A Pilot Trial to Prevent Intoxicated and Impaired Driving Among Adolescents

Statistical Analysis Plan

NCT04959461

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Data Analysis

Preliminary analysis will examine distributions of all outcome variables to first detect evidence of sparseness for categorical data and of non-normality for continuous variables using graphical evidence, examination of skewness, kurtosis, etc. Where sparseness exists in categorical variables, we will collapse to produce cell sizes sufficient for analysis. For continuous outcome measures that are unlikely to satisfy the normal distribution assumption, we will consider variable transformation. Missing data will be handled by imputing missing items from scales using within-scale mean imputation. To be imputed, there must be data on at least 50% of items comprising the scale, item-test correlations should be similar across items, and the overall reliability must be > .80. For loss to follow up, we will use full information maximum likelihood estimation or multiple imputation to obtain estimates that are consistent and unbiased. These two approaches are asymptotically equivalent and do not yield substantively different results. Balance equivalence will be evaluated by comparing variables from the baseline survey across experimental groups to assess balance of the randomization process. ANOVA or t-tests will be used to test for comparability of groups for continuous baseline measures, and categorical methods of analysis such as chi-square tests will be used to compare groups for discrete baseline measures (e.g., gender). Any statistically significant differences will be controlled for in subsequent analyses through addition of model covariates.

Aim 1 analytic plan (intervention effects). This analysis examines differences in alcohol and marijuana use, consequences, driving attitudes, and passenger behaviors at follow-up controlling for baseline and other socio-demographic characteristics. Analyses will use the standard intent-to-treat (ITT) approach, in which we will analyze participants as belonging to the group (web-CHAT or UC) they were randomized to, regardless of later non-response or loss at follow-up. We will compare outcomes between groups using a regression-based framework. To protect against inflated Type I error rates caused by multiple testing, we will carry out a multivariate test of the simultaneous effect of the intervention on outcomes at 3 and 6-months. Where this multivariate test is statistically significant, we will then use individual univariate tests at each follow-up.

The multilevel modeling framework means that an individual who only completes one of the outcome assessments will still have those data included in the analysis. This approach uses a full information maximum likelihood estimator, meaning that all information is included in the analysis under the assumption that the data are missing at random or missing completely at random. Where variables are not normally distributed, we will consider an alternative link function; for example, for outcomes which assess the number of events that have occurred, we will employ Poisson regression with standard errors adjusted for over-dispersion if necessary. Exploratory analysis can investigate whether efficacy varies as a function of other baseline measures (e.g., marijuana use severity, simultaneous alcohol and marijuana user). We will use standard multiplicative approaches229,230 to test effects, and in the case of continuous moderators, we will examine the regions of significance to determine the levels of marijuana severity where we have evidence of intervention efficacy. In addition, biological sex will be explored and accounted for as a covariate of interest in relevant analyses.

The flexibility of the multivariate multilevel framework allows for simultaneous inclusion of multiple repeated measures outcomes with varying distributional forms and scales of measurement. Thus, the final model can include different link functions such as linear, log, and logit. Moreover, not only can link functions vary among variables, but they can also vary across levels of the model. Not all software can

handle such complex models; however, we will use Mplus v8.1, which allows for inclusion of continuous, censored, binary, ordered, categorical (ordinal), unordered categorical (nominal), counts or combinations of these variable types. By the user specifying the variable type (e.g., binary/ categorical), the software updates the estimation method to incorporate varying functions (e.g., logit).

Aim 2 analytic plan (mediation). We will conduct mediation analyses to examine whether changes in self-efficacy, norms and beliefs (areas of focus in the intervention content) serve as explanatory mechanisms for our primary outcomes among newly licensed drivers who receive web-CHAT. This will allow us to leverage our novel dataset to explore predictors of behavior change, thereby improving the development of future interventions. Mediation analysis will be carried out within a structural equation modeling framework. We will first conduct a multivariate mediation test to determine if the total mediation effect is statistically significant to control Type I error rate. If the total mediated effect is significant, we will then examine the individual mediators to determine statistical significance. The estimate of the effect of the intervention on the outcome can be divided into the direct effect and the indirect (mediated) effect. Determining the total indirect effect is straightforward. For potential mediators 1 … k, we assess: $y_i = \beta_0 + \beta_1 int_i + \beta_k M_k + e_i$ where y_i represents the outcome of interest, β_0 is the intercept, β_1 the effect of the intervention (int_i; indexed with i to indicate the intervention status of individual i) and this represents the indirect effect. M_k represents the set of potential mediators, and β_k is the effect of the mediator on the outcome. Using a structural equation modeling framework, we will simultaneously estimate the effect of the intervention on the mediators: $M_{ki} = \delta_{k0} + \delta_k int_i + e_i$ where M_{ki} is the mediator k for individual i. δ_{k0} represents the intercept for mediator k, and δ_k represents the effect of the intervention on mediator k. The indirect effect via each potential mediator is given by the element-wise product of the vectors β_k and δ_k and the total mediation effect is β_k x δ_k'. The standard errors of the individual indirect effects will be estimated using bias-corrected bootstrapping.

Determining efficacy. The purpose of this R34 study is to document feasibility of our protocols and acceptability of our intervention; however, we recognize there are important lessons to be drawn from this pilot work to inform whether a larger trial will be pursued. We will determine efficacy on our primary outcomes using both clinical and statistical significance. We will examine clinically meaningful effects of the intervention by using effect sizes. If we find a small to moderate effect of the intervention, this will be an indication of efficacy. Of note, in the original CHAT intervention with 40 participants, some effects were not statistically significant, but effect sizes were over .80.2 If we find a statistically significant effect of the intervention compared to UC at an alpha of .05, then this indicates efficacy. It is also important to note that one of the main purposes of the R34 mechanism is to explore how this intervention works in this setting with this population, which will also provide crucial information on implementation efficacy.

Statistical power. For Aim 1, we consider only the univariate portion of the analysis because power estimation for the multivariate analysis depends on a range of factors (e.g., residual correlation of the outcome variables) for which we do not have sufficient information. For a continuous outcome, the necessary sample size depends on the correlation between the baseline and outcome measures, and assumes this multiple correlation will equal 0.6. Using a two-tailed test (=.05), with a moderate standardized effect size of (Cohen's d) 0.50, 80% power is achieved with a sample size of 24, thus, we are more than adequately powered with our proposed sample. CHAT has standardized effect sizes ranging from 0.31 to 0.86 for continuous measures of marijuana use frequency, number of friends who use, intentions, and marijuana-related consequences,33 and we are confident that our sample size is

sufficiently large to identify statistically significant effects for our outcomes. Within conditions (e.g., web-CHAT) and given the recruitment proportions of those who screen positive and negative on the CRAFFT, we have 80% power to detect an effect size of 0.57 between adolescents who score positive and negative on the CRAFT within conditions (e.g., within web-CHAT) on primary and secondary outcomes with a sample size of 74 in each group. Between conditions (web-CHAT vs UC) we have 80% power to detect a moderate effect size of 0.50 with an overall sample of 96.