Multidisciplinary Association for Psychedelic Studies
1215 Mission Street, Santa Cruz, CA 95060 USA
Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370

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Sarah A. Wattenberg MSW
Sr. Advisor on Substance Abuse Policy and Marijuana Research Review Committee Chairperson
Office of the Assistant Secretary of Health
U.S. Dept. of Health and Human Services

Ms. Sarah Wattenberg,

Hello again and best wishes from Rick Doblin, Ph.D., Executive Director of MAPS, a non-profit research and educational organization. I am writing you now in a belated response to your letter of September 21, 2011, reporting that all five Public Health Service (PHS) reviewers had recommended against approving the privately-funded, MAPS-sponsored, Food and Drug Administration (FDA)-approved drug development pilot study, "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)". I had submitted the protocol to you for review four months and three weeks previously on April 28, 2011.

In your letter, you concluded, "If you plan to submit a revised protocol, please forward it to my office for review." Attached for review is our revised FDA and University of Arizona Institutional Review Board (IRB)-approved protocol and informed consent form and related documents.

You highlighted in your letter four general issues raised by the reviewers regarding the protocol, to which I've responded below after this cover letter, followed after the references by another document in which we elaborate on the rationale for our protocol design decisions, as requested by the PHS reviewers. This document was initially submitted to the UArizona IRB.

When I submitted our initial protocol to you, it had been approved by FDA but had not yet been submitted to an IRB. In July 2012, after all five PHS reviewers rejected the protocol, Dr. Sue Sisley, Principle Investigator, submitted the unchanged FDA-approved protocol to the University of Arizona IRB. We also included in our submission your cover letter, the comments of all five PHS reviewers, our document discussing the rationale for our protocol design decisions, an informed consent form and related documents. The IRB reviewed all the information and accepted all the elements of our protocol design as originally approved by FDA, despite the critiques of the PHS reviewers.

However, the IRB did raise several new issues requiring additional safety measures and procedures. We then revised the protocol and resubmitted it to the IRB on October 14, 2012. On October 23, 2012, the IRB issued its final approval of the protocol and informed consent form. Below is a brief summary of the major changes. Submitted in a separate document is a comprehensive eight page list of the changes from the initial protocol to the IRB-approved version we are now submitting.

New Safety Measures in Revised IRB-Approved Protocol

The protocol now includes an assessment of suicidality and anxiety as well as assessments of PTSD symptoms and depression. New safety procedures include increased monitoring for psychiatric symptoms through daily telephone contact by research staff with the subjects during the first week of marijuana self-administration and mid-week for the second, third and fourth weeks. In addition, research staff will gather information on a regular basis from a personal contact selected by each subject who will independently verify marijuana self-administration and report any signs of behavioral change.

Additional new precautions include excluding from study participation any individuals with a first-degree relative with psychotic disorders and the evaluation of subjects' psychiatric status by the principle investigator if requested to do so by research staff.

Further substantive responses to the protocol design issues you raised in your letter of Sept. 21, 2011 and the document discussing the rationale for our protocol design choices, follow this cover letter, which concludes with the request discussed below.

A Plea for HHS to Defer Review of MAPS' Marijuana/PTSD protocol to FDA, IRB, DEA

I'm writing you to request that HHS eliminate the PHS review process for all privately-funded medical marijuana drug development studies and defer the review of MAPS' marijuana/PTSD protocol to FDA, IRB, and DEA, where Congress placed that responsibility. This is the accepted review process for privately-funded research with all other Schedule 1 drugs. Should MAPS or any other sponsor obtain approval for a medical marijuana study from FDA, IRB, DEA and the appropriate state authorities, we request that NIDA automatically agree to sell marijuana at cost so that the study can proceed.

I further request that you proceed with your review of our protocol in parallel with considering my request that the PHS protocol review process be eliminated. The protocol that MAPS is now submitting to you is a much delayed and much needed attempt to gather pilot data in 50 US veterans with chronic, treatment-resistant PTSD at a time when about 22 veterans and 1 active duty soldier commit suicide every day [1]. Rather than the four months and three weeks that the PHS review took last time, I hope that you can complete this new PHS review within the 30 days that FDA is required to respond to protocols submitted under IND.

Challenges to NIDA's Monopoly on the Supply of Marijuana for Privately-Funded Research

Starting in 2001, MAPS began sponsoring the efforts of Prof. Lyle Craker, UMass Amherst, Medicinal Plant Program, Department of Plant, Soil and Insect Sciences, to obtain a DEA license to produce a supply of medical marijuana under contract to MAPS to be used exclusively in federally-regulated research. In February 2007, after extensive legal hearings before DEA Administrative Law Judge (ALJ) Mary Ellen Bittner, Prof. Craker won his lawsuit against the DEA for refusing to issue him a license. DEA ALJ Bittner recommended to the DEA Administrator that it was in the public interest for DEA to license Prof. Craker to grow medical marijuana under contact to MAPS for privately-funded, federally-regulated research.

After failing to respond to the ALJ recommendation for almost two years, DEA Administrator Michelle Leonhart finally rejected ALJ Bittner's recommendation on January 14, 2009, six days before the inauguration of President Barak Obama. Prof. Craker subsequently sued DEA in the US First Circuit Court of Appeals. On April 5, 2013, after more than four additional years, the Court of Appeals accepted DEA's rationale for rejecting ALJ Bittner's recommendation, bringing to a conclusion our 12 year struggle. Out of necessity, MAPS and Dr. Sisley are now returning to the PHS to request approval to purchase NIDA marijuana at cost for our FDA and IRB-approved study.

PHS Review Biased Against Privately-Funded Medical Marijuana Drug Development Research

According to the May 21, 1999, Announcement of the Department of Health and Human Services' (HHS) Guidance on Procedures for the Provision of Marijuana for Medical Research, PHS protocol approval is currently required by the HHS before sponsors of privately-funded medical marijuana research can purchase at cost any of NIDA's research grade marijuana, for which it has a DEA-protected monopoly. Without PHS protocol approval, privately-funded medical marijuana drug development protocols cannot proceed.

In contrast, all other Schedule 1 drugs such as LSD, MDMA, psilocybin, mescaline, and DMT, are available from multiple DEA-licensed producers. Privately-funded drug development protocols studying the risks and benefits of all Schedule 1 drugs other than marijuana require approval from FDA, IRB, and DEA, but not the PHS. At present, PHS review and approval is required only for privately-funded medical marijuana drug development protocols, exists only because of NIDA's monopoly on DEA-licensed marijuana, protects no government funding, and asserts authority over drug development research that Congress created the FDA to review.

As you must know, the current HHS Guidance explicitly rejects providing marijuana to privately-funded medical marijuana drug development protocols seeking to obtain FDA approval for the prescription use of smoked marijuana in plant form. Section II of the Guidance, "Availability of Marijuana For Research Purposes", states, "The goal of this program must be to determine whether cannabinoid components of marijuana administered through an alternative delivery system can meet the standards enumerated under the Federal Food, Drug, and Cosmetic Act for commercial marketing of a medical product (see e.g., 21 U.S.C. 355). As the IOM report stated, "Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, nonsmoked cannabinoid delivery systems."

Our protocol directly compares safety and efficacy of smoked marijuana with marijuana inhaled via vaporization, a nonsmoked drug delivery method that avoids combustion, with our goal being to develop marijuana either smoked or vaporized into an FDA-approved prescription medicine. The protocol MAPS is submitting to you now for PHS review is therefore seeking to conduct research with the exact purpose which the HHS Guidance rejects as outside the boundaries of acceptable research, and yet FDA and the University of Arizona IRB have approved it.

As long as HHS's May 21, 1999, Guidance on Procedures for the Provision of Marijuana for Medical Research remains in force and is followed by PHS reviewers, the rejection of MAPS' revised protocol seems inevitable. When the DEA-protected NIDA monopoly and the PHS

review process operating under the HHS Guidance combine to block all efforts to develop the marijuana plant itself into an FDA-approved prescription medicine, science is preempted by politics. It is therefore only to be expected that when the science is blocked, advocates of the medical uses of marijuana will turn to politics to provide access for physicians and their patients to medical marijuana.

There are currently 20 medical marijuana states and the District of Columbia. Of these states, PTSD is an explicit qualifying condition for a medical marijuana recommendation in 5: New Mexico, Maine, Oregon, Connecticut, Delaware, and its use for PTSD is permitted in California, all without a single controlled study of the use of marijuana for PTSD. It is long past time to facilitate privately-funded, federally-regulated research into the use of marijuana in veterans with chronic, treatment-resistant PTSD, for which there are many positive anecdotal reports.

PHS Review is Inappropriate for Privately-Funded, FDA-regulated Research

Even if the HHS Guidance didn't explicitly reject providing NIDA marijuana at cost to privately-funded protocols seeking to develop the marijuana plant into an FDA-approved prescription medicine in smoked form, there is a fundamental mismatch when PHS reviewers evaluate a privately-funded drug development protocol design through the lens of basic science grant application standards.

PHS protocol reviewers have extensive and valuable experience reviewing grant applications submitted by academic researchers seeking National Institutes of Health (NIH) funding for basic science studies. NIH-funded basic science research is primarily about understanding mechanisms of action to gain insight into the processes and building blocks of life. In contrast, privately-funded drug development protocols are focused on proving safety and efficacy of an intervention or treatment that meets FDA standards. FDA does not require an understanding of mechanisms of action for approval for prescription use.

PHS reviewers of grant applications are stewards of public funds while privately-funded drug development studies are investing and risking private money, not public money. PHS reviewers of grant applications can appropriately require additional measures and tests to better understand mechanisms, or can require larger studies to reduce uncertainty, the cost of which will be paid by the NIH grant should the application be accepted. Such protocol critiques are justified for basic science purposes but are not required by FDA or an IRB and are inappropriate for privately-funded studies. Costs from additional research into mechanisms required by PHS reviewers must be paid by the private sponsors of the research, imposing in essence an arbitrary tax on privately-funded research into marijuana's potential medical uses.

Request to Waive PHS Review and Accept Approval by FDA, IRB, DEA, State Authorities

Fortunately, there is a way forward. The HHS Guidance states that "HHS will re-evaluate these procedures periodically..." As far as I can tell, the HHS Guidance document has not been reevaluated since it was written more than 14 years ago. The current NIH grant review process does a good job providing marijuana from NIDA's monopoly for NIH-funded basic science studies while ensuring that taxpayer funds are expended strategically. In contrast, the PHS review process exists only for marijuana and is a success only at obstructing privately-funded

medical marijuana drug development studies, an outcome contrary to the public interest. Approval from FDA, IRB, DEA and state authorities without additional and inappropriate PHS review should be sufficient for NIDA to permit privately-funded sponsors to purchase its marijuana at cost, especially since that protocol review process is sufficient for privately-funded research with MDMA, psilocybin, LSD, DMT, and all other Schedule 1 drugs.

I am writing specifically to request that you consider the approvals of MAPS' protocol from FDA and the University of Arizona IRB, subject to licensing by DEA and state authorities, as sufficient for this study to proceed. After licensing by DEA and the appropriate state authorities, NIDA could then provide the required marijuana at cost.

<u>New Promising but Uncontrolled Research into the Use of Marijuana for PTSD</u>

In addition to our protocol, I am submitting two papers that report on uncontrolled studies of the use of marijuana by subjects with PTSD. The paper discussing the results of a study conducted by New Mexico psychiatrist Dr. George Greer in 80 PTSD patients applying for enrollment in the New Mexico Medical Cannabis Program has recently been accepted for publication in a peer-reviewed journal indexed on Medline [2]. The other paper, reporting on a study conducted by the Israeli Ministry of Health in 29 Israeli Defense Force soldiers, is currently under review by a peer-reviewed journal indexed on Medline [3]. Both report promising findings and call for controlled studies, none of which have yet been permitted to be conducted.

We request that you thoughtfully consider our responses below regarding issues of protocol design raised by you and the PHS reviewers, ideally within the 30 day time frame required of FDA by Congress for the review of protocols submitted under FDA IND. In addition, we ask that you also carefully consider our request for HHS to end the PHS review process for privately-funded medical marijuana protocols. Rather, HHS should require NIDA to provide marijuana at cost after any privately-funded protocols have been approved by FDA, IRB, DEA and the appropriate state authorities, the same procedures that govern privately-funded research with all other Schedule 1 drugs.

Sincerely,

Rick Doblin PhD
Executive Director, MAPS

Response to Protocol Critiques in September 21,2011 Letter and Comments of PHS Reviewers

I address below the issues you raised in your cover letter. After the references to this section, I've included the document that we submitted to the IRB that provides additional information and justification for the protocol design choices reflected in our protocol.

1. There was substantial concern about the research expertise and research support to perform this study. No principal or co-investigators with substantial research experience are mentioned. While Dr. Sisley's CV indicates that she is an experienced clinician, she lacks sufficient research expertise. Specific expertise in PTSD is also needed. There is no evidence of institutional support for the research or availability of an independent entity for data collection, management, and analysis.

MAPS is the organizational sponsor of this drug development pilot study and is responsible for its scientific integrity. MAPS has substantial experience conducting FDA-regulated research in subjects with chronic, treatment-resistant PTSD. We've completed two promising pilot studies of MDMA-assisted psychotherapy in people with PTSD in the US and Switzerland with results published in the Journal of Psychopharmacology. MAPS is currently conducting additional MDMA/PTSD pilot studies in the US (Charleston, SC and Boulder, CO), Israel, and Canada. MAPS currently has a paper in the final stages of the review process at the Journal of Nervous and Mental Disease about the first study in over 45 years investigating LSD-assisted psychotherapy, in subjects with anxiety associated with end-of-life issues. MAPS has its own monitoring staff and excellent relationships with regulatory agencies and IRBs around the world.

As MAPS' Executive Director, I've focused a major section of my dissertation on the question of how to design successful double-blind studies with drugs such as marijuana, LSD and MDMA which have discernible subjective effects and complicate the creation of a successful double-blind. I have been designing and conducting FDA-regulated clinical trials for the last twenty years, am the first author on seven papers about original research that I conducted, and am second or last author on three papers about MAPS' MDMA/PTSD research.

MAPS' Director of Clinical Research is Amy Emerson. She has worked in clinical development and research for the last 15 years in the fields of immunology (Applied Immune Sciences), oncology (RPR), and most recently in vaccine development (Chiron and Novartis). Amy is responsible for ensuring that MAPS' drug development studies meet GCP standards, are monitored to pass FDA and DEA audits, and meet all regulatory reporting requirements.

Dr. Sisley is an experienced psychiatrist with expertise in use of telemedicine technology who has worked with PTSD patients. She has provided psychiatric evaluation and medication monitoring via telemedicine and has developed novel applications of telemedicine during her work at the Arizona Telemedicine Program and as the Director of Telemedicine at the Scottsdale Treatment Center.

As a new co-investigator with extensive expertise in treating PTSD, we have added Dr. Deborah Gilman, staff psychiatrist, Carl T.Hayden VA Medical Center, Phoenix, AZ. Attached is her CV.

Dr. Michael Mithoefer, Board Certified in Psychiatry, Emergency Medicine, and Internal Medicine, is PI on several of MAPS' Phase 2 MDMA/PTSD studies including our current study in 24 veterans and first responders, and is lead author on two scientific papers about MDMA/PTSD research published in the Journal of Psychopharmacology. Dr. Mithoefer is co-medical monitor on this study.

Dr. Julie Holland, psychiatrist, is a medical monitor on MAPS' study in 24 veterans and first responders, editor of Ecstasy: A Complete Guide and The Pot Book: A Complete Guide to Cannabis. Dr. Holland is co-medical monitor on this study.
The use of an independent entity for data collection, management and analysis is not required by FDA or by the IRB and is not standard operating procedure in FDA-regulated drug development studies. Dr. Sisley's study design calls for an independent rater who is not part of the treatment team to administer the outcome measures. MAPS collects and manages its own data with the understanding that FDA and IRBs can audit the data at any time. We use source records, Case Report Forms, electronic data management software, and we monitor the data for accuracy and integrity. There is no need or justification for PHS reviewers to require procedures that are not required by FDA or IRB.

2. The review panel had a number of concerns about the study design. The theoretical framework and justification for the complex study design need additional explanation. A simpler design might be preferable for this pilot study. There was concern about whether the study is adequately powered.

Pilot studies are often underpowered for statistical significance, as they are intended to spark further research. This is a privately-funded, FDA and IRB-approved exploratory study. This study is designed to gather preliminary evidence about the risks and benefits of a potential new treatment, not toward generating statistically significant results. It is too early in the research process for such designs which require preliminary data that does not yet exist and are larger and more expensive than we feel is justified at this time. If data from this study is promising, then it will serve as the basis for developing larger and higher-powered studies.

Nevertheless, since the size of the study seems to a major issue for the PHS reviewers, we are willing to increase the size of the study from 50 subjects to 70 subjects, enlarging the study by 40%. We will now have 7 subjects in each cell, rather than 5. This represents a substantial increase in the cost of the study and in the time it will take to complete, is not required by FDA or IRB, and will not be covered by an NIH grant but must be covered by our own fundraising efforts. If we are allowed to purchase NIDA marijuana to conduct this study, we will submit a protocol amendment to the FDA and the UArizona IRB proposing an increase in the size of the study to 70 subjects. We will submit documentation of the acceptance of this protocol amendment to NIDA and DEA prior to requesting supplies of study drug.

Study complexity is required in order to have a blinded study with inactive and active placebo marijuana strains and to gain information on the safety and efficacy of a drug delivery method, vaporization, that is the only non-smoking drug delivery device that uses whole plant marijuana and does not involve combustion[4], to compare with subjects who only smoke marijuana. Addressing study blinding with appropriate placebo controls is a challenging but important aspect of clinical trials with psychoactive substances [5, 6]. The impact played by cannabidiol in

the therapeutic properties of marijuana is now a focus of a growing number of investigations[7-11] , and the addition of a strain with and without this cannabinoid will permit exploration of cannabidiol versus THC in the anxiolytic effects of cannabis. Findings from this study will provide the basis for development of future studies focusing on areas of interest detected in this study.

Several reviewers expressed concern about use of self-titration within the study design. However, the use of self-regulated flexible dosing has occurred in other FDA-approved drug development studies, including a trial with an intranasal cannabis-based product [12-14]. We discuss this issue further in the document responding to the concerns of the PHS reviewers.

3. The study does not provide a basis for determining individual differences in efficacy, precluding predictive capacity for favorable responses. An analytic plan to assess individual differences would strengthen the potential value.

This is a preliminary exploratory study. We are primarily interested in group differences. Nevertheless, we are gathering a limited amount of demographic data that we will use to evaluate individual differences, including information on age, gender, race/ethnicity and past use of marijuana. Determining individual differences is not the purpose of this study and has not been required by FDA or IRB and is premature in a pilot study of safety and efficacy. PHS reviewers, coming from a basic science perspective, can see value in many additional measures and procedures that address questions that are not necessary or appropriate for our privately-funded drug development study at this time. Still, if one or more of the study findings are significant and have a large effect size, it will be possible to examine one or more of the demographic characteristics that we are collecting to determine if there are individual differences in response.

The primary purpose of the study is to compare the safety and efficacy of material with different levels of THC and cannabidiol and to assess the safety and efficacy of two drug delivery methods, smoking and vaporizing. In the proposed study, these goals are met by comparing subject outcomes from smoking or vaporizing five different potencies of marijuana. In addition, comparisons will be made between effects of potencies differing only by the presence or absence of cannabidiol by crossover of subjects in these conditions. Treatment efficacy is addressed through the primary outcome measure, the Clinician Administered PTSD Scale (CAPS), the gold standard measure of PTSD symptoms. The CAPS will be administered at baseline and after each study stage, permitting comparison of responses to each dose and both delivery methods over time. The measure possesses scores that permit examining individual symptom clusters.

Since the study is already addressing potency as well as drug delivery, it is not an appropriate vehicle for reliably assessing individual differences in safety and efficacy. It is more appropriate to test individual differences later in another study after overall effects can be assessed in this placebo-controlled study. Furthermore, the study employs a self-regulated dosing strategy, permitting variation in dosing within a set limit of no more than two rolled cigarettes per day (unrolled with marijuana placed in a vaporizer for subjects randomized to those groups), so that people may adopt different usage strategies. An analysis plan for evaluating individual differences in response is outside the scope of this research and would, as a result of adding further variables, weaken rather than strengthen statistical power and value of results.

We will be collecting information about daily use of marijuana that will include self-report of use and weighing any material subjects return. This allows for assessing individual usage patterns. However, at present, we first wish to gather information on treatment safety and efficacy before embarking upon examining individual differences in response.

4. A number of safety concerns were raised. Some reviewers were concerned about the use of drug-naïve participants. Documentation of an IRB review was not submitted.

The protocol now has IRB approval. Documentation of approval is attached along with this letter.

Safety is enhanced by the use of two extensive marijuana inhalation practice sessions occurring on the study site where all subjects, marijuana-naïve or marijuana-experienced, are exposed to the potency of marijuana they will receive. Practice sessions will occur in each of two subsequent four week dosing periods. There will be an assessment of suicidality, the addition of the Beck Anxiety Inventory to measure anxiety, continued contact by research staff with the participant, and instructions concerning driving. These all serve as means of addressing participant safety for both drug-naïve and drug-experienced subjects.

Further new precautions include excluding from study participation any individuals with a first-degree relative with psychotic disorders and the evaluation of subjects' psychiatric status by the principle investigator if requested to do so by research staff.

With respect to safety concerns relating to enrolling marijuana-naïve participants, only one of five reviewers recommended restricting enrollment to participants experienced with marijuana use. Two other PHS reviewers recommended enrolling only marijuana-naïve participants to ensure study blinding. Neither of these two reviewers provided evidence that past experience with marijuana would help people to detect the difference between four levels of THC or the presence or absence of cannabidiol. There was no consensus among the PHS reviewers concerning participant prior experience with marijuana and it is obviously not possible to satisfy conflicting recommendations.

By way of comparison, MAPS has recently completed the first study of the therapeutic use of LSD-assisted psychotherapy in over 40 years. The study was a small pilot study in 12 subjects with anxiety associated with end-of-life issues. The study was conducted in Switzerland with approval by SwissMedic, a Swiss IRB and the FDA, which evaluated the protocol before the study started. Of the 12 subjects, 11 were LSD-naïve. There were no drug-related Serious Adverse Events (SAEs), and no prolonged negative reactions. In comparison to LSD, the subjective effects of marijuana are milder and more easily controlled. Likewise, only one of the 12 participants in our Swiss study of MDMA-assisted psychotherapy in people with chronic, treatment-resistant PTSD reported prior use of ecstasy/MDMA[15].

In this exploratory study, we will analyze our data to see if there are any differences in response between drug-naïve and drug-experienced subjects.

The study would be too burdensome and costly to conduct in an inpatient setting. An FDA, IRB and DEA approved study conducted at UC Davis to assess the effects of marijuana in people

with multiple sclerosis is also an outpatient study and received study drug from NIDA. The outpatient nature of this clinical trial was acceptable for the approving agencies with the same study drug. Please see NCT#00682929.

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Rationale for Protocol Design Choices and Responses to Comments of PHS Reviewers
(from cover letter sent by Dr. Sue Sisley to the University of Arizona IRB on July 30, 2012)

INCLUSION/EXCLUSION CRITERIA: DEFINITION OF TREATMENT RESISTANCE

As stated in pp. 15-16 of the protocol, the study will enroll veterans with treatment-resistant PTSD arising from their service in the US military, with treatment resistance defined as still meeting criteria for PTSD diagnosis after treatment either with psychotherapy or pharmacotherapy. While we are willing to use a more stringent definition that requires treatment-resistance to both pharmacotherapy and psychotherapy, this would produce an unrepresentative sample since many veterans with PTSD have underutilized care for PTSD available to them or have not received appropriate care.

INCLUSION/EXCLUSION CRITERIA: MARIJUANA EXPERIENCED AND MARIJUANA NAIVE SUBJECTS

The study will enroll participants with and without any experience with marijuana, so long as they have not used marijuana within the month prior to study enrollment (p. 17 in the protocol). Marijuana is the most commonly used illicit drug in the US and a significant percentage of people with PTSD have used it (see p. 8 in the study protocol). To be representative of the larger population of veterans with PTSD the study needs to include subjects who have had previous experience with marijuana. If the study were limited only to subjects who had never used marijuana, the subjects would not be representative and recruitment would be seriously compromised.

SAFETY PROCEDURES

To ensure that both marijuana-naïve and marijuana-experienced subjects are prepared for the subjective experience of the specific potency of marijuana that they will receive in each of the two four week medication periods, the protocol includes a four-hour introductory session on each of two days in a row. In these introductory sessions, subjects gradually self-administer marijuana under supervision and with the support of research staff. Subjects will be administered the same potency they will receive during their four-week medication period using the same delivery system, smoked or vaporized. This identical procedure of two four-hour introductory sessions will be repeated before the four-week cross-over period. Should any subject experience substantial anxiety during the introductory sessions or adverse effects of a persistent nature beyond the time of the introductory sessions, the subject could withdraw from the study and/or the Principal Investigator could decide to exclude the subject from further participation. Subjects will be administered the Columbia Suicide Severity Rating Scale (CSSRS) at frequent intervals throughout the study and will meet with study staff on a weekly basis. Psychotherapists will be available should either subjects or experimenters request psychotherapeutic sessions due to increased signs of suicidality.

BLINDING

One of the major methodological challenges of medical marijuana research, indeed research with any psychoactive drug, is conducting a successful double-blind. We believe that almost all or perhaps even all subjects will be able to correctly guess whether they have been randomized to either an inactive placebo group or an active drug group. However, we are going to test that assumption in this specific subject population. As a result, this pilot study is designed as a dose-response study randomizing subjects to one of five potencies of marijuana, 0 % THC (inactive placebo), 2% THC, 6% THC, 6% THC and 6% CBD, and 12% THC. Subjects will be administered marijuana for a one-month daily dosing period followed by a two-week medication cessation period.

This study is designed to explore whether a dose-response design actually results in an effective double-blind in which the subjects, the Principal Investigator who interacts directly with each subject, and independent rater are indeed blinded to dose. In this protocol, we will ask all the subjects, the Principal Investigator, and the independent rater to guess which potency of marijuana the subject was randomized to receive.

We anticipate that subjects receiving the inactive placebo will accurately guess that they have received the inactive placebo, if not in the first few days, then sometime during the four-week medication period, and that the PI and independent rate will also guess correctly. In contrast, we anticipate that the subjects receiving one of the four doses of marijuana will demonstrate a substantial proportion of inaccurate guesses as to the dose they received, as will the PI and independent rater.

CROSSOVER DESIGN DETAILS

One of the main objectives of this study is to compare the effects of the two cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on PTSD symptoms. In the crossover period, we are primarily interested in learning more about the differences between 6% THC and 6% THC and 6% CBD, and also whether 12% THC will be well-tolerated by the subjects. We therefore plan to drop the inactive placebo which we anticipate will be accurately identified by the subjects, PI and independent rater. We also plan to drop the 2% THC doses from the crossover period since we anticipate 2% THC will show minimal efficacy and we want to learn more about CBD. Subjects who received 6% THC in the initial four-weeks will be assigned the 6% THC, 6% CBD marijuana in the crossover, and subjects who received the 6% THC, 6% CBD marijuana will be assigned the 6% THC marijuana in the crossover. Subjects who received either the inactive placebo or the 2% THC marijuana or the 12% THC will be randomized to either the 6% THC, 6% THC, 6% CBD, or 12% THC marijuana.

The partial crossover is a means of conducting a within-subjects comparison of the effects of marijuana with and without CBD. In addition, the blind will likely be even stronger in Stage 2 since all participants will be receiving marijuana containing at least 6% THC.

TWO-WEEK DRUG WASHOUT BETWEEN CROSSOVERS

The study contains a two week washout period of medication cessation to gather information on whether symptom relief, if any, fades during this time. In both Stage 1 and the crossover Stage 2,

primary and secondary outcome measures will be collected and compared after the four-week period of marijuana use and after the two week washout period. In addition, the two week washout period ensures that the effects of the marijuana administered during the Stage 2 crossover period are from that potency rather than the potency administered during the Stage 1 dosage period.

SUBJECT SELF-TITRATION

A secondary objective of this exploratory study (p. 11) is to gather information about the range of dosing schedules and amounts that different PTSD patients chose to self-administer. Different subjects may have different sensitivities to the effects of marijuana. Some subjects may use only at night before bed, others may use throughout the day. Some subjects may vary times of use and amounts on a daily basis as symptoms vary. Subject self-titration is an accepted part of drug development research, especially in exploratory protocols such as this one where there is an absence of prior data about the safety and efficacy of a range of doses.

Data about all of the individual subject dosing preferences would be lost with a fixed dosing schedule. Furthermore, some subjects could be required to use more marijuana than they needed for symptom relief, creating the possibility of adverse events due to the fixed dosing schedule.

Study participants will be permitted to smoke or vaporize up to two of NIDA's marijuana cigarettes per day (each about .9 gram), permitting self-titration but with an upper limit imposed for diversion control purposes. While having an upper limit on the amount of marijuana that can be used is not ideal from a dose-response perspective, we feel it is an acceptable compromise to conduct this exploratory study with a limit of two NIDA marijuana cigarettes per day. Should a substantial number of subjects use all of the marijuana allocated per day and indicate that they would have preferred more medication, we can adjust the amounts in subsequent studies if the data from this study justifies further research.

Participants will be instructed to save any unused marijuana each day in the packages provided, to be returned each week for the next week's supply. The remaining material is weighed each week and the amount of marijuana used will be assessed. Serum cannabinoid levels will be assessed weekly, permitting another means of estimating cannabinoid levels in each subject. The data analysis will use weight of remaining material as a covariate to assess self-titration across conditions (p. 43 of the protocol)..

In FDA drug development research with Sativex, an oral-mucosal spray that is 50% THC, 50% CBD, patient self-titration of the number of sprays is part of the protocol. For example, in a multi-site study of Sativex for pain relief in individuals with advanced malignancy, used a three-arm design, with low, medium and high doses. In each arm, patient self-titration of dosing was permitted, with the low arm permitting patients to decide to use a range of 1-4 sprays per day, the medium arm permitted 6-10 sprays per day, and the high arm permitted 11-16 sprays per day (see http://www.nextbio.com/b/search/individualtrial.nb?id=NCT00530764). In the Phase 3 studies with Zoloft for PTSD, subject self-titration was also part of the protocol, within limited ranges. These drug development designs included both self-titration and upper limits on medicine, as in our marijuana/PTSD study.

OUTPATIENT SETTING

Prior to starting the study, all participants will undergo two four-hour supervised training sessions where they experience the effects of the specific potency of marijuana they will receive using the specific dose delivery approach, either smoked or vaporized. After two four-hour training sessions, participants will commence using study marijuana at home rather than being restricted to an inpatient facility. The sponsor and investigators are seeking to examine changes in PTSD symptoms over a three month or longer period of time. Requiring subjects to live in an in-patient treatment facility for three or more months would fundamentally compromise subject recruitment and, if subjects could be found, be both cost prohibitive and involve research with a non-representative sample of subjects.

DIVERSION CONTROL AGREEMENT WITH FDA CONTROLLED SUBSTANCES STAFF

Multiple means of preventing and discouraging diversion are in place, through a multi-step process approved by FDA's Controlled Substances Staff. These include setting an upper limit of a maximum of two NIDA marijuana cigarettes that each subject can use per day, giving subjects only a one week supply at a time, and requiring subjects to store unused marijuana in a secure, locked box. In addition, all subjects will be required to record every time they medicate via portable digital camera that we will loan to them for the duration of the study, and every week they will bring in the video recording for review by experimental staff before being administered the next week's supply. Subjects will also be required to complete a Daily Marijuana Use Diary, and return any unused marijuana in the separate packages for each day's supply. The experimenters will also verify subject use by contacting another individual chosen by subject and agreed on by the experimenters, and also by taking weekly blood cannabinoid levels.

At the end of the cross-over medication period and the two week period of medication cessation, the subjects have the option to request that the unused marijuana be returned with the study extended ("Optional Stage 3") for the period of time it takes for the remaining marijuana to be used. This further reduces concerns that subjects will use more marijuana than they need for symptom control or will divert unused marijuana.

With these procedures in place, the FDA Controlled Substances Staff approved the outpatient design permitting subjects to self-administer study marijuana in their homes safely and with acceptable risk of diversion.

SPONSOR RESPONSIBILITIES TO GATHER, MONITOR, REPORT ON DATA.

This study is a drug development study. Unlike academic research, the sponsor is expected to maintain the data and analyze it, maintaining data in "locked" or tamper-proof formats. Specific procedures are followed to make sure the data is accurate, and once these are performed, the database is locked to prevent future alteration. The sponsor is committed to analyzing the data and submitting a Final Report to FDA. Consultation can be sought from individuals who are not part of MAPS, but the responsibility for the conduct of the study and for the gathering, monitoring and analyzing of the data rests with the sponsor.