

MAPS' Brief, Informal Response to Feb. 3, 2011, Advice/Information Request Letter
By Rick Doblin, Ph.D. and Ilsa Jerome, Ph.D.
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IND# 110513

Study Title: "Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Five Different Potencies of Smoked or Vaporized Marijuana in 50 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)"

To help expedite our call tomorrow, we're sending this brief reply to the Advice/Information Request Letter. In addition to the text below, we're sending a chart of various options for diversion control with advantages and disadvantages of each approach.

1. As currently proposed, the study would not be conducted in a manner to assure the safe and secure storage of marijuana, a Schedule I substance under the U.S. Controlled Substances Act. The drug will be self administered on a non-supervised outpatient basis. There are no provisions for maintaining the security and safety of the marijuana outside the investigator's direct control, including providing relevant training to the research subjects so as to prevent misuse, abuse, and diversion of the marijuana.

Our preferred approach is to provide each study participant with a means of recording their smoking or vaporizing of study marijuana, as through digital video camera (Flip, cost about \$225 each) or through video camera with internet connection. This approach can document that subjects use the marijuana themselves. Participants will be instructed to begin video recording upon starting to use their daily allotment of study marijuana and to record until they have completed smoking or vaporizing material. Participants will be observed smoking or vaporizing study material, and the recordings will be collected in real time (if over the internet) or collected at each weekly face to face meeting, with review by study staff before giving subjects their next week's supply. Participants not recording their own smoking or vaporizing study marijuana will be cause for removing an individual from further study participation.

We can also ask study participants to have a significant other verify that they are using the marijuana themselves.

2. You have not adequately described the proposed process by which the investigator would return any unused marijuana product to a particular research subject [upon request] for use outside of the proposed treatment arms in the protocol. You must demonstrate that this proposed activity is legal and consistent with DEA's administration of the Controlled Substances Act.

Participants who wish to receive their unused marijuana will continue to be enrolled in the study. The investigators would re-package the unused marijuana in similar packaging and participants would continue to use the material following the study protocol. They would continue to have weekly meetings with the investigators and undergo assessment until they exhausted their supply of remaining study marijuana.

3. As currently written, the protocol and consent do not adequately state the legal status of marijuana under current federal regulations.

We will add a statement to the protocol and consent stating that marijuana is a controlled substance that can only be used legally within the context of a clinical study.

4. The protocol and consent do not adequately address the subjects' potential legal risks of using marijuana and how these risks can be mitigated.

We will state in the protocol and consent that study participants may face risks from positive drug screens that might occur at the workplace and there is a risk that they may face potential arrest by the police for possession of marijuana as a result of taking part in the study. This risk may be mitigated by providing participant with a study participant identification card (e.g. "wallet card") stating that they are participating in a medical research study of marijuana and that they may test positive for marijuana and that they are permitted to use marijuana under the specific conditions of study participation.

5. The proposed schedule for clinical monitoring is not adequate. We request that investigators conduct at least weekly face-to-face visits. We recommend that assessments at these visits should include vital signs, serum cannabinoid levels, urine drug screen, CAPS, GAF, BDI-II, and CSSRS. We also request that you propose an instrument to monitor for general psychiatric symptoms, including psychotic symptoms, dissociative symptoms, depersonalization, and derealization. One example is the Brief Symptom Inventory, which is a broad survey of potential psychiatric symptoms.

Meetings currently described as telephone meetings will be transformed into face to face meetings with the investigators. It was already planned to administer BDI-II, GAF, and CSSRS during each meeting by telephone, and we would perform the same measures during a face to face meeting. We will add measurement of serum cannabinoid levels and an additional measure of psychiatric symptoms, such as the BSI.

Although the CAPS can be used to assess symptoms within the past week, the length of the measure makes it unwieldy for use in each weekly face to face meeting, and it is more common to use the measure to refer to symptoms within the past month. We could use a similar self-report measure, the Posttraumatic Diagnostic Scale. It takes ten minutes to complete, taps into the same DSM-IV criteria for PTSD, and produces a symptom severity score that can be compared with Global CAPS score.

6. The subject information and consent form states: "Whenever possible, make sure that you are not going to be driving up to three hours after your last time of marijuana use." We request that you strengthen the caution by the removing the phrase "whenever possible."

We will remove the qualifying phrase from the subject information and consent form.

7. Provide current Clinical Investigator's Brochure, which should be available from NIDA.
We will request a copy of the Investigator's Brochure from NIDA and will supply it to FDA.