

**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
CI	Clinical Investigator (e.g. lead investigator, co-investigators)
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
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-methylenedioxyamphetamine
NIDA	National Institute on Drug Abuse
PDS	Posttraumatic Diagnostic Scale
PSQI	Pittsburgh Sleep Quality Index
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
Stage 3	The optional third study arm
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, 4]. At present, there are no published data from a randomized, placebo-controlled, 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). Tolerability of smoked vs. vaporized marijuana will be compared within each condition. The study will consist of three arms. During the first arm (Stage 1), subjects will self-administer marijuana daily for four weeks on an outpatient basis. The second arm (Stage 2) will be a crossover arm involving another 4-week period of marijuana use followed by 2 weeks of cessation. There will also be an optional third arm (Stage 3) that will assess and monitor participants who request the return of any unused marijuana from the first two arms until they have consumed the remaining material. Symptoms of PTSD and depression will be assessed during a 4-week period of marijuana use and again two weeks after cessation of use in the first and second study arm, and until

all marijuana has been used or returned in the third study arm. Symptoms of PTSD and depression will be assessed 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.

## **2.1 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 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, after 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. There will also be an optional Stage 3 that will assess and monitor participants who request the return of any unused marijuana from Stage 1 or Stage 2 until they have consumed the remaining material.

## **2.2 Supporting Information**

### **2.2.1 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% [5, 6], and it can be especially resistant to pharmacotherapy with Selective Serotonin Reuptake Inhibitors (SSRIs) [7]. PTSD is common in other countries as well [8-12]. In U.S. soldiers returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [13], and it is estimated that the number of service members returning home with PTSD will be between 75,000 and 225,000 [14]. 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 [15]. 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 [16-18]. PTSD is typically a chronic illness [19, 20], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [10, 19, 21, 22].

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 [23, 24], 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 [25]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

There is limited data about whether or not patients with military 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" [26].

It has been noted [27-29] 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 [30]. 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, 31, 32]. 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].

### **2.2.2 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 cerebellar 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 [33].

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 [34-36]. 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 [37], and CB1 receptor antagonist SR141716 produced anxiogenic effects in the elevated plus-maze and the defensive withdrawal tests in adult rats [38, 39]. 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 cholecystinin (CCK), a peptide that may contribute to both anxiolytic and anxiogenic effects of THC and endocannabinoids [40-43]. 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 [44-46]. Studies in rodents suggest that cannabinoids and their interaction with endogenous opioids might also modulate anxiety [45, 47, 48]. 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 [49]. The synthetic cannabinoid nabilone was effective in reducing treatment-resistant nightmares in people with PTSD [50]. 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 [51]. 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 [52, 53]. An early safety study reported that CBD was tolerated when administered to humans for 30 days [54]. Research has investigated its potential as an anticonvulsant and anti-psychotic [55]. It may have 5HT1A agonist activity [56]. A series of studies in rodents and humans suggest that CBD possesses anxiolytic and potentially antipsychotic effects [55]. Administration of CBD was equal to a 5HT1A agonist and a benzodiazepine in reducing anxiety in the face of public speaking [57], and rats given CBD exhibited less anxiety

during the Vogel task, or “punished drinking,” wherein the animals can receive shocks from the drinking spout [58]. Research in mice found that CBD was comparable to the antidepressant imipramine in rodent tests of antidepressant-like effects [59]. One report found that CBD may oppose anxiogenic effects of THC in humans [60], and smoking marijuana with higher CBD levels was associated with less memory impairment and lower anxiety during intoxication in a naturalistic study [61]. However, another investigation found that cannabidiol levels made little difference on self-reported subjective effects, cognitive tasks or electroencephalography (EEG) [62]. 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 [63], and it appears that CBD attenuates amygdalar activation in response to facial expressions of fear in healthy subjects [64]. These investigations suggest that it is worth investigating the effects of the THC to cannabidiol ratio upon the effects of marijuana.

### **2.3 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 nearly absent or 6%, so that it matches THC levels in two of the potencies.

In order to investigate the impact of varying levels of THC upon PTSD symptoms and to provide a credible 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 [65-67]. Some studies have used 2% THC or marijuana with levels close to 2% as a lower dose comparison [62, 67], 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 dosages. Research investigating the effects of marijuana or THC in humans has used doses ranging from approximately 3% to 6% or higher [65, 67]. Several studies suggest that cannabidiol may be more strongly associated with reduced anxiety than THC, with some researchers reporting opposing effects of these chemicals [58, 60, 68, 69]. 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. Crossover of marijuana dose between Stage 1 and Stage 2 for people receiving the 6% THC and 6% THC/6% CBD 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 Objective

- 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, or 12% THC marijuana.

### 3.2 Secondary Objectives

- Assessing changes in Posttraumatic Diagnostic Scale (PDS) scores in participants in all five marijuana conditions.
- 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.
- Assessing changes in self-reported sleep quality via the Pittsburgh Sleep Quality Index (PSQI) in participants in all conditions.
- Examining self-reported sleep quality and anxiety through the Experiences with Self-Administering Marijuana Survey (ESAMS), a sponsor-developed self-report instrument, during periods of self-administration.
- Comparing scores on all outcome measures (CAPS, PDS, BDI-II, GAF and PSQI) in participants smoking versus vaporizing marijuana overall, and within all 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 via CAPS and PDS and depression via BDI-II, general psychological function via GAF, and self-reported sleep quality with PSQI within subjects.
- Gathering information on daily marijuana usage during drug administration, including information on amount, time, frequency and route of administration for participants in all five dose conditions, and weight of any unused marijuana.
- Exploring and examining the effects of self-titration, as measured via average monthly weight of consumed marijuana, defined as the difference between the weight of returned material from the original allotment, upon PTSD symptoms, depression symptoms, sleep quality, and general psychological function.
- Evaluating blood cannabinoid levels after four weeks of self-administration and after two weeks of cessation of use during Stage 1 and Stage 2 and during self-administration in Stage 3 and in all conditions.
- Exploring and examining symptoms of PTSD and depression and general psychological health, and any new PTSD treatments tried, 12 months after completing Stage 2.
- Exploring and examining symptoms of PTSD and depression, general psychological function and sleep quality throughout continued use of marijuana in Stage 3.

### 3.3 Safety Objectives

- Collecting information on tolerability through self-reported reactions and experiences of smoking and vaporizing marijuana during drug administration through daily completion of the ESAMS.
- Assessment of suicidality with the Columbia Suicide Severity Rating Scale (C-C-SSRS) on a weekly basis throughout all three stages.
- Assessment of psychiatric symptoms with the Brief Symptom Inventory (BSI) on a weekly basis throughout all three stages.
- Collection of vital signs from participants during each weekly visit to the study site during all three study arms.
- Collection of Adverse events and Serious Adverse Events 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), plus continued assessment of individuals who elect to use any remaining marijuana from either arm in Stage 3. 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.

To standardize method of drug administration and to assess psychological risk, 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 [66, 70]) 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 one week supply of marijuana, divided into seven daily packages of 2 rolled cigarettes and a storage box with a combination lock. 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, with a day defined as a period of 24 hours in this study. There will be no lower quantity limit, and participants do not have to use any of the daily allotment should they decide that symptoms do not require medication on any particular day. Self-titration is considered one of the clinical advantages of marijuana that this study will evaluate. Participants will receive seven daily packages of marijuana cigarettes each week. Participants will complete a daily diary of their marijuana use and a daily measure of their experiences with the study marijuana. Participants will be instructed to save any unused marijuana in that day's package. Subjects are required to return the unused amounts to the investigators during each weekly visit to the study site, when they will receive marijuana for the next week of the study. This will enable the research team to measure the amount of marijuana each subject consumed on each day over the week. Should subjects request it, all unused marijuana will be returned to them at the end of Stage 2, reducing the likelihood that any marijuana will be used unnecessarily or diverted during the four-week period of medication.

The investigators will provide subjects with portable video cameras, and subjects will be asked to record their use of marijuana. They will be instructed to follow a standard procedure for recording their self-administration of marijuana. Participants will be instructed to start each recording with an image of the locked box, record their use of the material and complete the recording with a shot of remaining unused material before closing the storage box. Recording their use of marijuana will permit the investigators to verify that participants are following the protocol and are using the study marijuana. Participants will save their recordings until their weekly meeting with the investigators. The investigators will collect recordings of participant self-administration of marijuana each week. In addition, the participant must designate an individual as an observer and witness that the marijuana is being used as directed and not diverted. An investigator will telephone the designated witness once a week to learn whether, in the view of the witness, the participant is using the marijuana and not giving it away or selling it to others. Having a secondary source of verification of self-administration will ensure that the marijuana is being used by the participant and not diverted.

During weekly visits, blood will be drawn to assess cannabinoid levels, and the investigators will assess vital signs, including blood pressure, heart rate and body

temperature. Participants will complete measures of self-reported PTSD symptoms, depression symptoms, and general psychiatric symptoms. The investigators will assess suicidality with the C-SSRS. Participants will return any unused marijuana, and they will receive another week's supply of marijuana. The investigators will collect a week of Daily Marijuana Use Diaries and ESAMS scales. The CAPS, the GAF and the PSQI will be administered at baseline, at the end of four weeks of marijuana self-administration and at two weeks of marijuana cessation.

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

During Stage 3, participants who choose to receive unused marijuana from Stage 1 and Stage 2 will continue to return for weekly evaluation of symptoms of PTSD and depression, psychiatric symptoms, general psychological function, vital signs and blood cannabinoid levels until the participant has consumed all the remaining marijuana. They will continue to record their smoking or vaporizing of the remaining marijuana. The CAPS, GAF and PSQI will not be administered during Stage 3 unless more than a month has elapsed between the end of Stage 2 and the end of Stage 3, when the participant no longer has any remaining marijuana.

Twelve months after undergoing their final Stage 2 study visit, participants will return to the study site for the long-term follow-up (LTFU). The Independent Rater will assess or administer self-report measures of symptoms of PTSD, depression, psychiatric symptoms, general psychological health and sleep quality, as appropriate. 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 study will last 15 months, with each participant completing the drug administration portion of the study two weeks after discontinuing marijuana self-administration at the end of Stage 2 or Stage 3, as appropriate. Participants who request and receive any remaining marijuana will continue drug administration until the participant has consumed all of the marijuana, with weekly assessments ending when all unused marijuana is consumed. The follow-up visit will occur 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. Randomization numbers will be linked to container assignments. The container assignments 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 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 the 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 and during any continued use of returned marijuana. 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 chronic PTSD arising from their service in the US armed forces and with duration of PTSD 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 chronic PTSD of at least six months duration.
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 investigators 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 which tests 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 [71, 72]. The independent rater will administer the CAPS at visits described in the Time and Events table.

The secondary measure of PTSD symptoms will be the PDS, a self-report measure designed to follow DSM IV criteria for assessing PTSD. The measure is derived from the Posttraumatic Symptom Scale – Self Report (PSS-SR), a measure also intended to tap into diagnostic criteria for PTSD. The PDS contains 49 items, with responses made on a four-point scale, ranging from 0 (“not at all”) to 3 (“five or more times a week”). The PDS consists of a list of 12 potential traumatic events, 12 items addressing elements of the traumatic event, of 17 symptom items, and nine items assessing impact on areas of life function. Items addressing elements of the traumatic event and life function are answered as either present or not present (Yes or No). The seventeen items are summed to create a symptom severity scale. Cronbach’s alpha for the symptom severity scale is 0.92. The PDS has test-retest reliability of 0.74 after a two-week and one-month interval, and subscales are inter-correlated, with correlations ranging from 0.73 to 0.82, and PDS scores had a moderate to good correlation with SCID diagnosis, with kappa = 0.65 [73]. The subjects will complete the PDS according to 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 a self-report measure of depressive symptoms that will serve as a measure of depression [74, 75]. It takes five to ten minutes to complete. Subjects will complete the BDI-II according to the Time and Events table.

The Daily Marijuana Use 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 amount of marijuana used, the times of day it is used, frequency of use per day, and route of administration (smoked or vaporized). 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 Pittsburgh Sleep Quality Index (PSQI) is a measure of self-reported sleep quality over the preceding month. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers. It consists of 19 items, with possible responses ranging from zero to 4 on a five-point Likert scale [76]. The PSQI consists of seven sub-scales; sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. These are all summed to produce a single global scale. Global scores can range from 0 to 21, with higher scores reflecting poorer sleep quality, and a score below 5 indicative of good sleep. It takes five to ten minutes to complete. Test-retest reliability ranges from 0.85 to 0.87, and it is internally consistent, with a Cronbach's alpha of 0.83[76, 77]. Global scores correlate with other measures of alertness and self-reported sleep quality [78]. Participants will complete the PSQI according to the Time and Events table.

Blood cannabinoid levels will be assessed at screening and on each weekly visit to the study site. Blood samples will be analyzed at the clinical laboratory used for the study. Assessing blood cannabinoid levels will further support absence of marijuana use during the several weeks to a month prior to the start of the study, and help estimate cannabinoid dose and confirm use of marijuana.

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, and will be completed by the subjects at the LTFU visit.

### **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, anxiety) 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 for all three study arms. Average scores on each item will be computed for each week of the study.

The BSI is the short form of the Symptoms Checklist 90-Revised and is designed to assess clinical and psychological symptoms [79, 80]. It contains 53 items and takes eight to 12 minutes to complete. It contains nine dimensions (Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism) and three global indices of distress (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total). Participants will complete the BSI according to the Time and Events table.

The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial [81]. 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 according to the Time and Events table.

Participant blood pressure (systolic/diastolic), heart rate and body temperature will be assessed at baseline and during each weekly visit during all three study arms, as described in the Time and Events table.

Adverse Events (AEs), including spontaneously reported reactions, will be collected as described in Section 8.0 of the protocol. Concomitant medications will be collected as described in Section 9.0 of the protocol.

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

Visit #	Pre-Study	V1, V2	V3, V4, V5	V6	V7	V8
Type of Visit	Screening may take place over more than one day	Introductory Sessions	Self-admin weekly visits	Outcome Measure 1	Assessment	Outcome Measure 2
Approximate Study Day	Up to one month prior to Visit 1	Day 0, Day 1	Week 1, Week 2, Week 3 post V1	Week 4 post V1	Week 5 post V1	Week 6 post V1
Visit Timing and Windows		Upon enrollment before self-admin	-3/+3 days	-3/+3 days	-3/+3 days	-3/+3 days
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	X	X	X	X
Collect Psychotherapy Information	X	X	X	X	X	X
Study Enrollment after meeting Inclusion/Exclusion		X				
Urine Drug Screen	X		X	X	X	X
Pregnancy Screen (if applicable)	X					
Complete Randomization Procedure		X				
Provide information on marijuana experience		X				
CAPS, PSQI, GAF	X			X		X
Serum cannabinoid levels	X		X	X	X	X
Vital signs		X	X	X	X	X
BDI-II, BSI, PDS	X		X	X	X	X
C-SSRS	X	X	X	X	X	X
Collect Daily marijuana use diary, ESAMS			X	X		
Belief of condition assignment				X		
Weigh Unused Marijuana			X	X		
Collect and Review Video Recordings			X	X		
Spontaneously Reported Reactions		X	X	X		
Adverse Events of Concern to the Participant		X	X	X		
Adverse Events Requiring Medical Attention		X	X	X	X	X
Adverse Events leading to withdrawal		X	X	X	X	X
Adverse Events related to changes in psychiatric status		X	X	X	X	X
Serious Adverse Events		X	X	X	X	X
Unblinding						
Study Termination						

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

Visit #	V9	V10, V11	V12, V13, V14	V15	V16	V17	Long-Term Follow Up
Type of Visit	Baseline #2	Introductory Sessions	Self-admin weekly visits	Outcome Measure 3	Assessment	Outcome Measure 4	Outcome Measure 5
Approximate Study Day	May be same day as V8	Day 43, Day 44	Week 1, Week 2, Week 3 post V10	Week 4 post V10	Week 5 post V10	Week 6 post V10	12 months after V17
Visit Timing and Windows	Within 1 week of V8	2 consecutive days within 5 days after V9	-3/+3 days	-3/+3 days	-3/+3 days	-3/+3 days	
Collect Concomitant Medication	X	X	X	X	X	X	X
Collect Psychotherapy Information	X	X	X	X	X	X	X
Study Enrollment after meeting Inclusion/Exclusion							
Urine Drug Screen	X			X	X	X	X
Pregnancy Screen (if applicable)	X						
Complete Randomization Procedure	X						
Provide information on marijuana experience		X					
Belief of Condition Assignment				X			
CAPS, PSQI, GAF	X			X		X	X
Serum cannabinoid levels	X		X	X	X	X	
Vital signs		X	X	X	X	X	
BDI-II, BSI, PDS	X		X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X
Collect Daily Marijuana Use Diary, ESAMS			X	X			
Weigh Unused Marijuana			X	X			
Collect and Review Video Recordings			X	X			
Spontaneously Reported Reactions		X	X	X	X		
Adverse Events of Concern to the Participant		X	X	X	X		
Adverse Events Requiring Medical Attention		X	X	X	X	X	X
Adverse Events leading to withdrawal		X	X	X	X	X	X
Adverse Events related to changes in psychiatric status		X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X
Unblinding						X	
Study Termination							X

**STAGE 3** will consist of unspecified weekly visits until all remaining marijuana is used, and will include daily diary, ESAMS, PDS, BSI, BDI-II, GAF, C-SSRS, vital signs, blood cannabinoid levels, urinary drug test, and if lasting over a month from end of Stage 2, CAPS and PSQI. This arm will not include a period of observation related to cessation of use.

## 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 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 and source records completed during screening. 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 PDS, PSQI, BSI and 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: these are essential to ensure that subjects have not used marijuana up to a month prior to the start of the study.
  - Blood cannabinoid levels: these are to further support absence of marijuana use during the days 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 enrolled.
- n) Issue a subject number.
- o) Throughout the study, concomitant medications and adverse events will be collected at each contact as described in Sections 8.0 and 9.0 of the protocol.
- p) If the participant continues to meet all inclusion criteria and no exclusion criteria, the investigators will schedule introductory sessions and the beginning of the first four-week period of active dosing.

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

- a) 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.
- b) Inquire about any possible changes in the participant's health to ensure they continue to meet eligibility criteria.
- 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 investigator will discuss locating another person who resides with the participant to verify appropriate use of marijuana and lack of diversion. The participant will provide the investigators with a telephone number to use to reach the secondary verifier ("observer and witness".)
- f) The participant will undergo two four-hour introductory sessions with the investigator, preferably on two consecutive days. The investigator 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.
- g) During the introductory sessions, the investigator will administer the C-SSRS.
- h) The investigator will introduce the participant to the daily diary and will instruct them on diary entry completion.
- i) Participants will receive a research subject identification card ("wallet card") stating that they are a research subject and may test positive for drugs and listing

- investigator contact information.
- j) 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.
  - k) The participant is required to self-administer marijuana using the method of administration and potency the subject has been randomized to use.
  - l) At the end of the second introductory session, the investigator will provide the participant with a supply of marijuana intended to last for one week of the four-week self-administration period, and a lockable storage box with private combination lock. The participant will be instructed to use no more than two cigarettes of marijuana per day.
  - m) The investigator will provide the participant with one week of daily marijuana use diary and ESAMS sheets.
  - n) The investigator will provide the participant with a portable video camera (for example, a Flip camera) and instruct the participant on the use of the camera, including standard recording of marijuana self-administration and saving recordings to the camera.

### **5.2.3 Daily Telephone Contact for the First Week of Stage 1**

- a) Starting after the second introductory session, one of the investigators will contact the subject via telephone or in person on a daily basis for one week.
- b) The daily telephone contact is expected to last between 5 and 15 minutes, or as long as necessary to address any subject's concerns and to assess the subject's wellbeing.
- c) The investigator will record general wellbeing after each telephone call.

### **5.2.4 Four weeks of Marijuana Self-administration during Stage 1**

- a) The participant will smoke or vaporize the marijuana supplied to them daily during this time period.
- b) They will record each use of the marijuana using the standard recording technique.
- c) If another person residing with the individual has agreed to serve as a witness to the marijuana use, that individual will note the marijuana use.
- d) The participant will complete a Daily Marijuana Use Diary.
- e) The participant will complete the ESAMS on a daily basis.
- f) The investigator will telephone the secondary verifier to receive information on whether the participant is using the marijuana as directed and not diverting it.
- g) The participant will undergo weekly assessments at the study site.

### **5.2.5 Weekly Evaluations for Weeks 1 to 3 of Stage 1**

- a) Participants will meet with the investigator at the study site once a week during the self-administration period.
- b) The investigator will administer the C-SSRS.

- c) The participant will return completed daily diary and ESAMS sheets.
- d) The participant will complete the PDS, BDI-II and BSI.
- e) A blood test to measure blood cannabinoid levels, a urinary drug screen to detect drugs of abuse and assessment of vital signs (blood pressure, pulse and body temperature) will be performed.
- f) The participant will bring the portable video camera to the study site. The investigator will copy all recording files, note the time and date stamp and save for review. Each recording will be reviewed, and the identity of the participant and the study material confirmed.
- g) The investigator will provide the participant with a week of daily marijuana use diary and ESAMS sheets.
- h) The investigator will return portable video cameras to participants. They will remove all recording files prior to returning the cameras.
- a) Subjects will return any unused marijuana from the last week of self-administration, and they will receive a supply of marijuana for the next week. The investigator will weigh any returned marijuana.
- i) The investigator will telephone the secondary verifier to collect reports of participant marijuana use within each week of use.
- j) Three identical weekly evaluations will occur, one per week.

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

- b) Participants will meet with the independent rater for a 60 to 90 minute face to face evaluation. This meeting will take place at the study site.
- c) The independent rater will administer the CAPS and GAF.
- d) Subjects will complete the PSQI, PDS, BSI and BDI-II.
- e) The investigator will administer the C-SSRS.
- f) A blood sample will be drawn to measure blood cannabinoid levels.
- g) A urinary drug screen will be performed.
- h) The investigators will assess vital signs.
- i) Recordings of marijuana use will be collected and saved, and the portable video camera will be returned to the participant. Recordings will be reviewed to confirm the identity of the participant and the marijuana.
- j) The participant and investigator will give written indications of their beliefs concerning participant condition assignment.
- k) Daily marijuana use diaries and daily ESAMS sheets will be collected.
- l) All remaining marijuana will be collected from the participant. The investigator will weigh any returned marijuana.
- m) The investigator and participant will discuss the two-week period of cessation of marijuana use.
- n) Information on changes in psychotherapy will be collected.

#### **5.2.7. Two weeks of Abstinence from Marijuana Self-Administration of Stage 1**

Participants will cease to self-administer marijuana for a two-week interval. The participant will not complete daily diaries or ESAMS during this interval.

### **5.2.8 Evaluation One week after Cessation of Marijuana Use of Stage 1**

- a) Participants will meet with the investigator one week after the participant has ceased marijuana self-administration.
- b) The participant will complete the PDS, BSI and BDI-II.
- d) The investigator will administer the C-SSRS.
- e) A blood sample will be drawn to measure blood cannabinoid levels.
- f) A urinary drug screen will be performed.
- g) The investigator will assess vital signs.
- h) Information on changes in psychotherapy will be collected.

### **5.2.9 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 and the GAF.
- c) The participant will complete the PSQI, PDS, BSI and BDI-II.
- d) The investigator will administer the C-SSRS.
- e) A blood sample will be drawn to measure blood cannabinoid levels.
- f) A urinary drug screen will be performed.
- g) The investigator will assess vital signs.
- h) Information on any changes in psychotherapy will be collected.
- i) 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.

### **5.2.10 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. Participants in the 6% THC marijuana group in Stage 1 will be assigned to 6% THC/6% CBD group during Stage 2. Participants 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) Use of the portable video camera and the standard format for recording marijuana use during the study will be reviewed.
- c) Information on changes in psychotherapy will be collected.
- d) The participants will undergo two introductory sessions wherein they will smoke or inhale the potency of marijuana they are assigned for Stage 2.
- e) Participants will receive the first of four one-week supplies of rolled marijuana cigarettes, and the participants will receive the locked storage box.

- f) 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.
- g) There will be a week of daily telephone contact with the subject as described in Section 5.2.3.
- h) Participants will self-administer marijuana according to their assigned drug delivery system (smoking or inhaling vapor) as described in Section 5.2.4.
- i) The participant will meet with the investigator once a week at the study site as described in Section 5.2.5.
- j) After the fourth week of self-administration, the subject will meet with the independent rater and investigator as described in Section 5.2.6. Participants will return any unused portions of marijuana to the investigators.
- k) Subjects will cease to use marijuana as described in Section 5.2.7.
- l) One week into this period of cessation of use, participants will meet with the investigator at the study site as described in Section 5.2.8.
- m) At the end of two weeks of cessation of use, participants will meet with the independent rater and the investigator as described in Section 5.2.9.
- n) At the last visit in Stage 2, 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.
- o) If subjects do not have any remaining unused marijuana or do not request to receive any of their returned marijuana, they may at this point change medications or increase medication doses, and subjects can change frequency or type of psychotherapy.
- p) If the participant does not have any remaining unused marijuana or does not wish to use the remainder of the material, then he or she will return the portable video camera and locked box to the investigators.

#### **5.2.11 Continued Follow-up of Participants who Request their Unused Marijuana**

- a) The investigators will return the unused portion of marijuana, if any, from both Stage 1 and Stage 2, to participants upon request.
- b) Participants who requested any remaining marijuana will retain the locked storage box and portable video camera for standard recording of marijuana use.
- c) Participants will continue to complete daily diary and ESAMS sheets.
- d) Recordings of participant marijuana use will be collected at each weekly assessment, and they will be reviewed to confirm the identity of the participant and the material used. Verification of appropriate participant use of the marijuana will be collected from the secondary verifier.
- e) The investigators will meet with the participant on a weekly basis for a 60-minute visit. They will assess the participant with the CSSRS and the participant will complete the PDS, BSI and BDI-II.
- f) If more than a month has elapsed between the end of Stage 2 and the last weekly evaluation for continued use of marijuana, the independent rater will administer the CAPS and GAF and the subject will complete the PSQI.

- g) Blood cannabinoid levels and vital signs will be assessed, and a urinary drug screen will be performed.
- h) Information on changes in psychotherapy will be collected.
- i) Continued weekly visits will end when the participant has used all of the remaining marijuana or does not wish to use the marijuana. If the participant does not wish to use the study material, he must return all remaining marijuana to the study site. The investigators will weigh any returned marijuana.
- j) The participant will return the portable video camera and locked box to the investigators.
- k) After using all remaining marijuana, participants may change identity and increase dose of medication, and they can change the type and frequency of psychotherapy they are undergoing.

### **5.2.12 12-Month Follow Up (Long-term Follow Up)**

- a) Participants will meet with the independent rater for a 60 to 90 minute evaluation. 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, and GAF.
- c) The subject will complete the PDS, PSQI, BSI and BDI-II.
- d) The investigator will administer the C-SSRS.
- e) A urinary drug test will be administered
- f) The participant will complete the LTFU questionnaire.
- g) The Memory Aid Card will not be collected, but information listed on it 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 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 [82]. 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 [83]. Currently, it is a Schedule 1 controlled substance, meaning that it is illegal to possess, sell or distribute marijuana outside of research studies. Individual states within the US have significantly reduced penalties for possessing small quantities of marijuana, have laws permitting physicians to recommend use of marijuana, or both types of legislation. 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 [60, 62, 84], and cannabidiol may possess therapeutic potential [55, 84]. The subjective and potentially therapeutic actions of marijuana may be directly or indirectly influenced by other compounds found in the plant [84].

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

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

This protocol will compare marijuana differing in THC or CBD content. Any unused portions of the marijuana that participants did not consume during each day will be collected on a weekly basis, with all 56 packages returned to the investigators at the end of the cumulative eight weeks of drug administration in Stage 1 and 2. Subjects may choose to receive the remainder of the marijuana as a part of Stage 3. Any unused marijuana will be tracked during the study and stored for drug accountability.

#### **6.2.1 Doses**

Study participants will be assigned to receive one of five potency conditions. Stage 1 will use 0% THC, 2% THC, 6% THC, 12% THC and 6% THC/6% CBD marijuana. Stage 2 will use 6% THC, 6% THC/6% CBD and 12% THC marijuana. 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 each weekly evaluation during the period of self-administration and at the conclusion of the four week period of active dosing, for precise weighing. Marijuana in Stage 3 will consist of any remaining material from the first two study arms.

**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

**6.2.2 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. The pharmacist will package all marijuana materials identically in separate packages, each containing two rolled cigarettes for each day’s use.

At the end of Stage 2, if subjects request to receive unused marijuana as a part of Stage 3, the pharmacist will repackage the unused marijuana as appropriate to method of drug delivery for that subject.

**6.2.3 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# <u>XXXX</u>
Investigational Product: Cannabis (marijuana)
Dose: Blinded
Randomization # <u>XXX</u>
Subject Number _____
Lot #: XXXXX
Day to be used (XX between 1-28)
Administer as per protocol
Caution-Limited by Law to Investigational Use Only

### 6.3 Substance Accountability

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

### 6.4 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 lead 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 lead 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 one 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 one week's worth of cigarettes at a time during the study. Participants will also receive a lockable box with a private combination lock for storage of the marijuana, and a portable video camera to record their use of marijuana 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 during each weekly evaluation. 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.

Participants who request the return of unused marijuana will receive it in repackaged form. Participant will retain the lockable box and portable video camera for the storage of the marijuana and recording their continued use for investigator review.

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

## **6.5 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. Weekly blood draws are also required to assess cannabinoid levels during marijuana self-administration and during cessation of use. Temporary discomfort, inflammation or infection could arise as a result of sampling blood at the punctured vein. Weekly measures of blood pressure and heart rate will be taken to assess drug effects and participant safety. Participants may experience mild discomfort from having blood pressure assessed. 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.

### **7.2 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 marijuana consumption.

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 [85]. 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 [86]. Marijuana may provoke psychotic symptoms or psychosis in vulnerable individuals without being a "cause" of psychosis [87, 88].

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 [89-91]. 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 [92].

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 [93]. This may be the result of people under the influence of marijuana overestimating their level of impairment, and thus driving more conservatively [93, 94]. 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 [95]. Nonetheless, epidemiological studies of road accidents have found a relationship between use of marijuana, including blood THC levels, and road accidents [96, 97], 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.

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 [98, 99]. There are a few reports of self-administration of THC in animals [100]. 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 [98].

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 [101]. 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 [101].

Regular and heavy marijuana use is associated with increased symptoms of chronic bronchitis, coughing, production of sputum, and wheezing [102, 103]. Regular marijuana use may impair function of alveolar macrophages, a type of immune cell found in the lung [103, 104]. 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 [102, 105, 106]. A review of literature addressing marijuana use and lung injury concluded that findings were often inconsistent [107]. Marijuana use does not appear to be associated with lung cancer [107-109]. 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 [110-112].

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 [113, 114]. However, marijuana and cannabinoids failed to affect immune function in HIV-positive individuals [65, 115]. 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 [116], and in vitro studies suggest that THC and marijuana may reduce immunosupportive Th1 cytokines and increase immunosuppressive Th2 cytokines [113, 117]. 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 [115, 118].

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 [85]).

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 [85, 119-122]. THC can pass into breast milk [122]. 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.

Participants may test positive after urinary assay for drugs of abuse, as those used for workplace drug testing or as a result of police response to a traffic violation. Even participants who are not using their marijuana on a daily basis may test positive for marijuana for up to three weeks after study participation. Testing positive for marijuana could pose risk of arrest or job termination.

### **7.3 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 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.

All study participants will be issued a study subject identification card (e.g. “wallet card”) stating that they may test positive for drugs of abuse as a result of being a research participant and containing contact information for the investigator, identifying the sponsor and the relevant institutional review board (IRB).

#### **7.4 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 the 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 Spontaneously Reported Reactions**

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 [62, 86]. Some participants may report feelings of paranoia or unusual thoughts [60]. The subjective effects of vaporized marijuana are not significantly different from those of smoked marijuana [111, 112].

### **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:

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

Adverse events that will be collected during the protocol are:

- All Adverse Events and spontaneously reported reactions will be collected throughout the four-week period of marijuana self-administration for all three study arms (Stage 1, Stage 2 and Stage 3).
- Events requiring medical attention will be collected from the first experimental session through the subject's final assessment at the end of Stage 3.

- 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.
- All SAEs will be collected throughout the study starting from enrollment.
- 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, and during continued use of returned unused marijuana. After a participant completes Stage 2 or Stage 3, as applicable, and before the 12 month follow-up, participants may change medication identity or dose as their prescribing physician sees fit. Subjects in therapy may change therapy type or frequency as their therapist sees fit. 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 lead 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, during each weekly visit to the study site during all three study arms.

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 all 50 participants enrolled in Stage 1. The sponsor will examine the effects of 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 marijuana potency as one between-subjects variable, drug delivery method (smoking or vaporizing) as another between-subjects condition, 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 no significant effect of drug delivery method, and no interaction between drug delivery method and marijuana potency, then subsequent analyses will examine potency only.

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.

If there is a significant interaction between either condition and time of administration, or a three way interaction between potency, drug delivery method and time, 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.

If initial analyses find a significant effect of drug delivery upon CAPS score, or if there is an interaction between drug delivery and potency, then a between subjects/ within-subjects analyses of variance with substance delivery method as a between-subject variable, and potency as another between-subjects variable when applicable, and time of assessment as a repeated measure will be performed upon CAPS scores, with p. set at 0.05.

The sponsor will perform the same series of analyses upon PDS symptom severity scores at baseline, at four weeks of self-administration and at two weeks of marijuana discontinuation to see the effects of marijuana potency and drug-delivery method upon PTSD symptom severity. The sponsor will correlate PDS symptom scores at these times with Global CAPS scores drawn from the same points in time. If there is a significant effect of time of administration, then an analysis including all six weekly administrations will be performed.

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, during each weekly evaluation) as a repeated measure with probability of rejecting the null hypothesis set at 0.05, and performing post-hoc tests upon any interactions. Similar analyses will be performed to examine PSQI scores at baseline, at four weeks of marijuana self-administration and two weeks after cessation of use. If an interaction between potency and time of administration or a three-way interaction between potency, drug delivery and time of administration is found, additional comparisons will examine this interaction between potency and time of administration.

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.

The sponsor will perform a repeated measures analysis of PDS severity, BDI-II, scores at baseline and at each of the six Stage 1 weekly assessments, with marijuana potency as a between-subjects analysis and with p. set at 0.05. If there is an effect of drug delivery upon any assessment or measure, or if there is an interaction between potency and drug delivery, then another repeated measures analysis will examine the effects of drug delivery and potency on PDS, BDI-II, PSQI and GAF scores at baseline and during the first through sixth weekly evaluations to detect any changes in symptoms of PTSD or depression, sleep quality or psychological health over this time period.

Since participants are permitted but not required to use the contents of two rolled cigarettes per day, variation in use is expected to occur. The sponsors will address self-titration by performing a secondary analysis of covariance with average monthly weight of consumed marijuana as the covariate upon symptoms of PTSD, depression, sleep quality and general life function. Weight of consumed marijuana will be defined as the difference between the weight of the returned material from the weight of the original allotment. This analysis will be able to take into account different levels of self-titration within the framework of a dose-response study. To further address the potential impact of self-titration upon symptoms of PTSD, depression, psychiatric symptoms and general well-being, weekly analyses of covariance will be conducted with weight of marijuana consumed per week serving as the covariate.

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 three potencies upon CAPS and PSQI scores. A similar repeated measures ANOVA will be performed on the secondary measure of PTSD symptoms, and measures of depression, general psychological function, and psychiatric symptoms, with potency as a between-subjects factor and time (baseline, at every weekly evaluation during self-administration and cessation of use) as a repeated measure. If an initial comparison indicates no significant differences in effects seen for each relevant potency (6% THC, 6% THC/6% CBD and 12% THC) during Stage 1 and Stage 2, then a within-subjects analysis of variance treating potency as a within-subjects factor and time as a repeated measure will be performed.

The sponsor will compare presence and level of blood cannabinoids during each assessment across the four-week period of self-administration, and during discontinuation 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. A similar analysis using drug delivery as between-subjects factor will also be performed. If it is found that drug delivery has a significant effect on blood cannabinoid levels, then an analysis comparing potency and drug delivery as between-subjects factors will be performed for each time point, with p. set at 0.05. Any interactions of drug delivery and potency are detected, further analysis, including post-hoc tests, will be used to determine the nature of that interaction, and corrections may be made for considering each time point separately.

The sponsor will compute descriptive statistics from the ESAMS, including mean value for each item across four weeks of use and peak value for each item per week when applicable, 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 vital signs, BSI and C-SSRS scores at each time point and Adverse Events, as described under Adverse Event Collection. Vital signs include systolic blood pressure, diastolic blood pressure, heart rate (pulse) and body temperature. 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 compute difference scores between baseline and each subsequent BSI Global Severity, anxiety and psychoticism score to create difference scores for each of six post-baseline time points. BSI difference scores from Stage 1 will be compared with a between-subjects analysis of variance, with potency condition as a between-subjects factor to detect any significant effect of marijuana potency upon psychiatric symptoms and psychosis.

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 [123] 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 0.6, 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, and 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 or co-investigators are 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 or co-investigator administering the consent process.

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, the portable video camera and lockable storage box, 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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