Study Protocol and Statistical Analysis Plan

Preventing Prescription Stimulant Diversion and Misuse Via a Web-Based Simulation Intervention

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1. **Statement of protocol design**: In this clinical trial, we compared the frequency of prescription stimulant diversion and misuse in college-attending emerging adults randomized to either (1) a web-based simulation intervention focused on stimulant diversion (i.e., giving, selling, or trading one's prescription medication) and stimulant misuse (i.e., using the medication differently from how it was prescribed) prevention, or (2) a web-based placebo presentation focused on psychological conditions commonly faced by college students. We randomized participants using the research randomizer website; participants were blind to their study group assignment. We recruited a total of 249 students. The principal and co-investigators, along with research assistants screened interested students to determine if they meet the eligibility criteria (i.e., a current prescription for a stimulant drug). Eligible participants were consented remotely and attended a one-hour remote session in which they completed a baseline questionnaire online (30 minutes) and then viewed the active simulation or the placebo presentation (30 minutes). One and two months after the baseline session, participants viewed two, 5-10 minute web-based info sessions respectively, that reinforced the content of either the active intervention or placebo. We then distributed web-based follow-up surveys 3 and 6 months after the baseline session.

2. **Characteristics of study data collection site(s)**: Data will be collected at three college/university sites: Trinity College (Hartford, CT); Texas State University (San Marcos, TX); University of Wyoming (Laramie, WY).

3. **Inclusion/exclusion criteria:** Inclusion criteria: Undergraduate or graduate students, between the ages of 17 and 25, who are prescribed a stimulant medication for ADHD or a related condition (or have had a prescription in the last three months). Students must plan to remain enrolled in one of the three data collecting colleges/universities before the conclusion of the study (i.e., 6 months after the projected date for the baseline session). Exclusion criteria: None.

4. **Randomization/stratification plan**: We used the research randomizer website (randomizer.org) to randomize participants to the active treatment or placebo condition (1:1). We stratified by history of prescription stimulant diversion (i.e., any instances of giving away, selling, or trading one's stimulant medication during one's lifetime).

5. **Definition of participants and plans to document participant flow:** Consistent with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting on randomized controlled trials, we tracked and report:
    - The number of individuals screened/assessed for eligibility.
    - The number of participants enrolled and randomized to each condition, and the number who received the placebo or active intervention. "Participant" was defined as someone who consented to participate. Reasons were provided in cases where participants missed any of the randomized intervention/placebo sessions.
    - The number of participants who participated in the 3- and 6-month follow-up assessments. Reasons for lack of participation in follow-up and/or discontinuation of intervention/placebo were provided.
    - The number of participants included in the analysis and reasons any participants were excluded, if necessary.

6. **Intervention definition**

- **Active intervention**: The 25-30 minute web-based simulation intervention, administered following the baseline survey, introduced the topics of non-medical prescription stimulant use, stimulant diversion, medical misuse and prescriber communication, and how they are interrelated. Module 1 discussed and depicted national prevalence rates of diversion and non-medical use of prescription stimulants (NMUPS) and risks associated with these behaviors. Module 2 taught effective strategies for resisting stimulant medication requests and allowed students to practice using these skills in interactive conversations with a virtual human. Module 3 taught behavioral strategies for communicating with one's prescriber, improving adherence, and reducing stimulant medication misuse.
    - Participants were invited via e-mail to view booster session #1 one month following the baseline session. The session, in the form of a slide deck, reviewed strategies that students could use to refuse requests for their stimulant medication from non-prescribed and prescribed students and strategies to communicate with their prescriber about their symptoms, dose, and side effects. Booster #2, administered two months later, reviewed the psychoeducational components of Modules 1 and 3 (e.g., lack of efficacy of stimulants for non-prescribed students; poorer academic/psychosocial outcomes associated with lack of adherence to medication). Each booster was administered online, lasted 5-10 minutes total, and contained 5 comprehension questions (multiple choice, true/false). Correct responses to each of the questions were viewable to participants.
- **Placebo intervention:** In the 25-30-minute web-based placebo tutorial, students learned about the prevalence of psychological disorders in college students, their etiologies, psychiatric medications, and videos of students' personal experiences navigating college with a diagnosis of an anxiety and learning disorder. Booster #1, one month following the baseline session, reviewed prevalence data and symptomatology for common psychological disorders. Booster #2, two months following the baseline, reviewed common forms of psychological and pharmacological treatment. Each booster was administered online, lasted about 5-10 minutes total, and contained 5 comprehension questions (multiple choice, true/false). Correct responses to each of the questions were viewable to participants.

7. **Regulatory Issues**
    - **Reporting mechanisms of the AEs/SAEs to the IRB and NIDA:** Research Assistants (RAs) report on AE/SAEs whenever they are detected during regular study contacts. Potential SAEs include: a) mental status deterioration to the extent that overnight hospitalization was needed (including clinically significant suicidal or homicidal ideation), b) physical health deterioration to a degree that acute, overnight medical services were needed, and c) clinically significant increases in substance use that necessitated inpatient hospitalization.
    - All research staff completed the required institutional training on research with Human Subjects and the IRB maintains copies of their certification. Study staff were trained in the monitoring and reporting of adverse events and understood that the responsibility is to document and report adverse events reported by study participants, independent of determinations made at the time or later of the relationship between the event and participation in the study. An Adverse Event Monitoring Form was completed for any suspected adverse events. The form

includes information about the details of the event, follow-up procedures as necessary (e.g., steps taken by RAs and PI), potential relation to study participation, and signature lines for all appropriate study personnel.
- RAs report SAEs immediately to the site PI after discovery. Deaths and possibly study-related SAEs are reported to the DSMB and the NIDA Program Officer within 72 hours of discovery and to the local IRB per policies. All SAEs are reported to the Data Safety Monitoring Board (DSMB) in quarterly reports.
- At monthly research team meetings, all adverse events were reviewed (cumulative and past month). Aggregate reports of AEs/SAEs were sent to the IRB annually as part of study continuations and quarterly to DSMB members as part of DSM reports.
- **Reporting mechanisms of IRB actions to NIDA:** The PI was responsible for informing NIDA of any actions taken by the Institutional Review Board as a result of its reviews of the project.
- **Report of changes or amendments to the protocol:** The PI reported major changes in the protocol or study, including protocol amendments, regulatory decisions such as suspension or termination of subject recruitment, changes in the IRB approval status, and other problems or issues that could have a significant impact on participants.

8. Outcome measures:

- **Primary**
  - **Frequency of diversion** will be assessed at baseline, 3- and 6-months. At baseline, participants will note how many times they have engaged in diversion (i.e., giving away, selling, or trading one's prescribed stimulant medication) during the previous year and in the last 90 days.
  - **Intention to divert** at all time points will be assessed with the following questions: "How likely is it that you will give away your stimulant medication in the next three months?" and "How likely is it that you will sell or trade your stimulant medication in the next three months?"
  - We will assess **medical misuse of prescription stimulants** by inquiring about ways in which students might be using their stimulant medication in different ways from how it was prescribed.
  - **User satisfaction** will be assessed immediately following the intervention. Specifically, we will assess the usefulness, information quality, and interface quality of the simulation.
  - **Usability of the simulation** will be assessed immediately following the intervention. Participants will indicate perceived usefulness, user control, and impact of the simulation.
  - **Booster engagement**. We will determine engagement in one or both online booster sessions by summing the number of correct answers to the five comprehension questions embedded in each of the two online boosters.
- **Secondary**
  - **Self-efficacy to resist diversion** will be assessed with two questions: "Please rate your confidence to (1) resist giving away your stimulant medication, (2) resist selling your stimulant medication."
  - **Resistance strategy use.** Participants who were approached for, but did not divert their stimulant medication, will be asked to indicate (open-ended response) how they turned down the request.

- **Perceived behavioral norms.** Participants will indicate, on a scale from 0-100, what percent of students, on average, engage in (1) diversion and (2) non-medical prescription stimulant use.
- **Risk perception.** Participants will report on perceived legal risks associated with prescription drug diversion and perceived harm from NMUPS and medical misuse.
- Participants will report on any **communication with their prescriber** regarding their adherence to their prescription or any concerns they have regarding the dose, frequency of administration, and/or side effects.
- We will assess **other substance use** (i.e., binge drinking, and/or marijuana, cocaine, heroin, methamphetamine, or hallucinogen use, or other prescription drug misuse) in the previous 90 days.

9. **Sample size.** To arrive at our anticipated sample size of 300 participants, we used the effect size (d=.20) from a meta-analysis of 43 interventions that evaluated longer-term effects of brief interactive interventions with college students on alcohol consumption. Power was estimated using generalized linear model in SAS where an exemplary data file was created assuming a stable (same) effect size of 0.2 across the 3- and 6-month time points with an autocorrelation of 0.6 and 150 students randomized to each condition (300 total). With a two-sided test and an alpha of 0.05, power is 0.80 to detect a significant treatment effect across the two time points. Assuming an attrition rate of 5% between time points (culminating in 270 students at month 6) power is 0.78 to detect a significant treatment effect across the six month trial. Only participants randomized to one of the two conditions will be included in the data analysis.

10. **Key adherence variables** will include whether participants respond to the questions associated with the 1-month follow-up booster, the 2-month follow-up booster, the 3-month follow-up survey, and the 6-month follow-up survey.

11. **Key safety variables.** Safety data will include treatment retention, study withdrawals, and AEs/SAEs by treatment condition.

12. **Data analysis plan:**

- We modeled **diversion risk** using the following indicators at baseline, 3- and 6-months: number of occasions when a participant sold his/her stimulant medication; gave his/her medication away; traded his/her medication in the last 90 days; and intention to divert in the next three months. We initially planned to model stimulant **medication misuse** using the following indicators at baseline, 3- and 6-months: the total number of occasions when a participant used an alternative route of administration, took more than his/her recommended dose, took less than his/her recommended dose, took someone else's stimulant medication, took a stimulant medication with alcohol or other drugs, or intentionally got high on his/her prescribed stimulant medication. We ultimately elected to operationalize medication misuse without the inclusion of taking less than one's recommended dose, given that prior research has typically not included this behavior in measures of medication misuse. Using Mplus statistical software, a SEM with the factors diversion risk and medication misuse measured at three time points (baseline, 3-month, 6-month follow-up) was be created. The model included autoregressive paths between sequential time points and treatment condition was an exogenous variable predictive

of the factors at each time point. This approach permitted tests for change across time and for the effect of treatment condition on each factor at each time point.
    - To test if the effects of the intervention on diversion risk or stimulant medication misuse at the six-month follow-up are moderated by demographic (i.e., sex, race/ethnicity, age, class year) or psychosocial factors (i.e., other substance use, history of conduct problems), a path model with intervention and the moderating factors (with product variables) as exogenous variables and diversion risk (and medication misuse, respectively) as endogenous variables will be run.
    - To determine whether the intervention produced change in our secondary outcomes, we examined whether there were differences between the treatment and placebo conditions in (1) self-efficacy to avoid diversion, (2) resistance strategy use, (3) knowledge about diversion and NMUPS norms and risks, and (4) prescriber communication. Knowledge about NMUPS norms and risks was measured at baseline and 3-months; resistance strategy use will be measured at 3- and 6-months. Prescriber communication and self-efficacy to avoid diversion were measured at baseline and at the 3- and 6- month follow-ups. Similar to the primary outcomes, SEM was used to model these outcomes and test if treatment condition is causal for any of these outcomes across time points they are measured.
    - If we show an effect of the intervention on one or both of our primary outcomes, we will assess the extent to which change in resistance strategy self-efficacy, knowledge about norms and risks, resistance strategy use, and/or prescriber communication mediated associations between the intervention and the primary outcomes (i.e., diversion risk, medication misuse). This was accomplished using a multilevel mediation model (where repeated measures are nested within students) in Mplus.
    - To assess **usability of, and satisfaction with the simulation**, we calculated means for the user satisfaction and usability measures and compared them to the control group.

13. **Interim Analyses and Rules for Stopping:** One year after the first participant was enrolled, and each year after, the investigators conducted interim analyses on the two primary outcomes, prescription stimulant diversion and misuse of one's prescribed stimulant medication, to ensure that differences between the active intervention and placebo groups were not unduly large. If there were a large effect (Cohen's *d* = .8) favoring the placebo group, the investigators would be concerned that the active intervention was iatrogenic and therefore would consider discontinuing the trial. On the other hand, if there were a large difference (Cohen's *d* = .8) favoring the active intervention group, the trial may need to be discontinued so that the placebo group could receive a more effective intervention.