

# Study Protocol and Statistical Analysis Plan

## A High School Program for Preventing Prescription Drug Misuse

ClinicalTrials.gov Identifier: NCT03219190

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### 1. Study Objectives

The primary objective of this study is to evaluate the effectiveness of an adapted, hybrid version of the Life Skills Training High School (LST-HS) program in reducing prescription drug misuse (PDM) behaviors and increasing the perceived risk of harm associated with PDM among high school students. Secondary outcomes include examining intervention effects on other forms of substance use and life skills. The study tests the hypothesis that the hybrid intervention will show improvements in the behavioral and skills outcomes when compared to a standard health education control group.

### 2. Study Design

- Study Type: Interventional (Clinical Trial)
- Design Model: Randomized Controlled Trial (RCT)
- Randomization Unit: School-level randomization to prevent contamination across conditions
- Masking: Open Label (Schools were assigned to either intervention or control conditions)
- Primary Purpose: Prevention
- Survey Time Points: pretest, posttest, 12-month follow-up, 24-month follow-up\*

### 3. Study Population and Eligibility

- Target Sample Size: 30 high schools, 3000 students\*
- Age/Grade: High school students
- Inclusion Criteria (Schools): High schools located in the U.S.
  - Access to web-enabled devices in classrooms or computer labs
  - Instruction provided in English
- Exclusion Criteria (Students): All students in the classroom were eligible to participate in the intervention. However, at the discretion of local school staff, students with significant cognitive impairment or severe learning disabilities were excused from completing the study questionnaire.
- *Protocol Updates: The COVID-19 pandemic caused significant delays in study implementation and data collection that required two changes to our original protocol: one affecting sample size and the other affecting follow up data collection. Our original aim was to recruit 30 schools and 3000 students. In response to COVID-19, we assessed a larger number of schools (N = 48) for eligibility in an attempt to over-recruit and account for higher expected dropout rates. Twenty-seven schools with 1804 students were recruited and randomized to conditions. Ultimately, nineteen high schools participated in the intervention (N = 10) or control (N = 9) conditions, and the final pre-post analysis sample size was N = 1235. Although the original protocol specified 12- and 24-month follow-ups, widespread school closures and access restrictions resulted in high attrition at the 12-month time point, rendering those data insufficient for meaningful analysis. The 24-month assessment was canceled because the study delays extended the timeline beyond the NIH/NIDA performance period. Consequently, the study analysis was limited to the pre-test and immediate post-test timeframe.*

## 4. Methodology and Interventions

### 4.1. Intervention Group: Hybrid LST-HS

The intervention consists of a hybrid adaptation of the evidence-based Life Skills Training program, delivered via eight e-learning modules and eight teacher-led classroom sessions.

- E-Learning Component: Provides didactic content through teen hosts and immersive, branched scenarios using animated characters
  - Personal Competence: Self-management skills (decision-making, coping, goal-setting)
  - Social Competence: Social skills (assertiveness, communication, relationship skills)
  - Drug Resistance: Refusal skills, pro-health norms, and content specific to prescription drug misuse and other forms of substance use
- Classroom Component: Facilitated by teachers, including reviews of concepts, role-plays, and small-group skills practice

### 4.2. Control Group: Treatment as Usual

- Students receive the existing school health education programming

## 5. Outcome Measures

### 5.1. Primary Outcomes

#### Prescription Drug Misuse (PDM)

Assessed using a 9-point Likert scale (1 = never to 9 = more than once a day) for the frequency of use without a doctor's prescription for:

- Sedatives (e.g., Xanax, Valium).
- Painkillers (e.g., OxyContin, Vicodin, Percocet, Codeine).
- Stimulants (e.g., Adderall, Ritalin, Concerta).

### 5.2. Secondary Outcomes

Other Substance Use: assessed using a 9-point Likert scale (1 = never to 9 = more than once a day) for the frequency of use:

- Alcohol use and alcohol intoxication
- Cigarette/tobacco use
- Marijuana use
- Inhalant use

Substance Use Intentions: intentions to use alcohol, get drunk, use tobacco, marijuana, and inhalants within the next year; measured on a 5-point scale from "Definitely Not" to "Definitely Will"

Perceived Risk of Harm of PDM: Assessed using a 4-point Likert scale (1 = no risk to 4 = great risk) regarding the perceived harm of using the three types of prescription medications regularly when prescribed for someone else.

Life Skills: Self-regulation skills: the ability to control one's thoughts, feelings, and behaviors; Communication skills: the ability to communicate effectively; Media resistance skills: the ability to resist messages from the media; Anxiety management skills: the ability to recognize and manage physical manifestations of anxiety; Refusal skills: the ability to resist pressure to use substances; All response options on a 5-point scale from "Strongly Disagree" to "Strongly Agree; except Communication skills, with response options on a 5-point scale from "Never" to "Always"

*Correction of Secondary Outcomes: The Secondary Outcomes section has been corrected to include variables that were specified in several sections of the original registration and collected during the trial, but were inadvertently omitted from the "Outcome Measures" field in the initial registration. These include: alcohol use, tobacco use, marijuana use, inhalant use, perceived risk of prescription sedative, painkiller, and stimulant misuse, and life skills (self-regulation, communication, media resistance, anxiety management, refusal skills).*

*Clarification on Terminology: Although our original grant application and ClinicalTrials.gov registration used the term Prescription Drug Abuse (PDA), we have updated our terminology and adopted the more contemporary term Prescription Drug Misuse (PDM) to align with current best practices. PDM is defined here as the use of prescription drugs without a doctor's prescription.*

## 6. Statistical Analysis Plan

- Analysis Level: Individual student level with adjustments for covariates
- Covariates: Pre-test scores, race/ethnicity, and gender
- Models: Generalized Linear Models (GLMs) with robust estimators to account for non-normal distributions; Mixed Models to control for school level clustering
- Significance: One-tailed significance tests ( $p < 0.05$ ) due to the unidirectional nature of hypothesized prevention effects and findings from previous studies testing the LST approach that have shown consistent prevention effects on cigarette smoking, alcohol use, marijuana use, and other forms of illicit drug use.