Reviewer #1

REVIEW OF PROTOCOL MJP-1 (Amendment 1):

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)

A. Significance. A blinded study of marijuana in the treatment of combat-related PTSD certainly does possess in theory (the comment "in theory" suggests that this reviewer may not permit the study to go forward) the ability to add to the knowledge base about the potential therapeutic role of marijuana and advance the scientific knowledge base. At the same time it would address an important problem, given the unmet treatment needs of many individuals with PTSD. Unfortunately, the amended protocol as presented falls short of these goals. "Adding to the knowledge base" is a basic science goal. MAPS' goal is drug development. FDA is the proper regulatory agency to review MAPS' privately funded protocols, not the PHS/NIDA review process which was set up to review applications seeking federal funding for research.

While the proposed study *is* directed at the treatment of a "serious or life-threatening condition" in the form of PTSD, the submitted and amended protocol does *not* describe "an adequate and well-controlled clinical study to evaluate the safety and effectiveness of marijuana or its constituent cannabinoids." The FDA has determined that it is an adequate and well-controlled study. Is this reviewer saying his judgment is more accurate than FDA's Division of Psychiatry Products, which has been charged by Congress to evaluate drug development protocols? Serious limitations in the design of the study, described in detail below, prevents this reviewer from endorsing this proposal without substantial improvements. Among other factors, problems with the current protocol range from an inadequate application of the principles of "treatment resistance"T-he principle of "treatment resistance" is shared, the degree of prior treatment that veterans will be required to have received from the VA is at issue here. The risks of the clinical use of marijuana are minimal, it doesn't need to be the last resort after all medications and psychotherapies have been tried. It's easy for us to add specifications for amounts of prior therapy but how many veterans have actually had those amounts? and "crossover" design (our crossover design is optimized to our research questions), to an excessively loose dosing strategy -- veering from fixed-dose to PRN without explanation (self-titration is one of the primary advantages of medical marijuana, our aim and the protocol does this just right, and self-titration will result in more precise dose-response relationships), to outcome measures that omit some core features of PTSD, such as avoidance, while emphasizing co morbid, non-PTSD measures such as mood (this comment shows more clearly than anything else so far that this reviewer doesn't understand this protocol or drug development research. Our primary outcome variable is the Clinician Administered PTSD Scale (CAPS), developed by the VA and accepted by FDA and the European Medicines Agency (EMEA) as the gold standard for measuring PTSD in

clinical drug development studies. The basic premise of the proposed relatively unstructured outpatient treatment should be revisited.

This protocol does include the study of a potential alternative to smoking in the form of vaporized drug administration.

Approach. The basic idea of a crossover trial, using various THC concentrations, including zero % as a placebo control, has merit. But the specifics of the plan rob the proposal of its scientific validity. The problems begin with the nature of the subjects, described as combat veterans with chronic PTSD that is **"treatment resistant."** The definition of treatment resistance presented, namely failure to respond to a single intervention, is not adequate, for two reasons: (1) the way available treatments are presented, lack of response to psychotherapy alone could constitute "treatment resistance," even if no medication whatsoever had ever been tried; Yes, this protocol is designed to enroll subjects with chronic PTSD who have failed to obtain relief either from medication or psychotherapy, both are not required. and (2) even if one accepts that a single treatment failure is equivalent to treatment resistance -- a questionable proposition -- the field has reached agreement that treatment failure must be defined in terms of having received an adequate trial, in other words, one that would be considered "therapeutic" in treatment responders; this is usually defined in terms of adequate dose and duration in the case of medication, and an adequate number of sessions (and completion of "homework" between sessions as prescribed) in the case of psychotherapy. These concepts do not seem to be part of the current proposal. The point is that failure to tolerate medication, which could involve taking only a dose or two, is not the same as treatment resistance. The current protocol thus would appear to be setting an inadequate threshold for the use of the marijuana intervention for these veterans, inconsistent with the 1997 NIH Workshop on medical marijuana. I was at that 1997 NIH Workshop and assume Reviewer #1 is referring to the definition of treatment resistance. Dr. Robert Temple, Associate Director for Medical Policy, FDA, outlined a series of guidelines regarding the design of research protocols for various potential medical uses of marijuana. Dr. Temple acknowledged the interaction between science and politics and suggested that although FDA regulations do not require a drug to be more effective or safer than other drugs in order for it to be approved for prescription use, that it would nevertheless be wise for medical marijuana advocates to seek to conduct studies with people suffering from serious diseases in whom the currently available medicines are not sufficient or have intolerable side effects. Dr. Temple's comments during the 1997 NIH Workshop were suggestions, not FDA requirements, and do not provide PHS/NIDA reviewers with sufficient justification to refuse to let our study go forward. If necessary, we can define minimum amount of medication period or refusal to try medication or certain period of psychotherapy,>

~~B.~~

In terms of the treatment trial itself, although there is merit to the multiple dose options (including a placebo-dose) to be randomly assigned to subjects in Stage 1, there are three major problematic aspects to the protocol: (1) The **very loose dosing policy** -- more appropriate for a Phase IV effectiveness study than a Phase II efficacy trial -- is not explained. Self-titration is described on Page 13 of the protocol as < Self-titration is considered one of the clinical advantages of marijuana that this study will evaluate.> We can provide more explanation, what does Reviewer #1 want explained about self-titration?- FDA is fine with self-titration in our Phase 2 study. Subjects will be instructed to use no more than two marijuana cigarettes per day, but may use them at any time they wish, may use only one rather than two, and are free to skip an entire day if they feel they do not need to smoke that day. While some phobic conditions, e.g. simple phobias or specific types of social phobias, have known triggers of symptoms and might be amenable to targeted dosing, most chronic anxiety disorders call for regular steady-state drug administration. In the case of PTSD, that is how the FDA-approved SSRIs are administered. The proper dosing of marijuana should be based on data from marijuana dose-response studies (like our protocol), not based on the way a different class of drugs, FDA-approved SSRI's, are dosed. It is not at all clear why the proposed "as-needed" dosing for medical marijuana would be preferred- MAPS is engaged in privately-funded marijuana drug development research, we should be free to study the doses we think will be most safe and effective, meaning self-titation, especially after we have obtained FDA permission for our study. When we can't even study the doses we want to study, -drug development research has been hijacked and obstructed by the PHS/NIDA. We could explain more about self-titration which looks necessary.Would that not undermine the presumed effort at understanding any dose-response relationship through the use of various THC-concentrations? No, we will get even more precise information about dosing by permitting self-titration. We will have a wider spread of doses and more data points through self-titration. Some explanation of why it is not preferable for subjects to reach steady-state concentrations - presumably different on average for the different dosage groups - is in order. People react differently, self-titration is an advantage, not a limitation. Some subjects may reach steady-state concentrations on their own, others may not. We prefer to leave this decision to the subjects., then we can compare. We can write more about this though it seems that since MAPS is risking its own funds, we should be able to choose what dose we want to study. How subjects are supposed to make their own dosing decisions is not stated; this does not appear to be keyed to any particular score on a self-rating scale. People know if they are suffering from symptoms such as PTSD, they can dose as they feel the need Is it reasonable for subjects to predict in advance what night will be free of nightmares? If patients want to smoke or vaporize every night before sleep, they can. We prefer to leave this decision to the patients.-(2) The purpose of the **open discontinuation of drug use** for two weeks between Stages 1 and 2 is not

explained. This seems to be the case, we didn't explain. Open discontinuation is to gather data on whether symptoms return and to provide a wash-out perjod before the crossover. If subjects have provided informed consent for blinded administration of any of 5 dose options, including zero-% THC, why break the blind in midstream by discontinuing treatment in such an open fashion? ***No blind has been broken, medication has ceased, Why not switch all subjects blindly to zero-%-THC marijuana during weeks 5 and 6, and then blindly re-assign them to their Stage 2 doses? This wouldn't be blinded to therapists and it almost certainly wouldn't be blinded to patients*** . It is unlikely that 0% THC would produce a successful double-blind in more than a few subjects, if that. We also want patients to stop smoking or vaporizing to see if there is a placebo effect, keeping all subjects on medication during these two –week cessation periods prevents us from seeing if there is a placebo effect. In other words, why not have a 14-week blinded trial, to include at least single-blind periods of placebo? Wouldn't that be a better way to evaluate the efficacy of the treatment and any dose-response relationship?No, it wouldn't be effective, it wouldn't be double-blind, it wouldn't permit us to see if there is a placebo effect. however, it would provide a washout period but only for THC, not for other ingredients in marijuana that also have some effect so we want a complete washout period (3) Although the trial is described as a **"crossover design**," in fact for at least 20 of the 50 subjects, the Stage 2 dose will be predetermined based on their Stage 1 assignment. While the others will be randomized to other doses, for reasons that are unexplained, the zero- and 2%-THC options are to be dropped in Stage 2. We do need to explain, the 0% is being dropped because we believe it is not likely to remain blind for virtually all subjects, the 2% is dropped since we are more interested in the comparison between 6% THC and ^%THC.6%CBD and because we think that 2 cigarettes of 2% THC will also not be enough. The four remaining patients in FDA's compassionate use program receive 10 cigarettes of 2% THC per day and we want to give these 0% and 2% subjects the opportunity to be their own controls at a higher dose. **A true crossover design would include having some subjects switch not only from placebo to active drug, but also the reverse.** We don't need to design a "true" crossover, we have designed a crossover that generates the information we more need for drug development purposes THCvTHC+CBD(The absence of a placebo option in Stage 2 not only forfeits an opportunity to learn more about the potential role of medical marijuana in PTSD, This is an extreme and unfounded statement, since we have Stage 1 with an 0%THC placebo and generate valuable dose-response information in Stage 2but would seem to undermine the anti-diversionary advantage of having some drug supplies be inactive; This doesn't work with psychoactive drugs, dose-response is the design that can actually be successfully double-blind, This reviewer is laboring unless the illusion that 0% THC will be an effective blind. This study will determine that in Stage 1, and we have designed Stage 2 crossover to gather other information. the multiple purposes of the blinding would seem to be undermined in Stage 2 if all subjects are told they have a 100%

certainty of receiving one of the higher THC doses. This reviewer doesn't understand that the dose-response design needs to be tested and is likely to be more effectve at blinding than their approach. Why are subjects given different information for the two stages -- why not simply advise that in either stage they might receive one of 5 dose levels? We believe that degree of deception is not necessary if only 3 dose levels are available in Stage 2. In any event, no rationale is provided for this deviation from usual crossover trial design or the absence of potentially informative placebo assignment in Stage 2.

Other problematic aspects of the approach include the lack of information about the conditions of smoking, e.g. location (must it be at home? N0, not necessary), presence of others (presumably one would not want a "party" to be built around the subjects' treatment- We absolutely don't want diversion but people can take the medication where and when they want), and steps that could be taken to guard against surreptitious use of illicit marijuana to supplement the provided study drug (we are taking blood cannabinoid levels, that's about as good as it gets). The use of an additional "witness" to verify that the subject is following the protocol appropriately sounds well-meaning, but would a housemate really be appropriate for this "policing" role? Do we really need this policing role? We have videos of medication ingestion and blood tests. What else is needed?

The issue of **co morbid depression** is not adequately addressed. We can address this. Many PTSD patients have comorbid depression. It is not necessary to exclude PTSD patients with comorbid depression While potential subjects felt to be at high risk for suicidality are to be screened out, it is unclear whether the limited SCID interview will actually seek to diagnose co morbid depression, Yes, that's the purpose of the SCID and if so, why that would or would not be an exclusion criterion. Would not be, I've explained above, we can add to protocol. In addition to the fact that co morbid issues should be a focus of later-phase trials, not Phase II,Not at all true, not how drug development studies get done, Phase 2 is for determining the patient population to be treated, that shouldn't be changed in Phase 3 for the first time. there seems to be no provision to account for co morbid depression in randomly assigning marijuana doses, which could potentially skew the findings. Not likely since many subjects will have co-morbid depression but we could institute stratified randomization However, it's not necessary for drug development In any event, the assessments ascribe much more in the way of effort and resources to the monitoring of depression -- a co morbid condition that is not an integral part of the definition of PTSD -- at the expense of core impairing symptoms of PTSD, such as daytime flashbacks and avoidance. The CAPS measures avoidance and flashbacks (intrusive thoughts). There is no problem with our measure of PTSD, the Reviewer doesn't understand that CAPS is the gold standard and we have other measures about depression precisely to help us explore the links between PTSD and co-morbid depression.

Furthermore, the idea that we need a homogenous patient population is wrong-headed. This is an initial, exploratory, pilot study underpowered for statistical significance. We want to enroll a range of different subjects, some marijuana-naive, some marijuana-experienced, some with co-morbid depression, some without comorbid depression, some who have had PTSD from Iraq and Afghanistan, some from Vietnam, some on medication, some off medication, some participating in psychotherapy, some not, but all with chronic PTSD of at least with over 50 on the CAPS. Conducting an exploratory study with a heterogeneous inclusion criteria is a perfectly acceptable approach for the first Phase 2 study testing a drug for a new clinical indication.

The application does *not* adequately identify potential problem areas and propose alternative approaches. For example, subjects are to videotape themselves using the prescribed marijuana, to be confirmed by the "verifier," but it is not explained how use of additional, non-study marijuana during the course of the study could be ascertained (other than in the zero-% THC group, who presumably should have negative urine tests). This reviewers seems to have missed the blood tests for cannabinoid blood levels, clearly mentioned numerous times in the protocol). Additionally, the "witness" is described as someone who "resides with the subject," but certainly there are many veterans with chronic PTSD who live alone; however, no alternative to a roommate or housemate is presented in the protocol. Witness is optional. Also, while concomitant medications will be permitted if unchanged during the study, a passing reference (protocol page 39) to "medications taken to treat adverse effects" is not explained; how will such meds be dealt with if they possess their own psychoactive properties? Their use will be recorded and whatever side effect profile they have will be noted.

Finally, it should be noted that given the Phase II nature of the proposed trial, should consideration be given to studying fewer subjects under more tightly-controlled conditions? For example, a "day hospital" or "methadone clinic" model, in which subjects smoked their prescribed marijuana under staff supervision (subjects can dose throughout the day, having them come to the clinic everytime they want to dose is not practical, nor is keeping them there all day) would permit daily objective assessments (most of the measures are self-report, and the CAPS is not designed to be administered every day) and somewhat more control over dosing (self-titration gives the patient the most control, Reviewer #1 wants standardized control. The lessons of self-titration of opiate pain meds in infusion pumps show people use less meds and report better pain control with self-titration) and remove concerns over misappropriation of the drug (our approach with video addresses that issue and giving people medicine as they live their lives at home is what we are ready to study), as none would leave the clinic with the subject. Ideally, at least intermittent sleep studies could provide data much more meaningful than subjective sleep reports, which are notoriously unreliable. What is unreliable about reports of nightmares or no nightmares? We don't need sleep studies, numerous marijuana sleep studies have already been conducted, though not in PTSD patients. This is again a suggestion coming from basic science, we don't need sleep studies for our Phase 2 drug development protocol. We also don't need brain

scans but this reviewer could just as easily ask for PET, SPECT and MRI scans, all of which would "advance the knowledge base" in PTSD patients but are not needed by FDA.

Concerns about the use of smoking as the mechanism of drug delivery are described below.

~~C.~~**B. Feasibility.** It is not clear who the scientific leader, i.e. Principal Investigator, of this study actually is. Suzanne A. Sisley, M.D., on the clinical faculty at the University of Arizona, is described as the "Clinical Investigator." Dr. Sisley, who is trained in psychiatry and internal medicine, is in private practice in Phoenix, and serves as Director of Telemedicine at the Scottsdale Treatment Institute -- specializing in "non-judgmental" treatment of substance use disorders -- the address of which (on East Camelback Road) matches that listed in the protocol for the "Research study site." Dr. Sisley's CV describes her as PI on "numerous clinical trials" for a variety of neuropsychiatric and medical disorders (not including PTSD), for the past 4 years, based at Contract Research Organization clinics in Mesa and Peoria, AZ. However, no publications or case reports are listed in her CV. Good point. Several presentations and abstracts are cited, all referring to the use of telemedicine in the treatment of addictive disorders.

Dr. Sisley would appear capable of handling the clinical responsibilities associated with the proposed trial. However, her research credentials appear sparse. She is not asking for a grant, MAPS is going to pay for the study and we are confident she can do an excellent job. It's our money, we should be able to choose our own team. –Unfortunately, no information about co-investigators is provided in the application and supplements. We can add that. The sponsors own "clinical research staff" apparently will monitor adherence to appropriate research procedures, both remotely and via in-person visits of unspecified frequency. Yes, we have our own monitoring staff. We can specific the frequency of our in-person visits Although that is somewhat reassuring, *it remains unclear whether the available research expertise is sufficient to conduct a complex outpatient clinical trial with a challenging PTSD patient sample. What additional staff and skills are needed?*

Dr. Sisley's base of operations at the *Scottsdale Treatment Institute* would appear to provide an appropriate infrastructure setting for an outpatient medical marijuana trial, given this site's usual clinical activities built around alcohol and substance use disorder treatment, some court-ordered. Insufficient information is provided to judge the adequacy of the required research and clinical personnel to conduct the proposed trial. What info on which staff is needed and why? Institutional support for the study appears present in the form of IRB approval from the University of Arizona. We do not have IRB approval from the UA and we have not claimed we have it,. However, there is no evidence that the submitted protocol has undergone scientific peer review at this or any other academic or Government research institution.Why is that necessary for a privately-funded study? This isn't necessary for studies with MDMA,LSD, psilocybin, etc. there is no need for yet more government reviews of what is to be privately-funded drug development research. This PHS/NIDA review is obstructing drug development research but freighting it with reviewers who evaluate grant applications seeking government funding.

~~D.~~C. **Human Subjects Protection.** The initial "practice" and acclimation sessions, whereby subjects begin the intervention trial under supervision, is a plus. Similarly, the routine use of the Columbia suicidality scale at weekly visits, with daily phone contact during the first week, are valuable safety measures. On the other hand, subjects are provided with little guidance in terms of when and under what conditions to use the marijuana at home, Self-titration- this is an exploratory study and we value self-titration, nor how to determine the appropriate dosage (from zero to two joints) on any given day They decide the appropriate dosel that is our treatment model.~~-~~

The main (it was just mentioned first, it's not the main measure, that's the Columbia suicidality scale) ~~-~~self-report measure listed in the protocol under "Safety Measures" is the "Experiences with Self-Administration of Marijuana Survey (**ESAMS**)." This scale apparently was developed by the applicants. No reference is presented for the ESAMS scale, and none is readily evident on the Internet. Thus, there is no evidence that this scale possesses appropriate psychometric properties to suggest its appropriateness for use in a clinical trial at this point. The ESAMS was developed for this study, it has not yet been used. It's not our main measure of safety and it's appropriate to add new measures to Phase 2 studies,

Longstanding issues regarding the safety of smoking as a means of drug delivery remain pertinent to the present proposal. We will evaluate reported side-effects including lung function. Marijuana is not linked to lung cancer. What safety concerns does this reviewer think is pertinent The major safety concern is the use of 0% placebo marijuana which is all risk and no benefit. B On the positive side, half the subjects would be randomized to the vaporized marijuana approach, presumably a safer alternative to smoking. It is noted that other than the "witness" function, the proposal makes no mention of other people around the subject. Are they at risk from "second-hand smoke"? No, since the subjects are not at risk from first hand smoke ~~-~~(with potential liability of the subject and/or the study sponsors).

While the applicants are appropriately aware of the potential pharmacological adverse effects of the intervention, they pay short shrift to the larger impact of participation in the study is likely to have on subjects' lives. Yet this reviewer proposes we consider completely disrupting their lives by making them go daily to a day-clinic to dose at standardized time. Prohibitions against driving for "up to three hours after smoking or vaporizing marijuana" during the trial, limiting the subjects' mobility, could work against any improvement in functioning and avoidance, The instruction not to drive while under the influence of marijuana does not reduce potential psychological effects that reduce avoidance essentially working against any therapeutic benefit of the drug.Does this reviewer think subjects should be permitted to drive at any time? *(The meaning of the phrase "up to three hours" after marijuana use in the consent form is not clear; does this mean a duration of under three hours prior to driving could be entertained?)*No, we can clarify. This driving restriction also might discourage use of the intervention during the day, when it could in fact be helpful. Transportation aside, it is unclear that subjects would be able to work or function in society if seem to be under the influence of the marijuana. This is an

exploratory study and we predict subjects will be able to function more effectively in society, If not, subjects can drop out of the study at any time, and we will monitor their reasons for doing so. Let the data resolve this question. –Similarly, given the restrictions on smoking in a growing number of public places, it is unclear how subjects will function outside their homes during the many weeks of the study. **The subjects already have chronic, treatment-resistant PTSD that impacts their ability to function in society. We need to evaluate the impact of marijuana on their lives They will decide where and when to dose, that's self-titration.**

Finally, the necessity of making available to the investigators someone residing with the subject to serve as a "verifier" of protocol compliance, appears absent from the consent form. We can add it to the consent form.

Reviewer #2

REVIEW OF PROTOCOL MJP-1 (Amendment 1):

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)

A. Significance. The need for improved treatment of post traumatic stress disorder among veterans of the current conflicts is a pressing national problem. The Institute of Medicine of the National Academy of Sciences recently completed a review of the efficacy of currently available treatments in response to a request from the Department of Veterans Affairs. The lack of evidence for clearly efficacious interventions is forcefully documented in this report. The analysis concluded that there is no conclusive evidence for efficacy of current treatments modalities. (See http://www.nap.edu/openbook.php?record_id=11955). The National Academy report includes a recommendation that funders should encourage investigation of the treatment of PTSD in diverse settings and by a broad community of investigators. Thus the study addresses an important problem and treatment of a condition for which current therapies are unsatisfactory.

A second argument for study of marijuana in patients with PTSD is to address potential safety issues. There are a number of safety issues about use of marijuana in individuals with PTSD, particularly the possibility that the drug may produce induce panic attacks of produce anxiety, paranoia or other dysphoric symptoms. We have safety procedures in place to monitor for these fearful side effects and provide support if they happen. .Carefully supervised dose escalation studies could help address these concerns. Studies to address safety issues in well characterized patients with PTSD of varying severity (we only enroll subjects with moderate to severe PTSD, over 50 on the CAPSand at various time points after the initial exposure or return from active duty would be appropriate. (Question ii and part of Question iv)

Nonetheless, the concerns outlined below under *Approach* and *Feasibility* raise substantial concerns and create major uncertainty about whether "bona fide scientific information that will add to the knowledge base on the potential application of marijuana based medications" is likely to arise from this study. (Question i and iii)

With regard to Question v, the study does not use a biopharmaceutical approach. The overall goal is to test whether smoked or vaporized marijuana of varying potency results in clinical improvement in symptoms of PTSD. It would appear that the investigator group is not primarily focused on a drug development approach. This comment assumes that only a "biopharmaceutical approach", presumably with fixed dosing, and pharmacokinetics and pharmacodynamics, indicates a drug development approach. That is not true. We have determined our own drug development strategy and have arrived at a different starting point than what this reviewer recommends. This is yet another indication that the PHS/NIDA reviewers do

not understand drug development the way the FDA does, and that HHS requiring protocols to be approved both by FDA and by PHS/NIDA reviewers, is a strategy for obstruction.

B. Approach. There are a number of concerns about the proposed approach:
The study cannot be effectively blinded, This is stated as fact, not as an assumption, when this dose-response design is the most likely design to succeed in producing a double-blind..since subjects with any experience with marijuana, are likely to be able to distinguish the low potency preparations from the higher potency preparations. This is an assumption that is likely to be largely false for a substantial amount of the subjects, with the exception of the 0% strain which all subjects, marijuana-experienced and marijuana-naïve, are likely to detect after days or week. The same protocol is being proposed for marijuana naïve subjects, for whom a 12% THC or 6%THC/6%CBD may have marked and unfamiliar effects that's why we have the two supervised introductory sessions, and for subjects with substantial marijuana experience. This would be a reason to perform the study in marijuana naïve subjects. This is an exploratory study that should not make assumptions and should enroll subjects with and without prior experience with marijuana. Attempt to determine whether patients accurately report prior experience would be critical. Not if we don't try to exclude all subjects with prior experience with marijuana. Alternatively, given the substantial safety concerns a dose escalation study would be a possible approach, with observed administration and careful symptom diaries.

The protocol does not adequately address the diversity of the Veteran PTSD population. Actually, in our MDMA/PTSD research, we are finding that the treatment approach is independent of the cause of the trauma. The timing of the intervention relative to the initial trauma, we enroll only subjects with chronic PTSD of six months for more, that's enough of a homogenous group for this initial exploratory study the nature of the residual symptoms (we require a 50 or greater on the CAPS, moderate to severe PTSD, that's homogeneous enough for this exploratory study, the presence of co-pathologies (we do not want to exclude people wth co-morbid depression and anxiety, so the variety is not a problem, it's an opportunity to gather information about people with a range of co-pathologies— all are likely to impact on whether there are any treatment benefits or adverse effects. A more thoughtful and reasoned approach we will not be able to satisfy this reviewer since don't agree on blinding and using only marijuana-naïve subjects and preliminary hypotheses about which symptom domains are like to benefit would strengthen confidence in this pilot study.

In part because the study cannot be blinded (this is an unfounded assumption) it is critical to insure absolute objectivity of the evaluation process. The plans for data management and study coordination are not adequate—. The approach we are taking is the approach the pharmaceutical industry takes all the time. It is not satisfactory for the sponsor (pages 41- 44) to undertake all data management and analysis. This is entirely within the standard approach for drug development studies. ~~It is critical to insure that data management, study coordination and data analysis be independent.~~ Not at all true or critical, not how drug development research is done.

We have blinded independent rater, that's important. The FDA will audit our data and decide if it is reliable.

C. Feasibility. The only investigators mentioned in the material provided to this reviewer are Dr. Rick Doblin as the Sponsor Designee and Dr. Sue Sisley, as Clinical Investigator. Neither individual would be considered to be expert in clinical investigation of PTSD. The sponsor does not need to be personally an expert in PTSD but I have learned quite a bit about the conduct of PTSD studies, and I'm a co-author of a paper on MDMA-assisted psychotherapy for PTSD. Sue Sisley has expertise in PTSD. The research infrastructure is not described in the application, and there is no evidence of institutional support in the materials I reviewed.

Therefore the protocol materials do not adequately address some major feasibility concerns.

~~D.~~ **Human Subjects Protection.** I was not provided any information about IRB review and cannot comment on the adequacy of protection of human subjects.

D. Reviewer #3

REVIEW OF PROTOCOL MJP-1 (Amendment 1):

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)

A. Significance. *Trauma/PTSD:* More than half of the adults in the United States report one or more lifetime events outside of normal human experience; in some studies, rates have been estimated in the 70-90 percent range. An estimated 60 percent of reported traumatic events involve the sudden unexpected death of someone close or a trauma suffered by someone close.1

Clinically significant responses to trauma include Acute Stress Disorder (ASD), Posttraumatic Stress Disorder (PTSD), Major Depressive Disorder, Traumatic Grief, and Adjustment Disorders. These Quick Facts will concentrate only on PTSD, with an emphasis on facts related to PTSD and SUDs (Substance Use Disorders).

Epidemiology: The development of PTSD is dependent upon many factors, especially the type of trauma itself. For example, in one survey in Detroit, 9.2 percent of persons experiencing a trauma developed PTSD, but half of those who had been raped or held captive, tortured, or kidnapped developed PTSD compared with 2.2 percent of those who learned of the rape, attack, or injury of a close relative.1 In a study of about 100,000 veterans in VA health facilities from 2001-2005, PTSD was the most common service-related mental health diagnosis (approximately 13,000 cases) and accounted for more than half of all mental health diagnoses and 13 percent of the study sample. During 2006 the VA reported providing treatment for 346,000 veterans diagnosed with PTSD.2 In the National Comorbidity Survey Replication, 6.8 percent of respondents were found to have a lifetime PTSD diagnosis and 3.6 percent a 12-month prevalence rate (N=5692).

PTSD patients have repeatedly been found to have a high rate of substance-related disorders. Since clients with SUDs have a higher incidence of trauma in their lives, it is unclear to what extent having a SUD predisposes one to develop PTSD in response to trauma or to what extent it is simply the greater rate of traumas that increases the association of having a lifetime SUD with that of having a lifetime PTSD. Even more difficult to discern are the relationships among increases in drinking following trauma (a common phenomenon) and the development of PTSD and/or a SUD.

Concerns:

While the sponsor's proposal addresses an important problem, PTSD, we have some concerns about the criteria by which participants are deemed to be "treatment-resistant". These subjects

have chronic PTSD. The treatments available to them from the VA have not reduced their PTSD below 50 on the CAPS, moderate to severe PTSD.

- Have these participants been given adequate time to evaluate whether the psychotherapeutic or pharmacologic therapies are effective? (a sufficient response time of at least 8 weeks is needed at which point the dose is either increased, discontinued and switched to another agent, or augmented with additional agents) Subjects who refuse to take medications, or drop out of medication regimens is less time than mentioned above, have not been able to obtain relief from those medications. They are treatment-resistant. Similarly, patients who find Prolonged Exposure to be retraumatizing and drop out clearly did not obtain the relief they sought from that treatment.
- The proposed study only indicates that the participant tries one or more of the following pharmaceutic agents and/or any form of psychotherapy.
- Have the conventional treatments for PTSD truly been exhausted Marijuana does not need to be the treatment of last resort, nor does the VA provide access to all conventional treatments.

B. Approach. All new patients should be screened for symptoms of PTSD initially and then on an annual basis, or more frequently; patients should be screened for symptoms of PTSD using paper-and-pencil or computer-based screening tools; these guidelines also recommend considering the following PTSD screening tools:

- Primary Care PTSD Screen (PC-PTSD)
- PTSD Brief Screen
- Short Screening Scale for DSM IV PTSD
- PTSD Checklist (PCL)

Based on a review of 90 randomized clinical trials of pharmacological and psychological treatments of PTSD, the Institute of Medicine (IOM) found they could endorse only exposure therapy as having demonstrated effectiveness. A substantial number of patients drop out of PE after finding it retraumatizing.

In a review of pharmacologic studies, Golier, Legge, and Yehuda (2007)10 concluded that the selective serotonin reuptake inhibitors fluoxetine, sertraline, and paroxetine are effective for reducing symptoms and improving outcomes, and that imipramine and phenelzine have also been found efficacious. This text suggests that SSRIs are effective for PTSD when we are talking about subjects with chronic PTSD who have not found relief from medication or psychotherapy or both.

Per the 2010 VA/DoD Clinical Practice Guideline on the Management of PTSD, the stepped care treatment of PTSD involves:

- Initial treatment: Psychotherapy or SSRI or SNRI
- Step 1: switch to another SSRI or SNRI and/or psychotherapy

- Step 2: add Atypical Antipsychotics (AAP) and/or psychotherapy; switch to Mirtazapine (MIRZ), Nefazadone or TCA
- Step 3: Switch to alternative step II or phenelzine TCA, or add AAP, or add psychotherapy

The National Center for PTSD suggests:

- Cognitive behavioral therapy (CBT) as one type of counseling. There are two forms that the VA provides: Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) therapy.
- Another kind of therapy is eye movement desensitization and reprocessing (EMDR).

Concerns:
How is vaporized marijuana being defined? What is inhaled from the Volcano bag.
How is the efficacy of each delivery system determined?

- Bioavailability (F) of smoked marijuana vs vaporized marijuana Dr. Donald Abrams has already conducted a study, referenced in our paper as #112

C. Feasibility.

Concerns:
How are they defining PTSD? CAPS How about co-morbidities? Not an exclusionary criteria, clearly stated in the protocol

- There seems to be a general lack of expertise in the area of PTSD. MAPS staff includes experts in PTSD,
- The clinical investigator, although in internist and psychiatrist, does not appear to have any clinical expertise in the treatment of PTSD patients. Sue has experience working with PTSD patients.
- The National Center for PTSD states that "having symptoms of PTSD does not always mean you have PTSD." Symptoms you may see for other mental health problems may look like symptoms for PTSD. We will use CAPS for diagnosis, trained independent raters.
- There appears to be a lack of outside/independent data analysis FDA will audit the data, we are a pharmaceutical company trying to do drug development research, we don't need outside/independent data analysis. That said, we will provide access to our raw data to anybody who requests it and we operate in a transparent manner

D. Human Subjects Protection.

Concerns:

- There appears no apparent documentation of IRB approval. If so, needs to be made more apparent, not clear if they had any comments or recommendations.

- Need to have a more controlled environment for subjects. It's important/ essential for our study, to permit outpatient treatment. We do not need to have a more controlled, in patient environment for subjects.

Reviewer #4

REVIEW OF PROTOCOL MJP-1 (Amendment 1):

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)

Summary. The study addresses an important problem: How to alleviate PTSD symptoms, particularly among individuals for whom those symptoms have proven intractable. However, important problems with the study design will substantially diminish the ability of the study to address this important question. As currently designed there are significant questions as to whether the study would provide any new knowledge relevant to the research question. This study would provide substantial new knowledge at no cost to the tax-payer, yet we can't proceed. In addition, there are significant feasibility concerns.

A. Significance. Whereas a lengthy list of objectives (one primary and many secondary) is provided, no hypotheses are specified. This is a drug development protocol and we do not need to have elaborate hypothesis for FDA approval. This request for hypothesis is another indication of a basic science approach The applicant stresses the 'pilot study' nature of the proposed study but the application describes a very complex, multi-staged design with significant technical and scientific challenges of a scope generally beyond a pilot study. This is the design we have chosen to start with, it makes sense to us and this is privately-funded study that the FDA has approved.

A significant concern is that the study will apparently include subjects with no prior exposure or experience with marijuana. Administration of a psychoactive drug with abuse potential to naïve subjects would be warranted only under very well justified circumstances, and demonstration of a therapeutic effect in drug-experienced subjects would be a pre-requisite condition. This reviewer #4 is claiming that we should only work with subjects who are experienced with marijuana. Reviewer #2 says we should only work with marijuana-naïve subjects.

There is a significant study design issue in that subjects who experience adverse effects in the screening session will not be entered into the study. This safety procedure makes total sense. In a test of whether marijuana is useful in the treatment of PTSD if only subjects with positive responses to marijuana are included then it is not a fair test. This is a total misunderstanding of clinical research. It's entirely appropriate to screen for the best responders to the treatment, what's essential is that the study population be adequately described and the results not overgeneralized.

There is no provision for evaluating individual differences in efficacy. We are gathering demographics but for example, we are not conducting genetic studies or brain scan studies. We don't need to do everything in this pilot study and can't afford to do so. Even if subjects are pre-

screened for positive responses, it is highly likely that there will be variability in the effects of marijuana across individuals. To translate that finding into guidelines for personalized therapies, it is essential that a study evaluate factors associated with them. While it is a good idea to try to identify what factors lead to positive outcomes, That is, how can we predict who (if anyone) will respond favorably to the study drug? No such analyses are proposed nor are many variables one might use to predict such variability included in the study protocol. We can think about what variables we can reasonably gather and analyze.

Also of concern, it is not clear how investigators will integrate data on alleviation of PTSD symptoms with data on global functioning to effectively address the question of efficacy. Reductions in CAPS are all that is needed for efficacy. That's how FDA will evaluate the outcomes. We can correlate GF data with CAPS data.

The investigators overlook the plethora of studies that address the comorbidity of PTSD and substance abuse/dependence disorders, including that involving marijuana. They argue that marijuana may provide a good alternative treatment to other drugs (e.g., benzodiazepines), which may lead to abuse and dependence. However, there is no indication that benzodiazepine use and/or alcohol use will be assessed in this study. We exclude people who are on benzos and do not permit them during the study. We have no policies regarding alcohol. In this context, it is important to specify why that is not a concern for marijuana. Abuse liability issues are important.

B. Approach. The lack of experimental control is a significant threat to the potential validity of this study. What important variables aren't controlled? Use of the study medication will take place outside of a controlled research environment. This is a take-home study, that is the essence of this design. While the investigators take steps to document use of study medication, there will be no control over use of non-study marijuana (or other drugs and medications). We are taking blood samples and will know if non-study marijuana is used or other drugs with urine tests as well. The use of non-study marijuana would critically affect the interpretation of study findings. Yes, that's true. That's why we do the blood tests.

The investigator describes previous research that suggests marijuana may have anxiogenic as well as anxiolytic effects. Individuals for whom it has anxiogenic effects will be able to opt out in the introductory sessions. Thus, the sample will be substantially biased in favor of finding effects of the study drug. This comment that we should not exclude subjects who have anxiety reactions in the two introductory sessions in which marijuana is administered under supervision, because "the sample will be substantially biased in favor of finding effects of the study drug" misunderstands drug development research where it is perfectly acceptable to focus on the most likely responders. In fact, we need to obtain the transcripts of the 1997 NIH workshop on marijuana cited by Reviewer #1 since Dr. Temple specifically discusses what I think he called " subject enrichment" or something like that, to indicate the acceptability of focusing clinical studies on the treatment responders.While "personalized medicine" (i.e., identifying therapies that work best for individuals) is a valid enterprise, YES, it is. the proposed study will not be able to identify

factors that predict efficacy in individuals (because those for whom it may not work will be excluded before any assessments—other than demographic and CAPS scores—are completed) We will gather information on the drop-outs and see if we can find any patterns that predict drop-outs. Of the subjects who enroll in the study, there will still be variability in response and we can evaluate what demographic and other data we have to see if there are predictive factors. ~~.~~

There are significant data analysis concerns.

a. The investigators themselves acknowledge that power is likely to be low. If the study drug is not found to be efficacious, there will be no way to determine if that is a true negative finding or if power was inadequate. This is a pilot study, we are looking at safety and do not need to find statistically significant efficacy, trends are all we need to find.
b. The investigators point out that their sample size will be sufficient to detect an effect size of 1.5. This would be a huge effect size for this type of study—and highly unlikely. We need to double-check this. Essentially, the study does not have the power to detect an effect of the magnitude that would realistically be obtained. This is a pilot study and does not need to generate statistically significant results. We should not have to start with a pilot study of 100 subjects!
c. The investigators also calculate power for detecting a difference between smoked and vaporized marijuana and argue that they would be able to detect an effect size of 0.8 with 79% power. It appears, however, that the question of smoked vs. vaporized is somewhat tangential to the larger aim of determining efficacy of marijuana for alleviating PTSD symptoms. It's related to determining safety. The larger and more important aim is significantly underpowered. (If the aim were solely to evaluate differences between smoked and vaporized marijuana, a more targeted study could be designed.) This is a pilot study and will generate a great deal of useful information. It's underpowered because it's an exploratory pilot study.
d. The investigators propose so many analyses (pp. 41-44) that some will produce significant results by chance alone. We will see about reducing analyses that aren't a priority, but we can correct for multiple analyses.
e. The investigators point out that there are no studies on which to base power analyses for the effect of the study drug on PTSD symptoms. There are, however, studies of the effects of marijuana on subjective reports that could have been used, at least to provide a rough guide of an effect size. We can try.

The inclusion/exclusion criteria further hamper the ability of the proposed study to address its aims:

a. Individuals who are currently getting psychotherapy as well as those who are on psychotherapeutic drugs will be included. This will introduce variability and will diminish the power of the study to detect effects of the study drug. Moreover, it will not

be possible to determine whether observed changes (improvements or declines) are due to the study drug or to other therapies. The other therapies are to be held constant and the subjects will have chronic PTSD despite their therapy or medication. We don't think we should encourage people in therapy to leave therapy, and medication is not a contraindication. The only change will be the study drug,

b. Although individuals with history of psychotic disorder, bipolar affective disorder, and various personality disorders will not be included but the criteria/instruments for diagnosing those disorders are not provided. SCID
c. Individuals with histories of any other Axis I disorders (one assumes) will be included. This will introduce significant variability into the study population and will thereby diminish the power of the study. It is appropriate to include them. This study is an initial pilot study and we have to start somewhere with limited number of subjects.

The investigators propose to test a range of doses. There are two serious methodological issues here. First, the THC content of the marijuana smoked may or may not be related to the 'dose' received. Marijuana smokers are reported to 'titrate' intake to reach a desired effect. The amount of THC absorbed is related to the THC content in the marijuana, but other factors such as depth of inhalation , time of breath-holding, etc will significantly impact the final 'dose'. While the investigators will utilize some standardized protocols developed for smoke exposure, This is the best it gets in the absence of biological indices (such as peak blood concentrations of THC) the potency of the marijuana smoked is a crude measure of dose. We wil take blood plasma samples. Secondly, even though the smoking protocol is explicit, the participants will determine how much to use each day. It would seem that this would seriously mitigate dose-response analyses. This increases the number of different data points about dosage and does not mitigate the dose-response analysis. The investigators need to specify why this would not be the case.

How frequently will the effects of the study drug be assessed? It appears that this will be done only weekly. The CAPS is not meant to be administered daily or even weekly. (The daily diary seems to include only information regarding the frequency and amount of study drug used; it does not seem to include any subjective reports.) We have sleep measures If effects will only be assessed on a weekly basis, it seems likely that important information will be missed. We are looking for long-term changes in the CAPS, that's the key outcome measure. We may miss some data but we can't gather everything. The investigators do not provide anything in their literature review to evaluate whether we might expect immediate vs. longer-term effects of marijuana. Immediate

The purpose of Stage 3 (in terms of hypotheses and analyses directed to those analyses) appears to be included as a condition intended to encourage adherence to the study protocol (in that subjects will presumably not be tempted to divert study marijuana or misrepresent the amount smoked because they will be able eventually receive all the marijuana for each condition). Is there evidence that such a strategy is effective? This has never been done before.

The investigators state that "if there is no significant effect of drug delivery method, and no interaction of drug delivery method and marijuana potency, then subsequent analyses will examine potency only" (p. 41). By convention, one may collapse across experimental conditions only if the p value associated with the F statistic is $p \geq .25$.

How will the investigator determine that a "serious suicide risk" exists? CSSRS

C. Feasibility. Only the CV of the principal investigator, Suzanne Sisley, is supplied. The PI is a psychiatrist in private practice with some experience in the addiction field. She has participated in several clinical trials but there is no demonstration of any experience in managing a clinical trial of the size and complexity of the proposed study. MAPS will manage this study

No biographical information is provided for other study personnel, so no comments can be made regarding the appropriateness of their qualifications.

No information is provided on the study site.

No supportive documentation is provided regarding the study locations, investigators, or institutional support, so no comments on the feasibility of adequate infrastructure can be made.

D. Human Subjects Protection. There are significant human subjects issues. For example, drug naïve subjects will be included in the study, Reviewer #2 said only marijuana-naïve subjects should be included no assurances can be provided that subjects will not co-administer drugs other than the study drug which can profoundly affect mood, psychomotor coordination, and judgment (with significant impact on driving behavior). We have urine and blood tests No institutional IRB review was provided.

Reviewer #5

REVIEW OF PROTOCOL MJP-1 (Amendment 1):

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)

A. Significance. The need for improved treatment of PTSD in veterans of the current wars is a serious problem. Individuals from diverse populations also suffer from PTSD and can experience a range of signs and symptoms. PTSD is a disorder that can develop following a traumatic event that threatens one's safety and results in feelings of helplessness. PTSD can affect those who personally experience the event, or who witness it, as well as emergency workers and law enforcement officers who aid in an emergency. It also occurs in friends and family of the victim of a trauma. Signs and symptoms of PTSD can range from experiencing flashbacks and nightmares to outbursts of anger to substance abuse and suicidal ideation. Treatments for PTSD include cognitive-behavioral therapy, family therapy, and antidepressant medication to relieve symptoms of depression and anxiety.

This study is a randomized, placebo controlled, triple-blind design in 50 participants, and consists of an initial randomized arm (stage 1) followed by a partially randomized arm (stage 2). The proposed research subjects are veterans with chronic, treatment resistant, military service-related PTSD. Subjects receive marijuana containing 0%, 2%, 6%, 12% THC[1] or 6% THC/6% CBD[2]. Marijuana is smoked or vaporized for four weeks, followed by a two week washout period where no marijuana is used. During the crossover arm [stage 2], subjects receive marijuana with 6% THC, 6% THC/6% CBD, or 12% THC. Marijuana is smoked or vaporized for 4 weeks, again followed by a 2 week washout period without marijuana. Self administration of the drug is intended for outpatient use.

Initially the Sponsor proposed that on request all unused marijuana from either study stage be returned to the subjects, with the intent of reducing the likelihood that marijuana will be used unnecessarily or diverted during the study. Because an FDA reviewer considered this unacceptable, the Sponsor proposed adding a stage 3 to the study for subjects to use up any remaining unused marijuana. This proposed solution was arbitrary But appropriate and necessary and the description of the purpose of stage 3 and the sort of data that would be obtained was not described. Same data as in Stage 1 and Stage 2 The protocol states that records pertaining to the use of Schedule 1 compounds are to be maintained in accordance with relevant federal and state regulations during the study. Forms will be provided to track drug accountability and administration throughout study, and drug accountability will be reviewed

[1] THC is delta-9-tetrahydrocannabinol, also known as dronabinol, a Schedule I substance in the Controlled Substances Act (CSA). THC is the principle psychoactive ingredient in cannabis.
[2] CBD is cannabidiol, another substance in cannabis. It is also in Schedule I in the CSA.

during routine monitoring visits. However, no details were provided about the forms or how drug accountability will be assessed during the trial. Those forms can be provided but are usually created after there is an approved protocol Of particular concern was the lack of details about assuring safety ??CSSRS and other measures and securing the marijuana supply in subjects' homes to avoid abuse or diversion. People will have half an ounce and one time and will have to video tape their use.

B. Approach. As currently proposed, the research study will not be conducted in a manner to assure the safety or security of marijuana, a Schedule I substance under the U.S. Controlled Substances Act (CSA). FDA's Controlled Substance Staff approved this design. The drug will be self administered in a non-supervised outpatient basis in a vulnerable patient population [military veterans suffering from chronic treatment resistant, military service related PTSD]. The subjects are vulnerable emotionally but they are trained soldiers so it's not likely they will be especially vulnerable to theft. There are no provisions for maintaining adequate security and safety of the marijuana outside the investigator's direct control, including providing relevant training to the research subjects on preventing abuse and diversion of the marijuana. We can create a training program for this half ounce of marijuana.

The protocol does not provide for adequate supervision and monitoring by the Sponsor and principal investigator. The Sponsor proposed solution for maintaining security is use of a box with a combination lock and a camera to record drug use along with use of a daily diary. This solution was approved by FDA's Controlled Substances Staff. The Sponsor proposes weekly marijuana distribution though there is a need for daily interactions of subjects with the investigator. Daily interactions, when needed, are on the phone. Better assurance and monitoring of driving after last use of marijuana is needed. Monitoring of driving> -In order for the study to be able to provide reliable data for continued evaluation and assessment of the usefulness of marijuana for PTSD, the subjects need to be administered marijuana under direct supervision. Turning this into an in-patient study ends the study, nobody will live in-patient for three months and that increases the study costs astronomically.The subjects should not be in control of the marijuana supply why not?, and need to be monitored for a sufficient period of time after marijuana dosing, until they no longer experience the CNS behavioral and cognitive effects of marijuana. Risks to the patient and possibly others, such as if driving a motor vehicle too soon after administration, would be minimized by this approach, in addition to yielding more reliable results.

In order to receive a DEA Schedule I license to conduct the study, the Sponsor needs to adequately describe the legal status of marijuana to the patients and should submit a proposed written description of the legal status prior to conducting the study. ?? All and any illegal substance or alcohol abuse should be cause for exclusion of subjects from the trial, because such activity would call into question the value of the study results because of possible additive or synergistic effects and interactions. Also, subjects being currently treated for PTSD with a legal medication should be excluded from the study. There is no reason to exclude patients on legal

medications, they do not need to taper since they are suffering from chronic PTSD and have not obtained the relief they are seeking from those drugs, which will be held constant during the marijuana trial.

The study cannot be effectively blinded, since subjects with marijuana experience, are likely to be able to distinguish low potency preparations from the higher potency preparations. This is an assumption that is not founded on data but is likely to be the case for the 0% placebo dose. The protocol applies to marijuana naïve subjects who may experience marked adverse and unfamiliar effects, as well as to subjects with extensive marijuana experience. This would be a reason to perform the study in a similarly experienced population. This is an exploratory study and we benefit from including both marijuana-naïve and marijuana-experienced subjects. It is critical that patients accurately report prior experience with marijuana.

The protocol does not adequately address the diversity of the veteran PTSD population how would we adequately address that diversity? We believe the treatment of PTSD is independent of the cause, we want to test that. -and the severity of the condition (we take people who only have 50 or above on the CAPS_ and the state of health of the veterans regarding serious physical injury. The timing of the intervention relative to initial trauma, nature of residual symptoms, presence of co-pathologies are all likely to affect treatment benefits or adverse effects.We don't need to homogenize beyond chronic treatment-resistant PTSD In addition, mention should be made of whether any individuals are currently undergoing treatment and whether any are currently being treated with antidepressants, such as sertraline or fluoxetine. Yes, this should be mentioned and monitored but these people don't need to be exluded or asked to taper off those medications.

C. Feasibility. The only investigators mentioned are Dr. Rick Doblin as the Sponsor designee and Dr. Sue Sisley as Clinical Investigator. Neither is demonstrated to be expert in clinical investigation of PTSD. Insufficient information is provided as to whether the research facility (Scotsdale Treatment Institute) can provide adequate support for PTSD research. Therefore, the protocol materials do not adequately address the feasibility of successful investigation. This is a review conducted of grants seeking federal money. If we invest private money and we fail, that is our loss. That's how FDA operates.

Plans for data management and study coordination are not adequate. It is not satisfactory for the sponsor to undertake all data management and analysis. Data management, study coordination, and data analysis should be independent. Why is this? This isn't the way the pharmaceutical industry operates. This is a drug development study, it's totally appropriate for the sponsor to undertake data management and analysis. FDA can and will audit the data if they want to do so.

Problems with the study design largely concern the lack of blinding for marijuana, (an assumption it will fail, not backed by data) lack of collection of pharmacokinetic blood level data

(why do we need this information, this is not a PK study, the lack of knowledge of how much of the marijuana active ingredients will actually be administeredwe have standardized puff and vaporization procedures that are used in all other marijuana studies, and blood tests, the varied histories of experience with marijuana and other controlled substances, and the unstructured manner in which dosing occurs self-titration is a strength of this design, not a weakness. The actual amount of active ingredients of marijuana that are administered to each subject remains unknown but we will still have a close approximation of dose.

D. Human Subjects Protection. Information was not provided about IRB review. Major risks identified relate to possible diversion and abuse, FDA Controlled Substances staff approved our approach adverse effects to the subjects we are closely monitoring it, and inadequate monitoring of the marijuana supply (blood tests and videos).