February 11, 2015

Rick Doblin, Ph.D.
Executive Director
Multidisciplinary Association for Psychedelic Studies (MAPS)
1215 Mission Street
Santa Cruz, CA 95060

Dear Dr. Doblin:

Thank you for the resubmission of the proposed, state funded study, "Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)."

The United States Department of Health and Human Services (HHS) conducted a third scientific review of the study to determine whether to recommend to the National Institute on Drug Abuse (NIDA) the release of research-grade marijuana to your organization.

The review committee notes that your organization's previous submission was approved on March 12, 2014 and that due to significant changes in the proposal, you have resubmitted it for review. The proposed study has been cleared for the purchase of research grade marijuana from NIDA. Notification of approval will be made to NIDA and FDA within two business days.

The clearance for this resubmission is not contingent on the following suggestions; however the review committee provides them for your consideration.

- The definition of 'treatment resistant' could acknowledge the distinction between failure to tolerate a medication and resistance to a trial of an adequate dose and duration of the drug. While 'unable-to-tolerate' participants need not be excluded, if they are more than occasional in the N, the description of subjects as 'treatment resistant' should be reconsidered.
- PRN dosing with an upper limit and no lower requirement is an atypical approach for treating an anxiety disorder. Treatments are typically used on a daily basis, with PRNs employed for clinical worsening or breakthrough symptoms; there is a concern about 'rebound' of symptoms with greater severity. Without a more standardized regimen, it will be difficult to establish efficacy; and the proposed quantitative measurements would be undermined.
- Tracking the number of patients who drop out of the study due to anxiogenic effects would be critical for accounting for selection bias in the final interpretation of the results.

- Limiting participants to two marijuana cigarettes a day may not be realistic and it may motivate subjects to seek additional marijuana from non-study sources. Participants who found relief during Stage 1 and are having difficulty navigating the two week washout, may also be motivated to obtain non-study marijuana.
- Related to the suicidality assessments, more detail about what would trigger alerting the site investigator and steps to be taken if suicidality appears during the trial would be helpful.
- We reiterate a previous recommendation to adhere to the National Advisory Council on Drug Abuse guidance on drug naïve subjects.

Through email correspondence, I know you are aware of the next steps and will not repeat them here. As of next week, I will no longer be in this position. However, you will receive an email with a new contact person by the end of the month.

Good luck with your research.

Sincerely,

Sarah A. Wattenberg, MSW
Senior Advisor for Substance Abuse Policy
Chairperson, Public Health Service Marijuana
Research Review Committee