appropriate link functions. Any outcomes from above if analyzed using mixed effect general linear models will treat subject as a random factor. Retention data will be displayed with Kaplan-Meier curves that show the observed probability of retention in the program until time t, over time. The survival data for TES-NAV+TAU and TAU groups will be analyzed using proportional hazards models that allows for multiple covariates, if needed. If proportional hazard assumption is not satisfied, the data will be analyzed using a non-parametric log-rank test. Covariates that are known to be related to the outcomes will be added to the models to improve the power for detecting significant differences.

Aim 2: Moderation and Mediation

Moderation Statistical Models: The effect of randomization to the TES-NAV+TAU arm will be estimated for subpopulation based on demographics and baseline characteristics. We will estimate the moderation effect on primary outcome using a similar model to Aim 1 primary outcome with the inclusion of moderator by treatment interaction: $\boldsymbol{Y_i = \beta_0 + \beta_1 I_i^M + \beta_2 M_i + \beta_3 I_i^M M_i + \beta_4 C_i + s_i}$ where M_i is the moderator status for i^{th} subject. Regardless of the significance of the interaction term, we will use the model to estimate the 95% confidence interval of the treatment effect for each level of the moderator variable. Heavily overlapping 95% confidence intervals will be indicative of no moderating mechanism.

Mediation Statistical Models: The effect of randomization to the TES-NAV+TAU arm will be estimated when adjusted for potential mediators. We will estimate the mediation effect on primary outcome using a similar model to Aim 1 with the inclusion of additional mediators as adjusting covariates: $\boldsymbol{Y_i = \beta_0 + \beta_1 I_i^M + \beta_2 N_i + \beta_3 C_i + s_i}$ where N_i is the mediator status for i^{th} subject. Regardless of the significance of the mediator term, we will use the model to estimate adjusted treatment effect 95% confidence intervals and compared to treatment effect confidence intervals estimated via primary Aim 1. Heavily overlapping 95% confidence intervals will be indicative of no mediation mechanism.

Aim 3 Cultural Factors

Statistical Model: *Longest weeks of consecutive abstinence (M8) and (M9) acceptability of TES-NAV will not differ by enculturation, ethnic identity, or tribal affiliation.* Enculturation and ethnic identity will be appropriately categorized into low, median, and high. Using longitudinal mixed effect general models with each TES-NAV+TAU participant as a random factor and autocorrelation AR(1) structure for within subject association, the

average weeks of abstinence and acceptability of TES-NAV for each level of enculturation, ethnic identity, and for each represented tribe will be estimated along with corresponding 95% confidence intervals. We will estimate 95% confidence intervals for each level of enculturation and ethnic identity and plot each distinct tribe using a Forest plot. We then will note estimated abstinence and acceptability by enculturation, ethnic identity, and tribe which does not overlap with others. Although, the 95% confidence interval can vary in length and center, the overlap will suggest that there are no meaningful differences on acceptance of TES-NAV.

Qualitative Analysis: We will use qualitative interviews (N=10; randomly selected 25% of TES-NAV participants) to describe and contextualize quantitative outcomes in Aim 2. Qualitative assessment will elicit rich descriptions of participants' experience with and reaction to TES-NAV in their own terms and language and provide complementary and elaborative data.[169-170] An initial interview guide will be developed by the Collaborative Board using experiences from the acceptability trial and adaptation process. Using Atlas.ti© software and a coding framework developed from the interview guide, research staff (Rieckmann, Turrigiano, Rossi will systematically code transcripts of the interviews, resolving discrepancies in consensus discussion. The *Grounded Theory* approach will guide analysis and help to illuminate the role of participants' enculturation and ethnic identity on their acceptance and overall experience with TES-NAV.

Data Management

All data will be collected at the recruitment site, saved to onsite electronic databases, and electronically exported at pre-planned intervals to the research team at Columbia University. To ensure data security, assessment data collected by research staff will be directly entered into computers with no personal identifiers and source documents will only identify participants by study ID. Access to computers used for data entry, data management, and analysis will be password protected and limited to study investigators. See human subjects for more detailed information on quality assurance monitoring, data integrity and data management.