Study: # 7280 entitled Treatment of Cannabis Use Disorder among adults with co-morbid Attention-Deficit/Hyperactivity Disorder

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NCT# NCT02803229

Statistical Analysis Plan (Grant): October 29, 2015

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Pre-application ● Application ○ Changed/Corrected Application

4.a. Federal Identifier
DA040832-01

b. Agency Routing Number

2. DATE SUBMITTED
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Application Identifier
PD/2015/01148

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 1672049940000

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County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
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6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1141410842A2

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

○ New ● Resubmission
○ Renewal ○ Continuation ○ Revision

If Revision, mark appropriate box(es).
○ A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Treatment of Cannabis Use Disorder and ADHD

12. PROPOSED PROJECT
Start Date* 07/01/2016
Ending Date* 06/30/2018

13. CONGRESSIONAL DISTRICTS OF
a. Applicant* NY-013

Tracking Number:

Funding Opportunity Number: . Received Date:

Adverse Effects Measures: The Systematic Assessment for Treatment and Emergent Events (SAFTEE)[74] will be performed weekly to identify any adverse symptoms. **THC Use Measure:** THC use will be measured weekly by the TLFB method[75] and confirmed by twice-weekly urine toxicology testing. **Marijuana Withdrawal Measure:** We will use the 10-item version of the Marijuana Withdrawal Checklist. (MWC)[76] each week to measure subject-rated withdrawal severity. **Clinical Status Measures:** The Clinical Global Impression Scale-Observer (CGI)[77] will be used on a weekly basis to measure the overall clinical status of the participant. **Mood Measure:** A structured version of the Hamilton Depression Scale (HAM-D)[78] will be used to assess depression at baseline and every 4 weeks during the study. ***Sleep Measure:*** *Participants will complete the Pittsburgh Sleep Quality Index (PSQI[79]) at baseline and every four weeks to assess retrospective sleep quality over the previous 1-month period.* ***Assessment of ADHD Symptoms:*** a. Conners' Adult ADHD Rating Scale Self-Report: Long Version: CAARS-S:L [80] is self-administered and includes 66-items assessing ADHD. Symptom frequency on each item is rated on a 4-point Likert scale. b. Adult ADHD Investigator Symptom Rating Scale: AISRS[81] The rater is provided with prompts to rate from 0 to 3 for each of the 18 items. c. CGI for ADHD symptoms. A scores of 1 or 2 (very much or much improved) is considered clinically meaningful. **Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ)-The QLESQ** (short form) [82] is a self-administered questionnaire consisting of 16-items that are rated from 1 (very poor) to 5 (very good).

Assessment of Impulsivity and Cognitive Functioning*:* **a. Barratt Impulsiveness Scale. (BIS-11)**[83] This is a 30 item questionnaire that has been used in several previous studies on impulsivity and aggression. [84-86] Subjects willing to participate in the brief human laboratory evaluations will have additional impulsivity measures: **b. Immediate Memory Task/Delayed Memory Task:** IMT/DMT[87, 88] and **Delayed Discount Program**[89]**:** These measure are the primary impulsivity measures used. They were chosen to include paradigms based on two different models of impulsivity (rapid response and delayed reward). The Delayed Discount Program is a 20 minute computer task that asks participants to choose between a hypothetical larger delayed reward against a range of smaller immediate rewards. To use the Two-Choice Paradigm in a repeated fashion session length will be limited to 20 minutes/session. **c. Letter-Number Sequencing**[90]**:** This task is part of the Weschler-III and measures working memory. **d. The GoStop Task**[91] measures one's ability to inhibit responses. The dependent measure is the proportion of inhibited responses to the total number of stop trials for each delay condition. **Assessment of Medication Compliance:** In prior trials, our group has provided reinforcement to facilitate return of pill bottles and unused medication, if any. Modest monetary incentives (e.g., $10 in vouchers) for returning the prior week's pill bottle are provided. Voucher reinforcement is tied solely to the return of the pill bottles. Blood levels will not be drawn for amphetamine since it is a short-acting substance and blood level testing may lead to false negative (i.e., underestimation of compliance) results. Instead, quantitative urine drug screens for amphetamine will be done at weeks 2, 4, 6, 8, 10, and 12. Study staff will be blind to these results. Active study medication and placebo will be packaged in matching gelatin capsules, to which 25 mg of riboflavin will be added. Riboflavin is excreted in the urine, and when present in significant concentrations it fluoresces when placed under ultraviolet (UV) light. This is a sensitive indicator when the medication was taken within the last eight hours.[92] Since MAS-XR is taken in a single morning/early afternoon dose fluorescence of urine during a day's visit should be sensitive to the morning dose.

3. Statistical Analysis:

a. Outcome measures: Primary marijuana outcome: Consecutive abstinence during last two weeks (weeks 10-11) of the study (dichotomous); Primary ADHD Outcome: 30% Reduction in ADHD symptoms using the AISRS at the end of the maintenance phase (dichotomous); Secondary Marijuana Outcomes: 1) quantity of marijuana use (dollar value of marijuana use/week, continuous); 2) Mean number of using days per week (count, longitudinal); 3) Withdrawal symptoms (Marijuana Withdrawal Measure, continuous, longitudinal); Secondary ADHD Outcomes: 1) Percentage of individuals with CGI $\leq$ 2 (dichotomous); 2) Mean change in AISRS and CAARS score (continuous); 3) Neuropsychological traits associated with ADHD and substance dependence, including measures of impulsivity and attention (e.g. Immediate and Delayed Memory Task, GoStop, Delayed Discounting program, continuous; Letter numbering sequencing task, continuous); Secondary Psychosocial functioning and Mood outcomes:1) Quality of life measure QLESQ (continuous; longitudinal); 2) HAM-D score (continuous, longitudinal); Secondary Tolerability and Retention outcomes:1) End of study retention (at the end of week 11; dichotomous); 2) Time to dropout (survival, censored); 3) Maximum tolerated dose (continuous); 4) Rates of adverse events (dichotomous); Mediators: 1) Reduction in ADHD symptoms (continuous); 2) Change in Impulsivity (continuous); 3) Change in sleep quality (continuous); 4) Cognitive deficits (continuous); Covariates: 1) baseline ADHD score using AISRS (continuous); 2) age (continuous).

b. Sample size and randomization: We propose to randomize a total of 40 participants. Participants will be randomly allocated (1:1) to receive either MAS-XR or placebo and stratified by ADHD symptom severity (measured during lead-in period). To protect allocation concealment, randomization will be carried out by the statistician and implemented by the pharmacist who are independent of the research team. Randomization sequences will be balanced in blocks of random size 2, 4 and 6.

c. Intent to Treat/ Dropouts and missing data: The primary analyses will be on the Intent-to-treat (ITT) sample of all randomized participants. Participants who drop out before the end of the trial and are not present the final two weeks of the trial (expected to be less than 30% of participants), they will be counted as non-abstinent and their 30% reduction in ADHD symptoms will be judged based on the last available observation.

Those participants will be included in the ITT analysis of primary and secondary outcomes. Comparison of the inference from ITT analysis assuming the dropouts to be non-abstinent to various models for the missingness will provide a measure of the validity of the efficacy estimate from the model assuming missing to be non-abstinent. One can also compute a local sensitivity index which measures the change in the estimated treatment effect in a neighborhood around the ITT assumption for missingness.[93] We plan to perform a sensitivity analysis based on these two approaches to assess the effect of the assumption of missing 'at random' on the inference of treatment effect.

d. Significance testing and preliminary analyses: Tests for main effects will be performed at two-tailed significance 5%. Before performing specific analyses, we will examine all variables for outliers. The distributions of all continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. Distribution of demographic variables and measures of baseline symptomatology will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. We will examine the associations between key baseline variables (demographics, measures of cannabis use disorder severity) and the primary abstinence outcome measure. Baseline variables strongly associated with outcome will be included as covariates in models used to test the study hypotheses. We will also explore effect moderation, i.e., baseline covariate by treatment interactions.

Hypotheses:

Primary Marijuana hypothesis: MAS-XR will be superior to placebo in promoting consecutive abstinence from marijuana use in the last 2 weeks of the study. Primary ADHD hypothesis: MAS-XR will be superior to placebo in promoting a 30% decrease of ADHD symptoms at the end of the study.The effect of treatment on both primary outcomes will be examined using logistic regressions adjusted for appropriate covariates (see Section 3.a.) which are known to be associated with each of the primary outcomes, respectively.

Secondary Marijuana hypothesis: Treatment will be superior to placebo in: 1) reducing quantity of marijuana use, 2) reducing the mean number of using days per week, and 3) reducing symptoms of THC withdrawal.

Secondary ADHD hypothesis: *Treatment will be superior to placebo in: 1) reducing the percentage of individuals with CGI≤ 2, 2) reducing the mean change from baseline in CAARS and AISRS, 3) reducing deficits in neuropsychological measures of impulsivity and attention*.

Secondary Psychosocial functioning and mood hypothesis: *Treatment will be superior to placebo in: 1) improving psychosocial functioning and quality of life, and 2) reducing mood scores*.

Secondary Retention hypothesis: Treatment will superior to placebo in subject retention. The secondary outcomes will be analyzed using generalized mixed effect models with appropriate link function (identity for continuous outcomes, binary for dichotomous outcomes), where subject will be treated as a random factor. Longitudinal outcomes will be analyzed similarly with generalized mixed effect models with time as fixed effect and GEE structure to model the within subject over-time correlations as autoregressive AR(1) process. Time to dropout will be analyzed using survival analyses and Kaplan-Meier method.

Secondary Tolerability hypotheses: *1) Subjects in treatment will achieve a maximum tolerated dose of 80 mg on average, and 2) will only demonstrate mild to moderate side effects. An average maximum dose achieved across all subjects will be computed with appropriate 95% confidence interval. If the confidence interval includes 80 mg, we can conclude that the average overall achieved maximum dose is not significantly different than desired 80 mg. Similar analyses will be carried out for side effect outcomes. Time to dropout survival analyses will be performed. Mediation exploratory hypothesis: Reduction in ADHD symptoms, change in impulsivity, change in sleep quality and other cognitive deficits will be tested as mediators of the relationship between treatment and cannabis use using the Baron and Kenny mediation framework.*

d. Power Analysis*:* There have been few clinical trials for CUD and ADHD and none using MAS-XR. The primary purpose of this proposed R21 is to estimate the 95% confidence interval for the effect size of ADHD and CUD measures of ADHD symptoms and marijuana use, for purposes of planning future studies, which will be done using confidence interval methodology. While improving ADHD symptoms is important, it would be more noteworthy if MAS-XR reduced marijuana use as well. Thus, the power analysis is based on the marijuana use outcome. The resulting 95% confidence interval provides considerably more information than testing a specific null hypothesis: it gives us a range of plausible parameter estimates for the difference of population proportion of consecutive abstinence between the PBO and MAS-XR. Such range of plausible effect sizes can be used to estimate potential effect size in larger clinical trials. The following power calculations are only in support of the study proposal and for the purpose of sample size calculation. With 20 participants per group, and assuming that the observed proportion meeting the primary outcome (abstinent in the last 2 weeks of the trial) in the placebo group ranges from 10% to 25% (which is what we have observed in our prior trials with this population), we have 80% power, at two-tailed alpha = .05, to detect an effect as follows: 10% on placebo vs 48% on MAS-XR; 15% vs 55%; 20% vs 63%; or 25% vs 69%. The power for 30% decrease in ADHD symptoms will be the same as in Table 2.

Table 2

%abstinence: PBO	10	15	20	25
% abstinence: MAS-XR **(80% power)**	**48**	**55**	**63**	**69**
% abstinence: MAS-XR (70% power)	43	50	57	64
% abstinence: MAS-XR (60% power)	39	46	53	60

4. Timeline: Two months will be required for staff training and preparation. Recruitment will continue for 19 months allowing all enrolled participants to complete the study within 2 years. This recruitment flow is feasible based on our past success in recruitment of individuals with CUD and substance abusers with ADHD.