

PROTOCOL MJP-1

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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)

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## 1.0 List of Abbreviations

AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI	Beck Depression Inventory
C	Celsius
CAPS	Clinician Administered PTSD Scale
CBD	Cannabidiol
THC	Tetrahydrocannabinol
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – IV
ESAMS	Experiences with Self-Administration of Marijuana Survey
ECG/EKG	Electrocardiogram
F	Fahrenheit
FDA	Food and Drug Administration
GABA	Gamma-amino-butyric acid
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloric acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
LTFU	Long-term (12-month) follow up
MAOI	Monoamine Oxidase Inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MDMA	3,4-methylenedioxymethamphetamine
NIDA	National Institute on Drug Abuse
PTSD	Posttraumatic Stress Disorder
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SOP(s)	Standard Operating Procedure(s)
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
Stage 1	The initial, fully randomized, blinded study arm

Stage 2	The second, partially randomized, blinded study arm
SUD	Subjective Units of Distress
THC	delta-9-tetrahydrocannabinol
U.S.	United States of America

## 2.0 Introduction

This study is sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a US-based, IRS-approved, non-profit research and educational organization. MAPS sponsors clinical research evaluating the potential of psychedelics and marijuana to become FDA-approved generic prescription medicines. MAPS' mission is 1) to treat conditions for which conventional medicines provide limited relief—such as posttraumatic stress disorder (PTSD), chronic pain, drug dependence, anxiety and depression associated with end-of-life issues—by developing psychedelics and marijuana into generic prescription medicines; 2) to treat many people by building a network of clinics where treatments can be provided; and 3) to educate the public honestly about the risks and benefits of psychedelics and marijuana.

MAPS is currently sponsoring a series of Phase 2 pilot studies in the U.S. and internationally, investigating the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in treating people with chronic, treatment-resistant posttraumatic stress disorder (PTSD). The promising results of our initial US MDMA/PTSD pilot study, mostly in women survivors of childhood sexual abuse or rape, were recently published [1]. MAPS is in the early stages of a US MDMA/PTSD study that will enroll 16 U.S. veterans with service-related PTSD.

MAPS is seeking to conduct the marijuana/PTSD pilot study described in this protocol in response to many anecdotal reports of marijuana being used successfully to some degree in people with chronic, treatment-resistant PTSD, including veterans with service-related PTSD. As of August 18, 2010, 633 of a total of 2316 individuals enrolled in the New Mexico medical marijuana program (27%) list PTSD as the primary condition they seek to treat with medical marijuana [2], making it the most common reason for enrollment. Research examining drug use in veterans with PTSD also found that marijuana was commonly used [3]. At present, there are no published data from a randomized, placebo-controlled, triple-blind study of the risks and benefits of marijuana for subjects with chronic PTSD from any cause.

In this groundbreaking randomized, triple-blind, placebo-controlled, crossover study, marijuana will be tested as a pharmacological agent to manage PTSD symptoms in 50 veterans. This will be the first controlled clinical trial testing the therapeutic potential of marijuana for treating PTSD. The study will examine two drug-delivery methods, smoking and vaporizing, and use four marijuana strains each with a different level of D9-tetrahydrocannabinol (THC) along with a fifth strain containing equal amounts of THC and cannabidiol (CBD). During the study, marijuana will be self-administered daily for four weeks on an out-patient basis. Tolerability of smoked vs. vaporized marijuana will be compared within each condition. Symptoms of PTSD and depression will be assessed after a 4-week period of marijuana use and again two weeks after cessation of use in each study arm. A crossover arm will involve another 4-week period of marijuana use followed by two weeks of cessation. Symptoms of PTSD and depression will be assessed at the end of the crossover period, at the end of the 2-week period of cessation, and again 12 months after the end of the crossover arm. Our goal is to investigate the premise that

using marijuana eases the symptoms of PTSD, specifically reducing nightmares, improving sleep, and improving mood.

## **2.2 Protocol Purpose**

The purpose of this protocol is to gather preliminary evidence regarding the safety and efficacy of five different potencies of marijuana for managing PTSD symptoms in veterans with chronic, treatment-resistant, military service-related PTSD. The protocol is also designed to gather comparative safety and efficacy data on two different delivery systems, smoking and vaporizing. This study follows 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). Participants will receive marijuana containing 0%, 2%, 6% or 12% THC or 6% THC/6% CBD. They will smoke or vaporize the study marijuana during a four-week period, and they will cease to use it for the two weeks following the period of self-administration. PTSD symptoms will be measured at the start of the study, at four weeks of marijuana self-administration and after two weeks of cessation of use for each study arm. During the crossover arm of the study, subjects will receive marijuana with 6% THC, 6% THC/6% CBD, or 12% THC and will continue to smoke or vaporize the material.

## **2.3 Supporting Information**

### **2.3.1 Condition**

PTSD is a serious, worldwide public health problem for which a wider array of effective treatments is needed. In the U.S., the lifetime prevalence of PTSD in the general population is between 6 and 10% [4, 5], and it can be especially resistant to pharmacotherapy with Selective Serotonin Reuptake Inhibitors (SSRIs) [6]. PTSD is common in other countries as well [7-11]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [12], and it is estimated that the number of service members returning home with PTSD will be between 75,000 and 225,000 [13]. In 2004, the U.S. Veterans Administration spent \$4.3 billion on PTSD disability payments to approximately 215,000 veterans, most of them from the Vietnam War [14]. Due to the Iraq and Afghanistan wars, the number of veterans disabled by PTSD, and the cost of providing disability payments, has increased substantially since 2004. In countries where there is endemic armed conflict, the incidence of PTSD in civilians is often far greater [15-17]. PTSD is typically a chronic illness [18, 19], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [9, 18, 20, 21].

An array of psychotherapeutic options exists for treating PTSD and two SSRIs (sertraline and paroxetine) are approved as PTSD treatments by the FDA. However, a significant percentage of PTSD patients fail to respond adequately to established PTSD psychotherapies [22, 23], or respond in ways that are statistically significant but clinically inadequate. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [24]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

There is limited data about whether or not patients with service-related PTSD are more difficult to treat than those with PTSD from other causes. A recent comprehensive review stated that, “Most, but not all, randomized clinical trials (RCTs) with combat (mostly Vietnam War) veterans showed less treatment efficacy than RCTs with nonveterans whose PTSD was related to other traumatic experiences.... Therefore some experts believe that combat veterans with PTSD are less responsive than survivors of other traumas to treatment. Such a conclusion is premature. ... More clinical trials with combat veterans would be important and welcome additions to this literature” [25].

It has been noted (e.g., [26-28]) that PTSD patients have a tendency toward using depressants and marijuana to alleviate their symptoms, such as avoidance and numbing, while stimulants, such as cocaine, may exacerbate symptoms [29]. On the basis of these findings, we expected that PTSD participants who used illicit drugs would be more likely to use depressants and marijuana as opposed to stimulants, suggesting that this population may be using marijuana and/or depressants to self-medicate one or more PTSD symptoms [3].

Self-reporting in PTSD clinical trials associated with the Veterans Administration (VA) system has raised some criticism, as disability compensation often depends on obtaining a PTSD diagnosis [3, 30, 31]. In addition, substance-use and reporting among individuals in this group is often under-reported due to the fact that such actions might jeopardize potential claims for disability compensation or result in arrest or prosecution. Due to these factors it is important to conduct clinical trials outside of this system in order to evaluate the safety and efficacy of marijuana in treating PTSD. However, a recent study has suggested that self-reports of substance use from veterans who seek help were valid [3].

### **2.3.2 Marijuana as a Treatment for PTSD Symptoms**

The principal active component in the complex mixture of cannabinoids present in the marijuana plant is D9-tetrahydrocannabinol (THC), which acts primarily as an agonist at the CB1 cannabinoid receptor. This receptor is found at high concentrations in the brain, including the basal ganglia and cerebellum regions, and also in the hippocampus and hypothalamus. THC has been shown to inhibit the release of a wide spectrum of neurotransmitters including L-glutamate, GABA, norepinephrine, dopamine, serotonin (5-HT), and acetylcholine [32].

The presence of CB1 receptors in the hippocampus, amygdala, prefrontal and anterior cingulate cortex suggests that endocannabinoids are involved in regulating anxiety, attention to and response to stressful situations, and may be involved in the extinction of conditioned fear [33-35]. Further support of this theory came from studies using CB1 receptor antagonists or CB1 receptor knockout mice. Several CB1 receptor agonists increased time mice spent in open arms of the elevated plus maze, a sign of reduced anxiety [36], and CB1 receptor antagonist SR141716 produced anxiogenic effects in the elevated plus-maze and the defensive withdrawal tests in adult rats [37, 38]. Furthermore, another selective CB1 receptor antagonist, AM251, increased anxiety-like behavior in

wild-type mice but had no effect in the knockouts, in support of a CB1 receptor-mediated anxiolysis.

Cannabinoids also modulate GABAergic transmission and the release of cholecystokinin (CCK), a peptide that may contribute to both anxiolytic and anxiogenic effects of THC and endocannabinoids [39-42]. Furthermore, cannabinoids enhance the release of endogenous opioids, and these may be involved in the functional interplay between the endocannabinoid and the opioid system and the production of analgesic responses. Some researchers hypothesize that the relationship between these two systems plays a role in antidepressant-like effects and in various addiction-related processes [43-45]. Studies in rodents suggest that cannabinoids and their interaction with endogenous opioids might also modulate anxiety [44, 46, 47]. Rodent studies detected antidepressant-like responses to CB1 antagonists, and CB1 antagonists can increase the synaptic concentration of biogenic amines, much like antidepressants do. Thus, pharmacological modulation of the endocannabinoid system holds considerable promise in the treatment of both anxiety-related and mood disorders.

The results of a recent study implicated endocannabinoids and CB1 receptors in the extinction of aversive memories by demonstrating that CB1 knockout mice show impaired extinction in auditory fear-conditioning tests, and this could be mimicked in wild-type mice by treatment with SR141716 [48]. The synthetic cannabinoid nabilone was effective in reducing treatment-resistant nightmares in people with PTSD [49]. These findings raise the possibility that pharmacological amplification of CB1 signaling, for example may have therapeutic value in obsessive-compulsive disorder or posttraumatic stress disorder.

Benzodiazepines and related GABA agonists are frequently used to treat anxiety and sleep disruption in PTSD. Other treatments, such as the centrally acting adrenergic alpha1 antagonist prazosin, have been investigated as a treatment for PTSD-related sleep disorders [50]. However, these compounds can produce physical dependence and are not always tolerated. Investigating alternate avenues of treatment for PTSD symptoms may lead to helping a greater number of individuals control their symptoms.

Marijuana contains other compounds of interest, including cannabidiol, (CBD) a constituent of marijuana that is not a CB1 or CB2 receptor agonist [51, 52]. An early safety study reported that CBD was tolerated when administered to humans for 30 days [53]. Research has investigated its potential as an anticonvulsant and anti-psychotic [54]. It may have 5HT1A agonist activity [55]. A series of studies in rodents and humans suggest that CBD possesses anxiolytic and potentially antipsychotic effects [54]. Administration of CBD was equal to a 5HT1A agonist and a benzodiazepine in reducing anxiety in the face of public speaking [56], and rats given CBD exhibited less anxiety during the Vogel task, or "punished drinking," wherein the animals can receive shocks from the drinking spout [57]. Research in mice found that CBD was comparable to the antidepressant imipramine in rodent tests of antidepressant-like effects [58]. One report found that CBD may oppose anxiogenic effects of THC in humans [59], and smoking marijuana with higher CBD levels was associated with less memory impairment and

lower anxiety during intoxication in a naturalistic study [60]. However, another investigation found that cannabidiol levels made little difference on self-reported subjective effects, cognitive tasks or electroencephalography (EEG) [61]. Veterans with PTSD observing fearful (afraid) facial expressions showed increased amygdalar activation, when compared with combat-exposed veterans who did not have a PTSD diagnosis [62], and it appears that CBD attenuates amygdalar activation in response to facial expressions of fear in healthy subjects [63]. These investigations suggest that it is worth investigating the effects of the THC to cannabidiol ratio upon the effects of marijuana.

## **2.4 Rationale for Potency Selection**

This study will employ marijuana that varies with respect to THC and CBD content. Levels of THC will be 0%, 2%, 6% and 12%. CBD will either be low or at 6%, so that it matches THC levels in one of the potencies.

In order to investigate the impact of varying levels of THC upon PTSD symptoms and to provide a credible study placebo, marijuana with different levels of THC was selected for use in this study. 0% THC marijuana has been used as placebo material in previous studies [64-66]. Some studies have used 2% THC or marijuana with levels close to 2% as a lower dose comparison [61, 66], which is expected to produce minimal effects. Marijuana with 6% THC is expected to produce reliable subjective effects, and the use of 12% THC marijuana will permit comparison across these different dosages. Research investigating the effects of marijuana or THC in humans have used doses ranging from approximately 3% to 6% or higher [64, 66]. Several studies suggest that cannabidiol may be more strongly associated with reduced anxiety than THC, with some researchers reporting opposing effects of these chemicals [57, 59, 67, 68]. In order to investigate and compare the effects of THC with those of CBD, the study will employ marijuana containing equal amounts of THC and CBD. Complete crossover from Stage 1 to Stage 2 of people receiving each of these potencies will permit a within-subjects comparison between marijuana with and without matching levels of THC and CBD.

## **3.0 Protocol Objectives**

The objective of this study is to investigate the safety and efficacy of five different potencies of marijuana as treatments in veterans diagnosed with chronic, treatment-resistant, service-related PTSD, and to compare the safety and efficacy of two substance delivery methods.

### **3.1 Primary Objectives**

- Assessing changes in PTSD symptoms via Clinician-Administered PTSD Scale (CAPS) in people self-administering up to 2 cigarettes per day of approximately 0.9 grams marijuana containing one of the following: 0% THC, 2% THC, 6% THC, 6% THC/6% CBD marijuana, or 12% THC.

### 3.2 Secondary Objectives

- Assessing changes in symptoms of depression using the Beck Depression Inventory-II (BDI-II) in participants in all conditions
- Assessing changes in quality of life and general psychological function through ratings on the Global Assessment of Function (GAF) for participants in all conditions.
- Comparing scores on all outcome measures (CAPS, BDI-II and GAF) in participants smoking versus vaporizing marijuana overall, and within each of the five marijuana conditions.
- Evaluating how accurately the investigators and participants guess marijuana condition assignment when asked to do so after four weeks of marijuana self-administration.
- Comparing Stage 1 and Stage 2 symptoms of PTSD and depression via CAPS and BDI-II, general psychological function via GAF within subjects.
- Gathering information on daily marijuana usage during the course of the protocol, including information on amount, time, frequency and route of administration for participants in all five dose conditions, and weight of any unused marijuana.
- Evaluating blood cannabinoid levels after four weeks of self-administration and after two weeks of cessation of use during Stage 1 and Stage 2.
- Exploring and examining symptoms of PTSD and depression and general psychological health, and any new PTSD treatments tried, 12 months after taking part in the study.

### 3.3 Safety Objectives

- Collecting information on tolerability through self-reported reactions and experiences of smoking and vaporizing marijuana through daily completion of the Experiences with Self-Administering Marijuana Survey (ESAMS), a sponsor-developed self-report instrument.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-C-SSRS) on a weekly basis.
- Adverse events and serious adverse events will be collected as described in Section 8.0 of the protocol.

### 4.0 Protocol Design

This study will enroll 50 subjects in a randomized, triple-blind, placebo-controlled pilot study of the effects of five different potencies of marijuana on participants with chronic, treatment-resistant, military-service-related PTSD. The study will consist of two triple-blind study arms, Stage 1 (fully randomized) and Stage 2 (partially randomized). Subjects in Stage 1 will be randomized into five groups of 10 subjects each, in which they will receive 0%, 2%, 6% or 12% THC or 6% THC/6% CBD. The 10 subjects within each marijuana condition will be further randomized into one of two means of drug delivery. Five will smoke the marijuana and five will vaporize the marijuana.

In Stage 2, the 30 subjects previously assigned to 0%, 2% or 12% THC marijuana will be randomly assigned to receive 6% THC, 12% THC or 6% THC/6% CBD marijuana. The 10 participants who received 6% THC marijuana during Stage 1 will receive 6% THC/6% CBD marijuana, and the 10 participants who received 6% THC/6% CBD marijuana during Stage 1 will receive 6% THC marijuana during Stage 2. Participants will continue to use the same drug delivery method they used in Stage 1.

The study will include a four-week period of marijuana self-administration followed by a two-week period of marijuana cessation during Stage 1, followed by another four-week period of marijuana self-administration and two-week period of cessation during Stage 2. Stage 2 will follow identical procedures and measures to those used in Stage 1.

Since some people report little to no effect the first time they try marijuana, this protocol will include two four-hour long introductory sessions as an added safety procedure prior to the initiation of the treatment phase. All participants will complete the introductory sessions on two consecutive days, whether or not they are marijuana-naïve. Introductory sessions at the study site will be conducted under guidance for practicing a standardized process of either smoking (Foltin puff procedure [65, 69]) or vaporizing. Study staff will teach subjects how to avoid or minimize the chance of an anxiety reaction. Participants will either find a ride away from the study site to their home or current place of residence, or the investigators will locate someone who will transport them from the study site to their home or current place of residence.

The introductory sessions will enable subjects who find the subjective effects of marijuana unpleasant to withdraw from the study if they choose to do so prior to entering the treatment phase. At the end of the second introductory session, subjects who decide to proceed into the full study will be provided with a two-week supply of marijuana, divided into 14 daily packages of 2 rolled cigarettes. Subjects randomized to vaporization instead of smoking will be provided with Volcano vaporizers to take home for the duration of the study.

There will be a daily upper quantity limit of two rolled cigarettes per day, which subjects may use at any time that day. One day in this study is defined as a period of 24 hours. There will be no lower quantity limit, should subjects decide that symptoms not require medication on any particular day. Self-titration is considered one of the clinical advantages of marijuana that this study will evaluate. The second and final two-week supply of marijuana, also divided into 14 daily packages of 2 rolled cigarettes of approximately 0.9 grams, will be provided to subjects at the end of the second week when they return to the study site for evaluation.

Subjects will be instructed to save any unused marijuana on a daily basis in that day's package. Subjects are required to return the unused amounts to the investigators at the end of the first two week period, when they will receive marijuana for the second two weeks, and at the end of the second two-week period. This will enable the research team to measure the amount of marijuana each subject consumed on each day.

Should subjects request it, all unused marijuana will be returned to them at the end of the study, reducing the likelihood that any marijuana will be used unnecessarily or diverted during the four-week period of medication.

As a safety measure, in order to check for potentially harmful adverse events, subjects will be contacted by research staff via telephone on a daily basis for the first week of marijuana self-administration. Should any subject require intervention, research staff will contact the Clinical Investigator and arrange for her to speak directly to the subject.

During Stage 1, PTSD symptoms, symptoms of depression, and general psychological function will be assessed at the end of the four-week medication period and again at the end of the two-week period of marijuana discontinuation for Stage 1. Symptoms of depression and general psychological function will be assessed at additional points; two weeks into the four-week period of marijuana self-administration and a week into the two-week period of discontinuation. Suicidality will be assessed on a weekly basis. Participants will keep a daily marijuana usage diary and measure of self-reported experiences with marijuana throughout the period of marijuana self-administration. The same schedule of measures will occur during Stage 2, with PTSD symptoms assessed twice, symptoms of depression and general psychological well-being four times, self-reported experiences with marijuana twice, and suicidality six times during Stage 2.

All participants will be enrolled in Stage 2. Participants assigned to 0%, 2% or 12% THC marijuana during Stage 1 will be randomly assigned to receive 6% THC, 6% THC/6% CBD or 12% THC marijuana during Stage 2 in a blinded fashion. Without breaking the study blind, participants assigned to the 6% THC or 6% THC/6% CBD marijuana will receive material from the other potency during Stage 2, so that participants in these two conditions are completely crossed-over with respect to potency. Participants will have two introductory sessions wherein they will smoke or inhale the new potency of marijuana assigned to them for Stage 2. Participants will receive a four-week supply of marijuana divided into two separate packages containing a two-week supply and they will continue to use the same drug delivery method (smoking or vaporizing) they were assigned at the start of the study. There will be four weeks of self-administration followed by two weeks of cessation of use, with assessments occurring after two weeks of self-administration, at the end of four weeks of self-administration, and two weeks after cessation of use. Serum cannabinoids will be assessed upon enrollment into Stage 2, after four weeks of self-administration and at the end of Stage 2, and suicidality will be assessed weekly. Stage 2 will use the same assessments and measures Stage 1.

Twelve months after undergoing their final Stage 2 study visit, participants will return to the study site for the long-term follow-up (LTFU). Symptoms of PTSD and depression will be assessed, and the independent rater will assess general psychological health with the GAF. The participant will complete a questionnaire gathering information on any changes in mental health and any new therapies for PTSD that he or she has undergone in the interval between the end of Stage 2 and the LTFU assessment.

#### **4.1 Planned Duration of Study**

The main study will last 16 months, with each participant completing the main study two weeks after discontinuing marijuana self-administration at the end of Stage 2, and the follow-up visit 12 months after the end of Stage 2. Assuming that ten participants can be enrolled each month, the study should take approximately 27 months to complete.

#### **4.2 Randomization and Subject Numbering**

An equal number of participants will be assigned to each arm of this study via blocked randomization to ensure that ten participants from among the total of 50 will randomly receive one of the five treatments. An unblinded randomization monitor will generate a list of randomized numbers. Randomization will be performed at least 24 hours before the two introductory sessions prior to the beginning of the four weeks of active dosing. Subjects will be assigned in a blinded fashion to the next available randomization number upon enrollment in the study. The randomization numbers will be pre-printed on the drug packaging labels. All participants will automatically be enrolled in the crossover without providing the investigators with information on actual condition assignment. Participants who received 0%, 2% or 12% THC in Stage 1 will be randomized to 6% THC, 6% THC/6% CBD or 12% THC conditions in a blinded fashion during the crossover arm, or Stage 2.

Participants who drop out or who are withdrawn by the Clinical Investigator prior to the end of Stage 1 will be replaced until 50 participants have completed Stage 1. Participants who drop out of Stage 2 will not be replaced. Replacement participants will be assigned the next randomization number. The blind may be broken for an individual participant if there is an adverse event or other emergency requiring knowledge of participant's condition assignment. For this purpose, the randomization monitor will provide the investigators with a numbered sealed envelope containing the condition assignment for each subject. These sealed envelopes will be opened only in the event that emergency unblinding is required. In all other cases, the blind will be maintained until all participants have completed the study. This will remain true for participants in the crossover arm. The investigators, independent rater and participant will be blind to condition assignment.

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet eligibility criteria will be enrolled in the study and assigned a five-digit subject number. The first two digits will always be "01" and will identify the study site. The next three digits identify the subject within the site and will be assigned sequentially, with 001 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 01001, second 01002, etc.

#### **4.3 Recruitment and Subject Population**

Candidates for participation will be 50 veterans with PTSD arising from their service in the US armed forces and with duration of symptoms lasting at least six months. A subject

would not be excluded for having more than one traumatic event, but would be excluded if the primary or traumatic event related to PTSD diagnosis was not related to military service. Participants must be at least 18 years old with a diagnosis of PTSD and a screening CAPS score equal to or greater than 50 at baseline evaluation. Participants may be men or women and of any race or ethnicity.

Participants will be treatment-resistant, having failed to obtain sufficient relief of their PTSD symptoms after trying either medication or psychotherapy.

Participants will be recruited via letters of referral sent to psychiatrists and psychotherapists within the state of Arizona, contact with veterans' organizations, advertisements or announcements placed in appropriate locations or on appropriate internet sites and the sponsor site, and word of mouth.

One of the investigators or their assistant will interview prospective participants by telephone to learn if they meet basic eligibility criteria. If the prospective participant is interested in taking part in the study, the investigators will provide them with consent materials for review and consideration. If, after review, an applicant remains interested in taking part in the study, then they will meet with one of the investigators to complete the consent process.

#### **4.3.1 Inclusion Criteria**

Individuals eligible to be enrolled into this protocol are participants who:

1. Meet DSM IV criteria for current PTSD of at least six months.
2. Have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
3. Have had unsuccessful treatment (defined as still meeting PTSD criteria post-treatment) with one or more of the following:
  - a. Treatment with a selective serotonin reuptake inhibitor (SSRI), Serotonin Norepinephrine Reuptake Inhibitor (SNRI), mirtazapine or a monoamine oxidase inhibitor (MAOI).
  - b. Any form of psychotherapy
4. Are at least 18 years old
5. Are willing to commit to medication dosing and to complete evaluation instruments and study visits.
6. Agree not to change the type or increase the frequency of current psychotherapy, if any, nor change therapists (if they are concurrently seeing an outside therapist).
7. Agree not to change the identity or increase the dosage or frequency of use of pharmacotherapy for treatment of PTSD or other psychiatric disorders.
8. If female participants of childbearing potential, must be willing to have pregnancy tests and must agree to use an effective form of birth control.
9. Are literate. They must be proficient in reading English, and they must be able to effectively communicate with the therapists and other site personnel.
10. Agree not to participate in any other interventional clinical trials during the study.

### **4.3.2 Exclusion Criteria**

Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control.
2. Have a history of or current primary psychotic disorder or bipolar affective disorder type 1.
3. Diagnosed with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. Have evidence of significant, uncontrolled hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, gastrointestinal, or neurological disease. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. Have any allergies to marijuana.
6. Would present a serious suicide risk as assessed by the investigators, or who are likely to require psychiatric hospitalization during the course of the study.
7. Meet DSM-IV criteria for substance abuse or dependence for any substance other than caffeine or nicotine in the past 60 days.
8. Are not able to give adequate informed consent.
9. Have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.
10. Have used marijuana within a month of starting the study.
11. Fail the initial urine drug screen and blood test, testing for illicit drug use within the prior month.

## **5.0 Methods**

### **5.1 Assessments and Measures**

#### **5.1.1 Outcome Measures**

The primary outcome measure will be the CAPS, a clinician-scored measure for PTSD diagnosis and measure of symptom intensity and severity. The CAPS provides a means to evaluate the frequency and intensity dimensions of each symptom, impact of symptoms on the patient's social and occupational functioning, overall severity of the symptom complex and global improvement since baseline and the validity of the ratings obtained. The CAPS takes approximately one hour to complete. The CAPS interviews have been determined to have good internal consistency, concurrent validity, and test/retest reliability [70, 71]. The independent rater will administer the CAPS at times and visits described on the Time and Events table.

The GAF is a measure of quality of life and general function made through observations. The GAF consists of a single score, with scores ranging from 0 to 100, with 100 reflecting superior function and zero reflecting serious risk of causing harm to the self or

others. The independent rater will assess the participants following the Time and Events schedule.

The BDI-II is a 21-item self-report measure of depressive symptoms that will serve as a measure of depression [72, 73]. It takes five to ten minutes to complete. Participants will complete the BDI-II in accordance with the times and visits listed in the Time and Events table.

The daily marijuana usage diary is an instrument developed by the sponsor and investigator to track and assess daily use of marijuana provided for the study. Information collected on this diary will include the amount of marijuana used, the time or times of day it is used, frequency of use per day, route of administration (smoked or vaporized), and amount used during each time of use. It will take approximately three to six minutes to complete. Participants will complete the diary near the end of the each day during the four-week period of marijuana self-administration in both Stage 1 and Stage 2.

The LTFU questionnaire is a sponsor-developed self-report instrument that will gather information on current psychiatric health and wellbeing, including the occurrence of new traumatic events, and questions concerning the number and type of new treatments for PTSD the participant has undergone since his or her final Stage 2 visit. The LTFU questionnaire takes approximately five minutes to complete.

### **5.1.2 Safety Measures**

The Experiences with Self-Administration of Marijuana Survey (ESAMS) is a self-report measure of perceived adverse events, and psychological and physiological experiences that occurred during smoking or vaporizing marijuana. These include physiological experiences (e.g. throat irritated), and psychological effects (e.g. sedated), effects on selected PTSD symptoms (nightmares, sleep quality) and an item asking about the participant's degree of satisfaction with the route of administration. Participants will respond to each item by marking a point on a 152 mm line. It will take between five and ten minutes to complete. There will be no total score, and each item will be considered an assessment of a specific effect. The ESAMS will be completed by the participant daily for the entire period of marijuana self-administration, and the measure will be collected at two weeks of marijuana self-administration and at the end of four weeks of self-administration for Stage 1, and following the same schedule during Stage 2. Average scores on each item will be computed for each stage of the study.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [74]. It consists of a "Baseline" form that assesses lifetime suicidal ideation, ideation intensity and behavior, and a form for assessing current suicidal ideation, and intensity. The C-SSRS consists of a series of questions, and can be administered during face-to-face interview or over the telephone. Whether or not subsequent questions are asked is dependent upon responses to initial questions. The C-SSRS will be administered six times during Stage 1; at baseline and on a weekly basis during each face to face visit or via telephone during the period of

marijuana self-administration and the period of abstinence from use. The C-SSRS will be administered following the same schedule for Stage 2.

Adverse Events (AEs), including spontaneously reported reactions, will be collected starting with the introductory sessions until the end of Stage 2, at the end of the two-week period of marijuana use cessation. AEs requiring medical attention, Serious Adverse Events (SAEs), AEs leading to withdrawal from the study, and changes to psychiatric status will be collected from the introductory sessions through study termination at the LTFU visit. All concomitant medications will be collected throughout the study.

**Schedule of Events and Procedures – Stage 1**

Visit #	Pre-Study	V1, V2	Self-Admin/V3	V4	V5	V6
Type of Visit	Screening may take place over more than one day	Introductory Sessions	2 wks after start of self-admin	Assessment / Evaluation 2	Assessment	Assessment/Evaluation 3
Approximate Study Day	Up to one month prior to Visit 1	Day 1, Day 2		4 w post V1	1 wk post marijuana cessation	6 wk post V1
Visit Timing and Windows		Upon enrollment before self-admin		-5 d + 4 day		-5 d + 4 day
Provide Informed Consent Materials	X					
Medical and Psychiatric History (by interview)	X					
General Physical Exam (BP, Pulse, Temp, brief systems check)	X					
Clinical Laboratory Tests, including HIV test	X					
Psychiatric interview (SCID)	X					
Collect Concomitant Medication	X	X				
Study Enrollment after meeting Inclusion/Exclusion		X				
Drug Screen	X					
Pregnancy Screen (if applicable)	X					
Complete Randomization Procedure		X				
CAPS	X			X		X
Serum cannabinoid levels	X			X		X
BDI-II, GAF, ESAMS	X		X <sup>A</sup>	X <sup>A</sup>	X	X
C-SSRS	X	X	X	X	X	X
Daily marijuana use diary			X	X	X	
Provide information on marijuana experience		X				
Assessment via telephone			X		X	
Face to face visit		X		X		X
Adverse Events Requiring Dr. Visit			X	X	X	X
Spontaneously Reported Reactions			X	X	X	X
Adverse Events that are of Concern to the Participant			X	X	X	X
Serious Adverse Events		X	X	X	X	X
Unblinding						
Study Termination						/

A= ESAMS administered only on V3 and V4

**Schedule of Events and Procedures – Stage 2**

Visit #	V7	Self-Admin/V8	V9	V10	V11
Type of Visit	May be same day as V6	2 wks after start of self-admin	Assessment / Evaluation 2	Assessment	Assessment/Evaluation 3
Approximate Study Day	Up to one month prior to Visit 1		4 w post V1	1 wk post marijuana cessation	6 wk post V1
Visit Timing and Windows			-5 d + 4 day		-5 d + 4 day
Collect Concomitant Medication	X				
Study Enrollment after meeting Inclusion/Exclusion					
Drug Screen	X				
Pregnancy Screen (if applicable)	X				
CAPS	X		X		X
Serum cannabinoid levels	X		X		
BDI-II, GAF, ESAMS	X	X <sup>A</sup>	X <sup>A</sup>	X	X
C-SSRS	X	X	X	X	X
Daily marijuana use diary		X	X	X	
Provide information on marijuana experience					
Assessment via telephone		X		X	
Face to face visit			X		X
Adverse Events Requiring Dr. Visit		X	X	X	X
Spontaneously Reported Reactions		X	X	X	X
Adverse Events that are of Concern to the Participant		X	X	X	X
Serious Adverse Events		X	X	X	X
Unblinding					X
Study Termination					X

A= ESAMS administered only on V8 and V9

**5.2 Study Procedures and Visit Descriptions**

**5.2.1 Prescreening, Screening and Baseline Evaluation (Pre-study)**

All individuals who enter screening, as defined in this section, should be assigned a screening number and recorded on the “subject screening log”. The subject screening number will be also be noted on the subject’s informed consent form. Subjects who do not meet all screening criteria at screening will not be enrolled. A case report form (CRF) will not be completed for subjects who are not enrolled. These subjects will be documented only on the screening log. The study staff should record either the reason why an individual was not enrolled or the enrollment date and assigned subject number on this log. It is the responsibility of the investigator to file this document in the investigator site file (ISF) to be readily available for on-site monitoring and/or for inspection by the relevant authorities.

The entire visit should take approximately 1.5 to 2.5 hours.

- a) Explain and obtain written informed consent from the subject. Written informed consent must be obtained prior to performing any study-specific tests or evaluations.
- b) Assign the subject a screening number. Complete the screening log.
- c) Participants will provide a medical and psychological history.
- d) The investigator will perform the relevant portions of the Structured Clinical Interview for Diagnoses (SCID) to assess study eligibility.
- e) The investigator will administer the C-SSRS to assess suicide risk.
- f) The participant will complete the BDI-II.
- g) A blinded independent rater will administer the CAPS and assess the participant on the GAF.
- h) To establish independent rater reliability, the investigators will have the option to video record the screening CAPS interview in as many instances as necessary.
- i) A physician will perform a general physical examination. The examination will involve the following procedures:
  - blood pressure
  - pulse
  - height/weight
  - body temperature
  - examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen and extremities
  - brief neurological exam (cranial nerves 2-12, sensory, motor, reflexes and cerebellar function)
  - electrocardiogram (ECG)
  - serum electrolytes, metabolic profile, urinalysis and complete blood count, including. The clinical laboratory values will not be captured in the CRF, but will be used to establish eligibility and will be kept with the subject's source record.
  - Urine drug screening. Urine drug screens are essential to ensure that subjects have not used marijuana up to a month prior to the start of the study.
  - Blood cannabinoid levels. Blood cannabinoids levels are to further support absence of marijuana use during the several weeks to a month prior to the start of the study
- j) If, upon examination, there are questions raised about possible medical problems, the investigators will request a review of participant medical records and request additional tests or assessments as indicated.
- k) Review with females of childbearing potential their ability to become pregnant and commitment to practice appropriate birth control as determined by the investigator for the total duration of the study.
- l) Perform a urine-dip pregnancy test on females with childbearing potential.
- m) After eligibility is confirmed the participant will be considered enrolled.

- n) Issue a subject number.
- o) If the participant continues to meet all inclusion criteria and no exclusion criteria, the investigators will schedule the introductory session and the beginning of the first four-week period of active dosing.

### **5.2.2 Introductory Session (Visit 1 and 2)**

- a) Inquire about any possible changes in the participant's health to ensure that subject continues to meet eligibility criteria.
- b) Collect information on any concomitant medication taken by the participant.
- c) Collect information on any changes in psychotherapy for the participant.
- d) Obtain from the participant the name and telephone number of an emergency contact for use throughout the study.
- e) The participant will undergo two four-hour introductory sessions with the investigator(s), preferably on two consecutive days. The investigator(s) will provide the participant with information about marijuana, including expected psychoactive and physical effects, and a standardized procedure for smoking marijuana (the "Foltin puff procedure.") or for using the Volcano vaporizer, depending on which method of administration the subject has been randomized to use. The investigators will introduce participants to the daily diary and will instruct them on diary entry completion. Participants will either arrange a ride from the study site to their home or current place of residence or the investigators will assist them in finding a means of transport from the study site.
- f) The participant is required to self-administer marijuana using the method of administration and potency the subject has been randomized to use.
- g) Randomization will occur prior to the day of the first introductory session. Participants will be assigned to receive marijuana containing 0% THC, 2% THC, 6% THC, 12% THC, or 6% THC/6% CBD.
- h) During the introductory session, the investigators will administer the C-SSRS.
- i) All SAEs will be recorded from the time the participant is enrolled at Visit 1.
- j) On the day of the second introductory session, the investigator will provide the participant with a supply of marijuana intended to last for the first two weeks of the four-week self-administration period. The participant will be instructed to use no more than two cigarettes of marijuana per day.
- k) The investigator will provide the participant with two weeks of daily marijuana use diary and ESAMS sheets.

### **5.2.3 Stage 1 (Four weeks of marijuana self-administration)**

- a) The participant will smoke or vaporize the marijuana supplied to him or her daily during this time period.
- b) The participant will complete a daily marijuana use diary. In the diary, he or she will record frequency of use per day, route of administration, and estimated amount used per occasion.
- c) The participant will complete the ESAMS on a daily basis.

- d) The independent rater will administer the C-SSRS on a weekly basis.

#### **5.2.4 Evaluation Two Weeks into Stage 1**

- a) Participants will meet with the independent rater for a 30 to 60 minute evaluation two weeks after the participant has commenced marijuana self-administration.
- b) The independent rater will administer the C-SSRS, and he or she will assess the participant on the GAF.
- c) The participant will return completed daily diary and ESAMS sheets.
- d) The participant will complete the BDI-II.
- e) Information on concomitant medications used during this time period will be collected.
- f) The investigator will provide the participant with two weeks of daily marijuana use diary and ESAMS sheets.
- g) At the end of the evaluation, subjects will return any unused marijuana from the last two weeks of self-administration, and they will receive a supply of marijuana for the remaining two-week period of medication.
- h) All SAEs and AEs will be recorded.

#### **5.2.5 Evaluation After Four Weeks of Marijuana Self-Administration in Stage 1**

- a) Participants will meet with the independent rater for a 60 to 90 minute face to face evaluation four weeks after the participant has commenced marijuana self-administration. This meeting will take place at the study site.
- b) The independent rater will administer the CAPS, and C-SSRS, and assess the participant on the GAF.
- c) The participant will complete the BDI-II.
- d) A blood test to measure blood cannabinoid levels will be administered.
- e) The participant and investigator will give written indications of their beliefs concerning participant condition assignment.
- f) Daily marijuana use diaries and daily ESAMS sheets will be collected.
- g) All remaining marijuana will be collected from the participant.
- h) The investigator and participant will discuss the two-week period of cessation of marijuana use.
- i) Information on concomitant medications used and changes in psychotherapy during this time period will be collected.
- j) All SAEs and AEs will be recorded.

#### **5.2.6. Two weeks of Abstinence from Marijuana self-Administration**

Participants will cease to self-administer marijuana for a two-week interval. During this period, all marijuana provided to the participant should be returned to the investigators. Then investigators will weigh any returned marijuana.

#### **5.2.7 Evaluation One week after Cessation of Marijuana Self-Administration**

- a) Participants will speak with the independent rater for a 30 to 60 minute evaluation one week after the participant has ceased marijuana self-administration. The meeting will occur via telephone.
- b) The independent rater will administer the C-SSRS, and assess the participant on the GAF.
- c) The participant will complete the BDI-II.
- d) Information on concomitant medications used and changes in psychotherapy during this time period will be collected.
- e) All SAEs and AEs will be recorded.

### **5.2.8 Evaluation After Two weeks of Abstinence from Marijuana Self-Administration at End of Stage 1**

- a) Participants will meet with the independent rater for a 60 to 90 minute evaluation two weeks after the participant has ceased to self-administer marijuana. This meeting will take place at the study site, and assessments will occur during a face-to-face meeting.
- b) The independent rater will administer the CAPS, C-SSRS, and assess the participant on the GAF.
- c) The participant will complete the BDI-II.
- d) A blood test to measure cannabinoid blood levels will be administered.
- e) Information on concomitant medications used and any changes in psychotherapy during this time period will be collected.
- f) All SAEs and AEs will be recorded.
- g) This is the last visit of Stage 1. After this assessment, participants will be enrolled in the crossover arm ("Stage 2"). Participants who drop out of the study after this point will not be replaced.

### **5.2.9 Stage 2 (Partially Randomized Crossover Arm)**

- a) Condition assignment in Stage 2 will be random for participants assigned to 0%, 2% and 12% THC marijuana conditions in Stage 1, and a complete crossover will occur for participants in the 6% THC and 6% THC/6% CBD conditions, meaning all participant assigned to 6% THC marijuana during Stage 1 will be assigned to 6% THC/6% CBD during Stage 2, and all participant who received 6% THC/6% CBD marijuana during Stage 1 will receive 6% THC marijuana in Stage 2. No one in Stage 2 will receive 0% or 2% THC marijuana. Participants will continue to use the same drug delivery system they used for the randomized arm (smoking or vaporizing).
- b) Information on concomitant medications used and changes in psychotherapy during Stage 2 will be collected.
- c) The participants will undergo two introductory sessions wherein they will smoke or inhale the potency of marijuana they are assigned for Stage 2.
- d) Participant will receive one two-week supply of rolled marijuana cigarettes followed two weeks later by another two-week supply, and they will self-administer these following their assigned drug delivery system (smoking or

- inhaling vapor). They will complete the daily diary of marijuana use and the ESAMS. The independent rater will administer the C-SSRS each week.
- e) After two weeks of self-administration, the participant will meet with the independent rater at the study site. The independent rater will assess them on C-SSRS and GAF.
  - f) The participant will complete the BDI-II.
  - g) At the end of four weeks of marijuana self-administration, participants will be assessed on CAPS and GAF. The participant will complete the BDI-II. The participant and investigators will give written, private indication of beliefs concerning condition assignment. Participant blood cannabinoid levels will be assessed.
  - h) Participants will return any unused portions of marijuana to the investigators. Participants will cease to use marijuana.
  - i) One week into this period of cessation of use, participants will reach the independent rater via telephone, and the participant will be assessed on the C-SSRS and GAF, and the participant will complete the BDI-II.
  - j) At the end of two weeks of cessation of use, participants will be assessed on the CAPS, and GAF, participants will complete the BDI-II and blood levels of cannabinoids will be assessed.
  - k) Subjects will receive a memory aid card for use between this visit and the 12-month follow up. Subjects will use this card to record AEs, medications, and changes in psychiatric status that they will be asked about at the LTFU visit.
  - l) The investigators will return unused portion of marijuana, if any, from both Stage 1 and Stage 2, to participants.

#### **5.2.10 12-Month Follow Up (Long-term Follow Up)**

- h) Participants will meet with the independent rater for a 60 to 90 minute evaluation two weeks after the participant has ceased to self-administer marijuana. This meeting will take place at the study site, and assessments will occur during a face-to-face meeting.
- i) The independent rater will administer the CAPS and BDI-II, and the independent rater will assess the participant on the GAF.
- j) The participant will complete an instrument gathering information on any medications or psychotherapies used in the interval between the end of Stage 2 and the 12-month follow up.
- k) All SAEs will be collected.

#### **5.3 Removal of Participants from the Study**

Participants can withdraw consent at any time without prejudice. The investigator can withdraw a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with the experimental procedures and related visits that are critical for safety, and this will be recorded in the participant's source records and CRF. If the investigator withdraws a participant from the session, the investigators will explain the reason for withdrawing the participant. Participants will be clinically monitored after withdrawal by the investigator, who will contact them a month after withdrawal. Whenever possible, the tests and evaluations listed for the termination

and outcome visits will be carried out. Efforts will be made to obtain information about AE resolutions, if applicable.

#### **5.4 Premature Discontinuation of the Study**

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform the study subjects and will arrange appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials will be returned to the sponsor, and will be treated in accordance with federal and local regulations

### **6.0 Investigational Product**

#### **6.1 Substance Description and Activity Related to Proposed Action**

The active material to be used in this protocol is dried plant material from the cannabis plant (marijuana). Cannabis refers to the genus within the cannabaceae family, containing possibly two species *c. sativa* and *c. indica*. They are hardy annual flowering plants, and dioecious, meaning there are male and female plants [75]. This plant or extracts from this plant have been used medicinally for thousands of years, and were legal in the US until 1937. Marijuana was removed from the United States Pharmacopeia and National Formulary [76]. It contains several active compounds, with THC acting as the chief psychoactive compound. THC acts on cannabinoid CB1 receptors in the brain, as well as CB2 receptors in the periphery, particularly within the immune system. These recently discovered receptors are activated by at least three endocannabinoids and endogenous fatty acids related to arachidonic acid. CB1 receptors are found throughout the human brain. Cannabidiol may also contribute to the psychoactive profile of marijuana [59, 61, 77], and cannabidiol may possess therapeutic potential [54, 77]. The subjective and potentially therapeutic actions of marijuana may be directly or indirectly influenced by other compounds found in the plant [77].

The marijuana to be used in this study will be provided at cost by NIDA, should the study receive all the required regulatory approvals.

#### **6.3 Substance Potencies, Packaging and Labeling**

This protocol will follow a randomized, active placebo-controlled, triple-blind design comparing marijuana differing in THC or CBD content with a crossover arm for participants assigned to two of the five conditions. The study will use 0% THC, 2% THC, 6% THC, 12% THC and 6% THC/6% CBD marijuana. The crossover arm will use 6% THC, 6% THC/6% CBD and 12% THC marijuana. In Stage 2, participants who previously received 0%, 2% or 12% marijuana will be randomized to receive one of these three doses, while participants who initially received 6% THC or 6% THC/6% CBD will receive the other strain during Stage 2 in a non-randomized but blinded manner

All five potencies of marijuana will be supplied by the National Institute on Drug Abuse (NIDA) in the form of rolled cigarettes of approximately 0.9 grams each.

The pharmacist will package all marijuana materials identically in separate packages, each containing two rolled cigarettes. These packages will be used to store any unused portions of the cigarettes that participants did not consume during each day, with all 28 packages returned to the investigators at the end of the four-week period of medication.

**6.3.1 Doses**

Study participants will be assigned to receive one of five potency conditions, as noted below. Participants will be introduced to the marijuana potency and drug delivery method they will receive for the study during introductory sessions during which they will smoke or vaporize material from a rolled cigarette. Participants will be supplied with 2 rolled marijuana cigarettes per day for self-administration daily during a four-week period. Any unused portions of the cigarettes not used each day will be placed in the packaging for that day, with all unused material returned to the investigators during the assessment two weeks after self-administration and at the conclusion of the four week period of active dosing, for precise weighing. During Stage 2, as described above, participants will receive marijuana with 6% or 12% THC, or they will receive marijuana with 6% THC and 6% CBD.

**Marijuana Doses in Stage 1**

Dose	Number of Participants receiving dose	Smoked marijuana	Vaporized Marijuana
0% THC marijuana	10	5	5
2% THC marijuana	10	5	5
6% THC marijuana	10	5	5
12% THC marijuana	10	5	5
6% THC/6% CBD marijuana	10	5	5

**Marijuana doses in Stage 2**

Dose	Number of Participants receiving dose	Smoked* Marijuana	Vaporized* Marijuana
6% THC marijuana	20	10	10
12% THC marijuana	10	5	5
6% THC/6% CBD marijuana	20	10	10

\*All subjects will maintain the same drug delivery assignment throughout Stage 2

**6.3.2 Packaging**

Marijuana will be sent in the form of rolled cigarettes weighing approximately 0.9 grams each from the National Institute of Drug Abuse (NIDA) to the pharmacy at the University of Arizona. The marijuana will be received by the investigator, who will be the holder of a Schedule 1 license. The investigator will oversee packaging of the marijuana cigarettes by the pharmacist in a manner that will maintain the blind. Marijuana cigarettes of varying potencies will be sorted into individual packages of 2 cigarettes each for each day's use.

### 6.3.3 Labeling

Each potency of marijuana will come in large tins labeled by NIDA. The pharmacist will package 2 cigarettes in separate packages (plastic bags), each with a blinded label including the protocol number, substance name, unique container number, sponsor name, subject number, randomization number, day of use (from 1-28 for Stage 1, and from 42-70 for Stage 2) and a statement that the material is for use only in clinical trials. Two rolled cigarettes will be set aside for use during each of two introductory sessions, with marijuana potency matching condition assignment for each subject. There will be one set for Stage 1 and another for Stage 2. Blinded labels will be provided by the sponsor and applied by the pharmacist. The package labels will not contain any information about the potency of the marijuana in the cigarettes in order to assure blinding of subject and investigators. The unblinded randomization monitor will maintain a record linking the randomization number to the potency of the marijuana provided to that subject.

Box Label	
MAPS Study#	XXXX
Investigational Product:	Cannabis (marijuana)
Dose:	Blinded
Randomization #	XXX
Subject Number	_____
Lot #:	XXXXX
Day to be used	(XX between 1-28)
Administer as per protocol	
Caution-Limited by Law to Investigational Use Only	

### 6.4 Substance Accountability

Forms will be provided to track drug accountability and administration throughout the study. Drug accountability will be reviewed during routine monitoring visits.

### 6.5 Substance Storage and Handling

Cannabis (marijuana) is a Schedule 1 substance and will be stored and handled in compliance with relevant Federal and State regulations. In accordance with Drug Enforcement Administration (DEA) requirements, the Clinical Investigator will be responsible for storing and dispensing the marijuana. It will be stored in a safe mounted to the floor that has been inspected and approved by the DEA for this purpose. Only the Clinical Investigator with the Schedule 1 license will have the combination to the safe. The room in which the safe is mounted will have an alarm system and will be locked whenever the investigator is not present.

Investigational product will only be removed from the safe for one subject at a time upon starting the study. Participants will receive the marijuana as a two week supply over the course of the study, totaling 56 cigarettes, in 28 separate packages of 2 cigarettes each, which will be the daily supply. Participants will be given two weeks worth of cigarettes at a time during the study. Subjects will be expected to discontinue use for two weeks after the four-week period. Subjects will be instructed to save any unused marijuana in each day's package and to return it to the investigators for weighing at the two-week point and at the conclusion of the four week period of active dosing. Subjects will have their unused marijuana returned after the evaluation that takes place at the end of the two-week period of abstinence.

Nearly all of the same procedures described above will be followed for participants entering the crossover arm, Stage 2. Participants will follow the same schedule of events, assessments and measures and will use the same drug delivery system that they used during the randomized arm. At the end of the crossover arm, the investigators will return any unused marijuana from the crossover arm to participants who complete the crossover arm.

Records pertaining to the use of Schedule 1 compounds will be maintained in accordance with relevant Federal and State Regulations.

## **6.6 Substance Stability**

Information on the amount of THC and CBD and stability of these compounds will be provided by the National Institute on Drug Abuse (NIDA) and an additional analysis from an independent testing laboratory with required DEA registration. Information on each potency of marijuana must be one year old or less. Should NIDA decline to provide analysis conducted within one year of the provision of the marijuana to the study, MAPS will obtain an analysis from an independent testing laboratory with DEA registration.

## **7.0 Risks of Participation**

### **7.1 Risks of Screening, Assessments and Measures**

Blood draws and a full medical examination are required to establish eligibility for the study. Blood draws are also required to assess cannabinoid levels at four weeks of marijuana self-administration and at two weeks of cessation of use. Temporary discomfort, inflammation or infection could arise as a result of sampling blood at the punctured vein. Submitting to a full medical examination may also cause discomfort or psychological distress. Since medical examinations and blood draws are required to establish eligibility for the study, they cannot be omitted from the protocol. Psychological assessments will be obtained through interviews. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. Because psychiatric interviews and discussion of PTSD symptoms are used during screening, they cannot be avoided. The investigators have experience working with people with PTSD, and they will seek to reduce anxiety and distress during these interviews.

### 7.3 Risks of Self-administering Marijuana

There is an extensive literature on the risks of habitual marijuana use in humans, and a sizeable but considerably smaller literature on the acute effects of marijuana, including adverse events. Most risks associated with ingesting or inhaling marijuana relate to its psychoactive effects, though marijuana can also produce acute effects on the cardiovascular system and continued use can produce effects on the pulmonary system. Psychoactive and acute cardiovascular effects are transient and dissipate after the effects of the substance have waned. Most research examining risks of marijuana examine smoked marijuana, as vaporization is a relatively recent form of taking marijuana.

Marijuana can alter mood, affect, and perception, producing increases in positive and negative mood states (as euphoria and anxiety), and intensifying sensory experiences, such as music seeming more intense [78]. Marijuana can impair attention and memory, and slow psychomotor performance. In a review of the literature, subjective effects were more strongly associated with marijuana than other effects [79]. Marijuana may provoke psychotic symptoms or psychosis in vulnerable individuals without being a "cause" of psychosis [80, 81].

Regular, heavy use of marijuana is associated with impairments in cognitive function, especially in the area of short-term memory and executive functioning, with impairment retained up to a week after abstaining from use, but no longer detectable after 28 days of abstinence [82-84]. Since marijuana interferes with attention, alters mood and may generate shifts in sensory attention and perception, it is not surprising that regular use may be taxing on cognitive task performance. The degree of potential impairment experienced after a month of daily use cannot be estimated from these findings. It is likely that if impaired cognitive function is present, it will not remain after prolonged abstinence [85].

Though a review of studies found that marijuana impairs most skills used in driving motor vehicles, driving and simulation studies fail to find strong effects of marijuana upon driving [86]. This may be the result of people under the influence of marijuana overestimating their level of impairment, and thus driving more conservatively [86, 87]. Researchers conducting controlled studies of people driving under the influence of marijuana reported that effects, while present, were relatively small and comparable to other medicines or alcohol [88]. Nonetheless, epidemiological studies of road accidents have found a relationship between use of marijuana, including blood THC levels, and road accidents [89, 90], with higher levels of THC associated with greater impairment in driving. Sewell and colleagues concluded that a review of the literature suggests a degree of inter-individual variability in degree of impairment experienced by drivers after marijuana, including less impairment in experienced users. They recommend that people not drive or use heavy machinery for up to three hours after marijuana use, and that people using marijuana seek a designated driver whenever possible.

Like many substances that produce increased positive mood and relaxation, marijuana can produce substance abuse or dependence in some people, with approximately 4% to

9% percent of people experiencing dependence upon marijuana [91, 92]. There are a few reports of self-administration of THC in animals [93]. The rate at which people who try marijuana become dependent is estimated as either slightly lower than or similar to that for alcohol, and higher than rates of dependence for hallucinogenic (psychedelic) compounds [91].

Acutely, marijuana increases heart rate, increases supine blood pressure, and, after higher doses, produces orthostatic hypotension; it increases cardiac output, decreases peripheral vascular resistance, and dose-dependently decreases maximum exercise performance. Changes in cardiovascular function may occur with prolonged use. These include: hypotension when lying down, an increase in blood volume, slowed heart rate and diminished circulatory response to exercise [94]. Orthostatic hypotension may be reduced. These findings are in line with findings in animals of enhanced parasympathetic activity. After reviewing the literature, Jones concluded that the cardiovascular effects of marijuana posed little risk to young, healthy adults, while increased cardiac work, increased hypotension and increased catecholamines might pose greater risk for older adults [94].

Regular and heavy marijuana use is associated with increased symptoms of chronic bronchitis, coughing, production of sputum, and wheezing [95, 96]. Regular marijuana use may impair function of alveolar macrophages, a type of immune cell found in the lung [96, 97]. Reduced alveolar macrophages could place individuals at increased risk of lung infection. One of three studies of lung function in people reporting regular, and often heavy, use of smoked marijuana failed to find a reduction in lung function, and another found reduced lung function but concluded that this was related to confounding factors [95, 98, 99]. A review of literature addressing marijuana use and lung injury concluded that findings were often inconsistent [100]. Marijuana use does not appear to be associated with lung cancer [100-102]. Rather, the positive association between extended periods of marijuana use and lung cancer may be related to other confounding factors, as cigarette smoking. Duration of use in the studies reviewed by Hashibe and colleagues is considerably longer than the four-week period occurring in this study.

Study participants will be using marijuana daily, but use will be restricted to two four-week periods separated by a two-week interval of cessation of use. To date, no equivalent studies have examined the effects of inhaling vaporized marijuana, but since vaporization does not involve combustion, vaporized marijuana may be less irritating to the lungs. An examination of vaporized delivery of THC found the method produced equivalent or similar psychological and physiological effects with fewer respiratory disadvantages [103-105].

The immunological effects of marijuana and cannabinoids are complex and largely appear to arise from effects on CB2 receptors rather than central CB1 receptors. Some of the benefits of marijuana, such as for multiple sclerosis, may relate in part to anti-inflammatory and immunosuppressive effects [106, 107]. However, marijuana and cannabinoids failed to affect immune function in HIV-positive individuals [64, 108]. Regular marijuana users have greater numbers of a cannabinoid receptor implicated in

regulating immune function, the CB2 receptor, which is generally considered to have immunosuppressive and anti-inflammatory effects [109], and in vitro studies suggest that THC and marijuana may reduce immunosupportive Th1 cytokines and increase immunosuppressive Th2 cytokines [106, 110]. It is possible that marijuana may increase the risk of opportunistic infections. However, in studies of HIV-positive individuals using either marijuana or oral THC (as dronabinol) failed to find any changes in T-cell (CD4 or CD8) profiles, findings which do not support at least this form of immunosuppression [108, 111].

Participants who receive the 0% THC marijuana cigarettes are exposed to combustion products without receiving either THC or CBD. They will also be less likely to experience the adverse effects associated with marijuana and THC described above, such as anxiety or impaired performance on tests of cognitive function.

Beyond these risks, there are only a few reports of adverse effects occurring outside the organs and systems listed above, there are no known effects on the liver (and only a few case reports of effects on the kidneys [78]).

Regular use of marijuana throughout pregnancy may have effects on birth weight, specific tasks involving visual analysis or processing. However, to date there are no reports of teratological effects from marijuana use [78, 112-115]. THC can pass into breast milk [115]. Women of childbearing potential enrolled in this study will be required to use an effective method of birth control, and the study will exclude participants who are pregnant or lactating.

#### **7.4 Risk Mitigation**

Marijuana is associated with acute risks as well as risks of continued daily use. Chief amongst these are unwanted psychological effects, including anxiety or paranoia, cardiovascular and pulmonary effects, impaired driving and abuse liability.

The investigators will minimize risks by carefully screening participants for the presence of any contraindicating factors and by carefully preparing participants for the expected effects of marijuana. Contraindicating factors include presence or history of psychotic disorder, cerebrovascular, cardiovascular or coronary conditions, and past or current substance abuse. Prior to receiving supplies of marijuana, study participants will be prepared for the effects of the substance during two extensive supervised introductory sessions. They will be informed of what to expect and they will have an opportunity to smoke or vaporize the marijuana that they have been randomly assigned to receive in the presence of the investigators. Taking these steps will help participants become familiar with the subjective effects of marijuana.

The investigators will address a number of risks by enrolling participants without contraindicating conditions, including psychotic disorders and major medical conditions affecting the heart or lungs. Participants who pose a major suicide risk will not be enrolled in the study. Participants who have smoked or otherwise ingested marijuana in

the month prior to enrollment will not be enrolled in the study. Neither will any participant that the investigator or medical monitor believes has contraindicating history of or current substance abuse or dependence.

Untoward psychological reactions to marijuana will be dealt with by preparing participants for the subjective effects of the substance, and through first smoking or vaporizing marijuana in the presence of the investigators during two introductory sessions. During this time, the investigators will be able to help address any anxiety or paranoid feelings occurring during the first experience.

Participants will be informed of the effects that marijuana might have on driving and they will be advised to avoid driving immediately after use whenever possible by seeking a designated driver and by waiting up to three hours after use prior to driving a motor vehicle. Participants will arrange rides home after each introductory session, and if they are unable to do so, the investigators will assist them in locating a ride from the study site.

Potential reproductive risks will be mitigated by restricting enrollment to women who are not pregnant or lactating, and by requiring that women of childbearing potential use an effective form of birth control.

### **7.5 Medical Emergencies**

Because participants will be self-administering marijuana during a four-week period, the study site will not have any specific equipment for addressing medical emergencies. If a participant experiences a medical emergency during the study period, he or she will be directed to call the investigator's 24-hour telephone line, and then if needed call 911.

### **8.0 Adverse Events**

An Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. This definition includes concurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event. All AEs will be monitored by the investigators until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the protocol, a clinical assessment will be made by the investigator and/or Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

- Mild: no limitation in normal daily activity
- Moderate: some limitation in normal daily activity
- Severe: unable to perform normal daily activity

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

#### 1. Not Related

The AE is not related if exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.

#### 2. Possibly Related

The administration of the investigational product and AE are considered reasonably related in time and the AE could be explained by causes other than exposure to the investigational product.

#### 3. Probably Related

Exposure to the investigational product and AE are reasonably related in time and the investigational product is more likely than other causes to be responsible for the AE, or is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

### **8.1 Common Expected Adverse Events**

Some common expected adverse events and spontaneously reported reactions to smoked marijuana reported in studies of human volunteers are altered time perception, anxiety, difficulty concentrating, difficulty remembering things, dry mouth, feeling intoxicated (as drug effect, feeling high), feeling hungry, perceptual alteration (as enhanced sensation), sedation and feeling stimulated [61, 79]. Some participants may report feelings of paranoia or unusual thoughts [59]. The subjective effects of vaporized marijuana are not significantly different from those of smoked marijuana [104, 105].

### **8.2 Serious Adverse Events**

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life-threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above

AEs which do not fall into these categories are defined as non-serious. It should be noted that a severe adverse event need not be serious in nature and that a SAE need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as a study-related SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

### **8.3 Adverse Event Collection**

All SAEs will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study drug or not, have to be reported within 24 hours or at the latest on the following working day by telephone or fax to either of the following:

#### **Medical Monitor and Study Monitor:**

Contact information for the medical monitor and study monitor will be provided in separate documents.

Adverse events that will be collected for the duration of the protocol are:

- All Adverse Events, and spontaneously reported reactions will be collected throughout the four-week period of marijuana self-administration for the randomized arm (Stage 1) and the second four-week period of marijuana self-administration for the crossover arm (Stage 2).

- Events requiring medical attention will be collected from the first experimental session through the subject's final assessment at the end of Stage 2.
- Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition.
- Any AE leading to withdrawal from the protocol will be collected throughout the study.
- All AEs related to changes in psychiatric status will be collected throughout the study.

## 9.0 Collection of Concomitant Medications

Information about all concomitant medications, over the counter (OTC) and prescription, will be collected from screening up to the day of the final study visit of Stage 2. Information on new psychiatric medications will be gathered on the day of the 12-month follow up study visit. Medications taken during the course of the protocol, including medications taken to treat AEs, will be recorded on a concomitant medications form (CRF).

## 10.0 Clinical Laboratory Assessments

The Clinical Investigator or qualified study personnel will examine laboratory assessments gathered in screening for assessing participant eligibility. The investigator will use a list of normal ranges to conclude whether participants are eligible for the protocol, and will indicate justification for admitting participants with abnormal values.

The following laboratory assessments will be performed as a part of screening

Serum electrolytes and the **metabolic profile**, which includes:

ALT/SGPT;  
albumin:globulin (A:G) ratio;  
albumin, serum;  
alkaline phosphatase, serum;  
AST/SGOT;  
bilirubin, total;  
BUN;  
BUN:creatinine ratio;  
calcium, serum;  
carbon dioxide;  
chloride, serum;  
creatinine, serum;  
globulin, total;  
glucose, serum;  
potassium, serum;  
protein, total, serum;  
sodium, serum;

**CBC, which includes:**

Hematocrit;  
hemoglobin;  
MCV;  
MCH;  
MCHC;  
RDW;  
percentage and absolute differential counts;  
RBC;  
red cell count;  
WBC;

**Urinalysis, which includes:**

Color;  
appearance;  
specific gravity;  
pH;  
protein;  
glucose;  
ketones;  
occult blood;  
leukocyte esterase;  
nitrite;  
bilirubin;  
urobilinogen;

**Thyroid function, which includes:**

TSH high sensitivity, if abnormal, test will be followed by;  
Free T4;  
Free T3.

Blood cannabinoid levels will be measured at screening, four weeks after marijuana self-administration and two weeks after discontinuing marijuana self-administration in Stage 2 and Stage 2.

A urine-dip pregnancy test for females of childbearing potential will be performed as well.

A urine drug screen will be administered at screening at the study site.

Clinical laboratory assessments will be performed at:

LabCorp  
9465 E Ironwood Square Dr. 103  
Scottsdale, AZ 85258

## **11.0 Study Monitoring, Auditing and Documentation**

Investigators and/or their study staff will be trained prior to the start of the protocol by the sponsor's clinical research staff. The clinical study site will be monitored by site visits and remote communication to the investigator by representatives of the sponsor. The site will be monitored as appropriate for the rate of enrollment. During each monitoring visit, source data verification will be performed by a Clinical Research Associate (CRA) to ensure compliance, including accurate and complete recording of data on CRFs, source documents, and drug accountability records. A CRF collation supplied by the sponsor will be completed for each participant enrolled. Monitoring and auditing procedures of the sponsor will be followed, in order to comply with Good Clinical Practice (GCP) guidelines and to ensure validity of the study data.

The sponsor will review the study documentation used for planning, conducting and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes at minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

During or after the clinical protocol, the regulatory authorities, the IRB, and/or representatives of the sponsor may request access to all source documents, CRFs and other protocol documentation for on-site audit or inspection.

## **12.0 Data Analysis**

The sponsor will examine data from the 50 participants enrolled in Stage 1. The sponsor will examine the effects the five dose conditions (marijuana containing 0%, 2%, 6% and 12% THC and marijuana with a 6% THC/6% CBD ratio) on PTSD symptoms, assessed by CAPS global score. Between subjects / within-subjects analyses of variance (ANOVA) will be conducted, with condition as a between-subjects variable and time of administration (baseline, at four weeks of self-administration in Stage 1 and two weeks after cessation of use) as a repeated measure. The sponsor will perform post-hoc tests on any interaction and probability of rejecting the null hypothesis will be set at 0.05. If there is a significant interaction between condition and time of administration, the investigators will perform separate between-subjects / within-subjects ANOVAs on CAPS sub-scale scores to examine whether any facet of PTSD symptoms is particularly affected by one or more potency of marijuana in this study.

The sponsor will compare demographics and baseline CAPS scores of participants who withdraw from the study prior to initiating self-administration and participants who complete the study in an "intent to treat" analysis.

The sponsor will examine the effects of marijuana containing 0%, 2%, 6% or 12% THC and marijuana containing 6% THC/6% CBD on symptoms of depression and quality of life through performing between subjects / within-subjects ANOVAs on BDI-II and GAF scores during Stage 1, with condition as a between-subjects variable and time of administration (baseline, at two weeks of self-administration, at four weeks of self-

administration, at one week of discontinuation of use, at two weeks of a discontinuation of use) as a repeated measure with probability of rejecting the null hypothesis set at 0.05, and performing post-hoc tests upon any interactions. If an effect of time of administration is found, additional comparisons will examine BDI-II and GAF scores at baseline, two weeks after marijuana self-administration, four weeks after marijuana self-administration, one week and two weeks after abstention from marijuana self-administration.

Using between subjects/ within-subjects analyses of variance with substance delivery method as a between-subject variable and time of assessment as a repeated measure, the sponsor will compare effects of smoked versus vaporized marijuana on changes in symptoms of PTSD, depression and general psychological function. If there are effects for marijuana potency and substance delivery system, exploratory analyses may consider potential interactions between marijuana potency and drug delivery by performing an analysis on time of assessment of symptoms at one or more time point that will treat both conditions as between-subjects variables.

Examining data from Stage 2, the sponsor will conduct within-subjects analysis of variance with marijuana potency (6% THC versus 6% THC/6% CBD and 12% THC) as a between-subjects variable and time of administration (baseline, at four weeks of self-administration, at two weeks of discontinuation of use) as a repeated measure to compare the effects of the two potencies upon symptoms of PTSD. A similar repeated measures ANOVA will be performed on measures of depression and general psychological function, with potency as a between-subjects factor and time (baseline, at two weeks of self-administration, at four weeks of self-administration, at a week of discontinuation of use, at two weeks of discontinued use) as a repeated measure. If an initial comparison indicates no significant differences in effects seen for each relevant dose (6% THC, 6% THC/6% CBD and 12% THC) during Stage 1 and Stage 2, then a within-subjects analysis of variance treating dose as a within-subjects factor and time as a repeated measure will be performed.

The sponsor will conduct an additional analysis correlating actual amount of marijuana used by each subject with outcome measures, using the weight of any marijuana returned to estimate actual amount of THC and CBD consumed. The analyses will note inherent differences in drug delivery method that arise because participants may not inhale an entire bag filled with vapors even though they have vaporized a portion of the material. In addition, a correlational analysis of route of administration and outcome measures will be performed.

The sponsor will compare presence and level of blood cannabinoids after four weeks of marijuana self-administration and after two weeks of cessation of use. Analyses will compare blood cannabinoids across all five conditions and both drug delivery methods, and within-subjects analyses will compare blood cannabinoid levels during Stage 1 and levels at Stage 2, with marijuana potency as a within-subject factor.

The sponsor will compute descriptive statistics from the ESAMS, including mean value for each item across four weeks of use, and exploratory analyses will be performed that

will compare different responses as a function of marijuana potency and drug delivery system. The data will be examined to see whether there are any possible interactions between potency and drug delivery system. Exploratory analyses will also compare responses to the ESAMS during the randomized arm with ESAMS responses on the crossover arm in all participants taking part in the crossover.

The sponsor will collect and maintain data for assessment of safety, including C-SSRS scores at each time point and Adverse Events, as described under Adverse Event Collection. Safety analyses will examine data from study subjects, including the period of marijuana self-administration and the period of abstinence from marijuana. The sponsor will compute descriptive statistics for these variables when applicable, including separate descriptive statistics for safety data in participants smoking and vaporizing marijuana. The sponsor will compare adverse events in people assigned each strain of marijuana and each drug delivery method. The sponsor may formally or informally compare expected and other adverse events profiles in people assigned to each of the five marijuana potencies and two each of the two drug delivery systems.

The sponsor will perform exploratory analyses comparing CAPS and BDI-II scores at the end of Stage 2 and at the long-term follow-up visit. The sponsor will gather descriptive statistics on presence or absence of a new traumatic event, number and type of new PTSD treatments reported by the participant during the interval between the end of Stage 2 and the long-term follow-up.

## **12.1 Statistical Power**

The proposed study is a pilot investigation intended to gather preliminary data on the safety and efficacy of marijuana in people with chronic, treatment-resistant PTSD. Because of their exploratory nature, pilot studies are often underpowered for detecting the desired effect. Because it is a pilot study in a small sample, statistical power is difficult to assess but it is likely to be low. This study will be the first to examine the effects of marijuana on PTSD, and the literature does not permit a basis for calculating actual effect size for any study effect.

Using Lenth's [116] applications for calculating statistical power and comparing samples of ten using a t-test and estimated effect size, the study is underpowered for detecting moderate differences (when an effect size of .6, power was 0.23) but sufficient to detect larger effects (if there is an effect size of 1.5, power = 0.886). This means that the study is likely sufficiently powered to detect differences between 0% or 2% THC marijuana and 6% THC or 12% THC marijuana, but it may not be sufficiently powered to detect differences between more closely related doses. Currently, we have no expectations as to what the true effect size will be for any of the given conditions.

The same program was used to compute sample size needed to detect a small difference in mean in two samples of 25 participants. A comparison with results computed from programs designed by Lenth indicated that if effect size were 0.5, power is at 0.41, if effect size is 0.8, power is at 0.79, and that when effect size is 1, power will be 0.94.

Hence it seems likely that the study will detect differences in effects of smoked versus vaporized marijuana, and that failure to detect statistically significant findings is likely due to lack of effect or a low to moderate effect size.

Two paired t-tests, one comparing a group of 10 with a group of 20 and the other two groups of 20, was used to assess the power of the crossover arm to detect differences in effects on PTSD symptoms between the three conditions in Stage 2, 6% THC, 6% THC/6% CBD and 12% THC marijuana. As noted assuming scores similar to those above, the study will be underpowered to detect differences of effect size of 0.5 or smaller when comparing two groups of 20, will be powerful enough detect significant differences when effect size is large (as 1 or 1.5). Hence the study is powered to detect moderate to large differences between 6% THC and 6% THC/6% CBD marijuana in the crossover arm. When considering differences between either of these conditions and 12% THC marijuana, the study will have less power, with an effect size of 1 with samples of 10 and 20 resulting in a power of 0.7, and an effect with an effect size of 0.5 having power of 0.24.

### **13.0 Informed Consent**

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. Information about events during the course of the study must be given both orally and written, in an understandable form. In addition to the explanation of evaluation, introductory sessions, periods of marijuana self-administration and periods of abstinence from marijuana, the information should include that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified, according to applicable local regulations. The subject should have the opportunity to inquire about details of the study and to consider whether or not to participate.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the investigator.

The investigator will provide a copy of the signed ICF to the subject, and will maintain the original in the investigator's study file.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive approval from an IRB before use.

Written consent to take part in the study session includes giving the investigators permission to view the participant's recent medical records to assess study eligibility, if needed. Information necessary for study participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

The subject should be informed in a timely manner if new information becomes available that may affect the decision to take part in the study. The communication of this information should be documented.

Participants can withdraw consent for participation in the protocol at any time without prejudice. If a subject withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization or equivalent form, MAPS will have full access to the subject's medical records, including termination visit information. If a participant revokes only the HIPAA authorization, MAPS will have full access to all of the participant's medical records prior to the date and time of revocation.

### **13.1 Confidentiality**

Every effort will be made to strictly safeguard the confidentiality of participants in their role as research subjects. Removing identifying information from data and restricting access to researchers directly involved in assessing the participants should prevent the dissemination of confidential data, with or without identifying information. Despite this, privacy cannot be guaranteed. Except for the screening log, the informed consent and a subject contact information sheet, all data will be identified only by the participant's initials on the source document and three-digit subject number numeric code. If past medical records are needed participants will sign forms for the release of information upon consent to permit screening for protocol enrollment. All assessment records will be kept in a locked file drawer or cabinet, and access to measures will be limited to regulatory agencies, researchers, and individuals analyzing data. Researchers, other than the investigators directly involved in the protocol, with access to data will not be provided with any information that would identify participants by name or by other means, such as social security number.

Maintaining data in a secure environment will prevent the accidental or deliberate examination or removal of data.

### **13.2 Costs to Participants**

The Sponsor of this study will cover the costs that are directly related to this study. This includes the costs for introductory sessions, for the psychological and laboratory testing, for medical examinations and the study drug. The subject, their private medical insurance (if any), and the public health insurance plan will not be charged for any procedures done solely for the purpose of the study.

Charges for treatment of the participant's condition that are unrelated to the research study or any of its procedures will continue to be billed to the health insurance provider of the participant or to the participant him or herself. It is anticipated that there will not be any charges for treatment that is unrelated to the study.

### **13.3 Treatment and Compensation for Study Related Injury**

Treatment of a study-related emergency would first be billed to a participant's health insurance provider. The sponsor will cover any direct costs relating to the treatment of a study-related emergency that are not covered by a participant's health insurance. The

study involves self-administration of the study drug. Participants will be directed to go to the nearest emergency department if they experience a medical emergency.

#### **14.0 Record Retention**

Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records.

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