I. Executive Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)3 non-profit, is the study sponsor, working in collaboration with the University of Colorado, University of Pennsylvania, Johns Hopkins University, and Dr. Sisley. The proposed pilot Phase 2 outpatient randomized, placebo-controlled, triple-blind, crossover, multi-site study will gather preliminary evidence of the safety and efficacy of 4 potencies of smoked marijuana to manage chronic, treatment-resistant posttraumatic stress disorder (PTSD) symptoms among 76 US veterans. The study is the first randomized controlled trial (RCT) to test the therapeutic potential of smoked marijuana and its components as a treatment for PTSD. This study is essential for understanding potential risks and therapeutic benefits of marijuana for PTSD patients. Results will provide physicians, patients, scientists and regulators in Colorado and elsewhere with critical knowledge regarding whether marijuana benefits individuals with PTSD, whether adverse consequences occur, and the impact of cannabis type on outcomes. It will help guide decisions about whether PTSD should be an approved indication for medical marijuana.

After initial screening, including two weeks of verified non-use, smoked marijuana containing 4 different ratios of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) will be tested in 3 distinct study stages. In Stage 1, participants will be randomized to one of four marijuana conditions based on cannabinoid content: High THC/Low CBD (*High THC*), Low THC/High CBD (*High CBD*), High THC/High CBD (*THC/CBD*) or Low THC/Low CBD (*placebo*). Stage 1 will last for 3 weeks, during which time participants will be allowed to self-administer up to 1.8 g of marijuana daily. Following a 2-week washout period of biochemically confirmed marijuana abstinence; participants will be randomized to one of the 3 "active" marijuana conditions (High THC, High CBD, and THC/CBD) for Stage 2. Drug assignment for Stage 2 will be conducted such that the drug condition will be different than that assigned in Stage 1. Stage 2 will permit a within-subjects comparison of symptom change as a function of marijuana type, including differences in personal marijuana type preference. To discourage diversion of unused marijuana and encourage participant use of in a naturalistic ad-lib fashion, unused marijuana from Stage 1 and 2 will be offered to participants in an optional Stage 3 that will occur during the first 2 months of a 6-month follow-up period. Study duration for each participant will be eight months. Marijuana will be obtained from the NIDA drug supply program, composition will be laboratory verified, and it will be stored in compliance with DEA regulations.

Clinical and statistical significance will be determined by prospective analysis of study data, including marijuana type comparison with respect to objective observer-blind Clinician Administered PTSD Scale (CAPS-5) diagnosis and symptom severity determined at Baseline and end of Stage 1 (Primary Aim). The study is powered to have 82% chance of detecting a medium effect size of 0.4 or greater [1]. Specifically, an "intent to treat" (ITT) analysis using generalized linear modeling (GLM) will be employed to examine change in CAPS scores as a function of marijuana type [2]. Secondary outcomes will include sleep quality, assessed objectively (i.e., Actigraphy) and via self-report, as well as co-occurring psychopathology and psychosocial functioning. Adverse effects will be ascertained at least weekly throughout the active treatment and discontinuation phases of the study based on clinician assessment and participant self-reports. Cannabinoids and biomarkers of inflammation in blood and urine will be measured as secondary outcome measures and to confirm self-reported compliance with required periods of abstinence. Study results will provide novel and heretofore-unknown information regarding the safety and effect size of various doses (and ratios of THC/CBD) compared to placebo among veterans suffering from chronic, treatment-resistant PTSD.

II. Description of Key Personnel

Marcel O. Bonn-Miller, PhD, Coordinating PI, is a Research Health Science Specialist at the National Center for PTSD and Center for Innovation to Implementation at the VA Palo Alto Health Care System as well as Center of Excellence in Substance Abuse Treatment and Education at the Philadelphia VAMC, and Adjunct Assistant Professor in the Department of Psychiatry at the University of Pennsylvania Perelman School of Medicine. He received his B.A. and Ph.D. in Clinical Psychology from the University of Vermont and was a Postdoctoral Fellow at Stanford University School of Medicine. Dr. Bonn-Miller has dedicated his career to understanding the interrelations between cannabis use and PTSD symptomatology, with the aim of informing intervention and prevention strategies. Dr. Bonn-Miller is internationally recognized as a leading expert in the study of cannabis use among individuals with PTSD, with emphasis on a military veteran population. He has served as PI or Co-I on dozens of grants varying in focus from experimental laboratory-controlled to prospective outcome studies, including a VA Career Development Award. Approximately 49 of his 96 peer-reviewed empirical publications have investigated cannabis comorbidity, most with a focus on PTSD. The proposed study is a logical extension of his work demonstrating coping-oriented cannabis use, including use for alleviation of sleep problems, among veterans suffering from PTSD. Given his expertise, resources, collaborations, and extensive experience, Dr. Bonn-Miller is uniquely positioned to serve as Coordinating Principal Investigator for the proposed project overseeing the successful completion of the grant. Dr. Bonn-Miller's clinical and veteran-centered expertise complements expertise of the site PIs. His established relationships with VA leadership will ensure findings are published in high-impact academic journals and disseminated to key stakeholders within the VA Health Care System.

Paula Riggs, MD, Co-Investigator and Senior Scientific Advisor, has degrees from the University of Colorado, Denver (UCD) (B.A., M.A.) and the UCD School of Medicine (M.D.) where she also completed her post-doctoral training in child psychiatry. She is currently a Professor in the Department of Psychiatry, School of Medicine, at UCD, and Director, Division of Substance Dependence at the UCD School of Medicine since 2011. Dr. Riggs is a board-certified adult and child/adolescent psychiatrist with qualifications in addiction psychiatry. Dr. Riggs has extensive experience in clinical trial design, methodology, and implementation. She conducted the first RCTs of combined pharmacotherapy and behavioral interventions for adolescents, and is internationally recognized for her treatment research and clinical expertise in treating adolescents with co-occurring psychiatric and substance use disorders. She has been the PI on six NIDA-funded grant awards, including a recently completed NIDA R01, a randomized, placebo controlled trial of bupropion for ADHD in adolescents with substance use disorders. She was also the PI of a multi-site trial conducted in the NIDA Clinical Trials Network (CTN). In addition to her own federally funded clinical trials, she chaired the Protocol Review Committee in the NIDA CTN for two years and served as a standing member of the NIH Scientific Review Group (NIDA-E) for more than 10 years. She has served on the editorial board and was an Associate Editor of the Journal of the American Academy of Child and Adolescent Psychiatry. As a former CTN Principal Investigator, Dr. Riggs also consulted on the development, design, methodology, and implementation of numerous multi-site trials conducted in the NIDA CTN. Dr. Riggs will play a crucial role in ensuring the highest standards of scientific integrity are maintained throughout this study.

Ryan Vandrey, PhD, Site PI at John Hopkins University School of Medicine, is an experimental psychologist with degrees from the University of Delaware (BA) and University of

Vermont (PhD). He completed his post-doctoral training at Johns Hopkins University and is currently an Associate Professor in the School of Medicine at the Behavioral Pharmacology Research Unit (BPRU). He has received multiple NIH research grants, been contracted to conduct research for the Substance Abuse and Mental Health Services Administration (SAMHSA), and been a Co-I on projects for the National Cancer Institute (NCI) and pharmaceutical industry clinical trials. Dr. Vandrey has authored over 30 publications in peer-reviewed scientific journals and 8 book chapters, is currently a member of the NIH IRB for addiction research, and has served as advisor to the State of Maryland on development of medical cannabis and legislation regarding scheduling of synthetic drugs. Dr. Vandrey has extensive research experience involving evaluation of the acute and chronic effects of cannabinoids, and in the conduct of multi-site clinical trials. His laboratory is fully equipped for conducting the proposed study procedures and he has extensive experience managing clinical research with controlled substances. This includes laboratory studies characterizing the cannabis withdrawal syndrome that occurs in a subset of individuals following abrupt cessation of heavy cannabis use, and evaluating acute and chronic effects of cannabis and THC delivered via different routes of administration. Dr. Vandrey's research includes assessments of subjective drug effects, physiological measures, subjective and objective measures of sleep, cognitive performance effects, and pharmacokinetic biomarkers of cannabinoid exposure. He has also been collaborating with Drs. Bonn-Miller and Babson for the past 2 years evaluating the interaction of cannabis and sleep among individuals with PTSD. He is an internationally recognized expert on cannabis behavioral pharmacology who can advise the research team on study design, delivery and dissemination of findings.

Suzanne Sisley, MD, Site PI in Arizona, has degrees from Arizona University (B.S.), and the University of Arizona, Tucson (M.D.). She completed post-doctoral residencies in internal medicine and psychiatry at Good Samaritan Regional Medical Center in Phoenix, AZ. She is an experienced board-certified adult psychiatrist with expertise in telemedicine. For three years, she worked with PTSD patients as a psychiatrist at the Phoenix VA. For over 14 years, she has provided psychiatric evaluation and medication monitoring via telemedicine and developed novel applications of telemedicine at the Arizona Telemedicine Program and as Director of Telemedicine at the Scottsdale Treatment Center. For the past nine years, she has served at the University of Arizona College of Medicine as attending physician for a large outpatient adult psychiatry clinic with over 1,200 cases a year. She provided direct supervision of adult crisis cases in psychiatric emergency rooms and urgent care centers across Arizona. For three years, Dr. Sisley served as Sub-I in a series of Phase 3 and 4 clinical trials conducted at Pivotal Research Centers performed on novel psychoactive drugs examining the range of physiological and psychological effects of administering study drugs on adults. Dr. Sisley has invested the last four years in obtaining approval and funding for the proposed study, and is fully committed to seeing this study through completion in service of the 600,000 veterans in Arizona.

Amy Emerson, BS, MAPS' Director of Clinical Research, brings 19 years of pharmaceutical development and research experience in Phase 1 through Phase 3 RCTs. Her professional at Novartis, Chiron and other pharmaceutical companies experience spans various fields including vaccines, three of which are approved as new biologics. Over the last 11 years Amy has built MAPS' clinical department and managed the PTSD clinical development program. Amy ensures that MAPS' drug development studies meet ICH/GCP standards, are able to pass FDA and DEA audits, and meet all regulatory reporting requirements.

III. Narrative/Research Plan

A. Background & Significance

Significance*:* This pilot study will gather preliminary evidence of the safety and efficacy of four types of smoked marijuana to manage chronic, treatment-resistant PTSD among veterans. By working with chronic treatment resistant veterans, we address a national emergency and limit variability at the potential expense of generalizability. Further research will be needed to determine if these results will apply to other groups of PTSD sufferers. Smoked marijuana will be tested in two stages of three weeks each (Stage 1 and Stage 2), with two-week cessation after each stage, verified by blood/urine cannabinoid analysis. The study will produce preliminary evidence of the differential efficacy of three distinct marijuana potency types: High THC/Low CBD (*High THC*); Low THC/High CBD (*High CBD*); High THC/High CBD (*THC/CBD*) in comparison to a placebo control (Low THC/Low CBD), and will help elucidate whether the ratio of THC to CBD is a significant factor in the attenuation of PTSD symptoms. This study is critically important for understanding the potential risks and benefits of marijuana as a treatment for PTSD and can inform the development of larger randomized controlled clinical trials. *Ad-lib* self-administration of smoked marijuana with a range of THC and CBD ratios will be used in this study to provide a naturalistic comparison that is generalizable to what many veterans are currently using to manage PTSD symptoms in states with legalized medical marijuana. Anecdotal reports from Veterans Alliance for Medical Marijuana (VAMM) indicate that veterans prefer a balanced THC to CBD intake for management of PTSD symptoms. Results will provide information regarding marijuana dosing, composition, side effects, and specific areas of benefit to clinicians and legislators considering marijuana as an acceptable treatment for PTSD. This study will also provide information on the predictive value of selected biomarkers of inflammation, and effects of marijuana potency upon these biomarkers as a measure of PTSD treatment response.

Specific aims:

Primary aim: Compare 4 types of smoked marijuana (High THC, High CBD, THC/CBD, and Placebo) on PTSD symptom severity during 3-weeks of *ad-libitum* self-administration during Stage 1. We hypothesize that those receiving High THC, High CBD, and THC/CBD marijuana will have reduced PTSD and associated symptoms of anxiety, depression, and insomnia, and improved psychosocial functioning compared with those receiving placebo.

Secondary aims:

1. Evaluate whether the ratio of THC to CBD in marijuana differentially affects PTSD-related clinical outcomes. We hypothesize that THC/CBD will be superior to High THC and High CBD.
2. Evaluate whether markers of inflammation (C-reactive Protein (CRP), Interleukin-1beta (IL-1β), and Interleukin-6 (IL-6)) levels in blood predict PTSD severity at baseline and treatment outcome as a function of marijuana dose. We hypothesize that markers of inflammation will have predictive power and will correlate with PTSD-related outcomes.
3. Evaluate the effects of smoked marijuana among individuals with PTSD in both controlled laboratory and outpatient settings. We hypothesize that High THC and THC/CBD marijuana will produce greater subjective ratings of intoxication and side effects compared with High CBD and Placebo, and that adverse events attributable to marijuana will be mild and uncommon.

Background: 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% [3, 4]. Incidence of PTSD in U.S. Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans is as high as 18% [3]. PTSD is typically a

chronic illness [5], associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide [5, 6]. A significant percentage of PTSD patients fail to respond adequately to established treatments [7], or respond in ways that are statistically significant but clinically inadequate [8]. These findings suggest there is substantial need for innovative treatments for PTSD.

Given evidence highlighting marijuana as a possible means of improving sleep [9], with retrospective reports of marijuana use and associated psychopathology indicating reductions in PTSD symptoms after use [10], it is not surprising that population-based studies have found PTSD to be associated with increased marijuana use [11]. These reports support further investigation into marijuana as a potential PTSD treatment. In addition, whole plant marijuana contains two major active constituents, THC and CBD, in addition to numerous other compounds. Research indicates that THC acts upon receptors in brain areas involved in memory and fear processing, and preclinical studies in rodents suggest cannabinoids reduce fear [12, 13]. Research in mice found that CBD was comparable to the antidepressant imipramine in tests of antidepressant-like effects [14]. Further, CBD may oppose anxiogenic effects of THC in humans [15, 16], and a naturalistic study found smoking marijuana with higher CBD levels was associated with less memory impairment and lower anxiety during intoxication [17]. It appears that CBD attenuates amygdalar activation in response to facial expressions of fear in healthy subjects [18], a potentially beneficial effect for people with PTSD, who may exhibit enhanced amygdalar reactivity to fearful faces [19]. These studies suggest that it is worth investigating the effects of marijuana that varies in THC and CBD content on the ability to suppress symptoms of PTSD.

Another potential mechanism by which marijuana may confer benefit in the treatment of PTSD is reduced inflammation. A longitudinal study in U.S. Marines reported an association between higher pre-deployment levels of CRP as a predictor or risk factor for post-deployment development of PTSD and development of PTSD symptoms post-deployment [20]. In other research, reduction in PTSD symptoms following treatment with SSRIs is associated with a reduction in IL-1β [21], and women whose PTSD symptoms are in remission exhibit lower levels of CRP and IL-6 compared with those with current PTSD [22]. Further, a meta-analysis supported a link between IL-1β and IL-6 and exposure to trauma [23] and stress-related elevation in IL-6 may be higher with PTSD [22, 24]. Because both THC and CBD have potent anti-inflammatory and immunomodulatory properties [25, 26], marijuana use may have therapeutic benefit in PTSD treatment simply by reducing inflammation. We plan to assess biomarkers of inflammation at baseline and post-treatment to extend this important line of research evaluating whether these biomarkers can predict treatment response, and to investigate whether the anti-inflammatory properties of THC/CBD mediates the treatment effect marijuana on PTSD symptom expression.

Publication Plan: The investigators recognize the importance of communicating medical research and scientific data. The sponsor will work in close collaboration with the Coordinating PI and Co-investigators to implement the study, acquire, analyze, interpret data, and describe the results in line with requirements of top-tier peer-reviewed scientific journals and presentation of results at national scientific meetings. All study data will be in the public domain, with no claims of intellectual or proprietary property rights. The publication policy and budget will be included in each subcontract. In line with requirements for publishing, this study is powered to detect moderate differences between groups and includes the appropriate study design and statistical analysis methods to support this plan. All publications will follow the ICMJE (International Community of Medical Journal Editors) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, unless other guidelines are required by the

journal. Due regard shall be given to both investigators and MAPS' mutual legitimate interests, e.g., manuscript authorship, journal selection, and coordinating with other ongoing studies in the same field. All authors will have access to the statistical reports and tables and will be expected to provide substantial intellectual and scientific contributions to the manuscript.

References

1. Watts, B.V., et al., *Meta-analysis of the efficacy of treatments for posttraumatic stress disorder.* J Clin Psychiatry, 2013. **74**(6): p. e541-50.
2. White, I.R., J. Carpenter, and N.J. Horton, *Including all individuals is not enough: lessons for intention-to-treat analysis.* Clin Trials, 2012. **9**(4): p. 396-407.
3. Kessler, R.C., et al., *Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**(6): p. 593-602.
4. Resnick, H.S., et al., *Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women.* J Consult Clin Psychol, 1993. **61**(6): p. 984-91.
5. Kessler, R.C., et al., *Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**(6): p. 617-27.
6. Breslau, N., *The epidemiology of posttraumatic stress disorder: what is the extent of the problem?* J Clin Psychiatry, 2001. **62 Suppl 17**: p. 16-22.
7. Foa, E.B., et al., *A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims.* J Consult Clin Psychol, 1999. **67**(2): p. 194-200.
8. Committee on Treatment of Posttraumatic Stress Disorder, *Treatment of posttraumatic stress disorder: An assessment of the evidence*. 2008, Washington DC: National Academies Press.
9. Bonn-Miller, M.O., K.A. Babson, and R. Vandrey, *Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD.* Drug Alcohol Depend, 2014. **136**: p. 162-5.
10. Greer, G.R., C.S. Grob, and A.L. Halberstadt, *PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program.* J Psychoactive Drugs, 2014. **46**(1): p. 73-7.
11. Cougle, J.R., et al., *Posttraumatic stress disorder and cannabis use in a nationally representative sample.* Psychol Addict Behav, 2011. **25**(3): p. 554-8.
12. Patel, S. and C.J. Hillard, *Adaptations in endocannabinoid signaling in response to repeated homotypic stress: a novel mechanism for stress habituation.* Eur J Neurosci, 2008. **27**(11): p. 2821-9.
13. Pistis, M., et al., *Cannabinoids modulate neuronal firing in the rat basolateral amygdala: evidence for CB1- and non-CB1-mediated actions.* Neuropharmacology, 2004. **46**(1): p. 115-25.
14. Zanelati, T.V., et al., *Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors.* Br J Pharmacol, 2010. **159**(1): p. 122-8.
15. Bhattacharyya, S., et al., *Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology.* Neuropsychopharmacology, 2010. **35**(3): p. 764-74.
16. Crippa, J.A., et al., *Cannabis and anxiety: a critical review of the evidence.* Hum Psychopharmacol, 2009. **24**(7): p. 515-23.

17. Morgan, C.J., et al., *Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study.* Br J Psychiatry, 2010. **197**: p. 285-90.
18. Fusar-Poli, P., et al., *Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing.* Arch Gen Psychiatry, 2009. **66**(1): p. 95-105.
19. Rauch, S.L., et al., *Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study.* Biol Psychiatry, 2000. **47**(9): p. 769-76.
20. Eraly, S.A., et al., *Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk.* JAMA Psychiatry, 2014. **71**(4): p. 423-31.
21. Tucker, P., et al., *Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder.* Biol Psychiatry, 2004. **56**(2): p. 121-8.
22. Newton, T.L., et al., *Interleukin-6 and soluble interleukin-6 receptor levels in posttraumatic stress disorder: associations with lifetime diagnostic status and psychological context.* Biol Psychol, 2014. **99**: p. 150-9.
23. Tursich, M., et al., *Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis.* Transl Psychiatry, 2014. **4**: p. e413.
24. Gill, J.M., et al., *Women in recovery from PTSD have similar inflammation and quality of life as non-traumatized controls.* J Psychosom Res, 2013. **74**(4): p. 301-6.
25. Mechoulam, R., et al., *Cannabidiol--recent advances.* Chem Biodivers, 2007. **4**(8): p. 1678-92.
26. Rajavashisth, T.B., et al., *Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III.* BMJ Open, 2012. **2**: p. e000494.
27. Desrosiers, N.A., et al., *Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis.* Clin Chem, 2014. **60**(4): p. 631-43.

B. Capacity/Program Infrastructure

MAPS is the organizational entity sponsoring this study and is a 501(c)3 non-profit research and educational organization. MAPS currently has an open Investigational New Drug application (IND) #110513 for marijuana with the FDA and previous Public Health Services approval of the protocol. MAPS has been an international pharmaceutical sponsor since 2000, with experience in oversight of nine Phase 2 clinical trials of drug-assisted therapy using Schedule 1 controlled substances for PTSD, anxiety associated with life-threatening illness, and social anxiety. MAPS has experience sponsoring studies conducted by investigators in private practice and institutional settings. Results of three completed MAPS-sponsored studies with these controlled substances have been successfully published in peer-reviewed scientific journals with additional plans for publications upon completion of ongoing studies. MAPS-sponsored studies have successfully passed all DEA and IRB audits/inspections. MAPS employs two Medical Monitors to ensure sponsor oversight of safety issues and proper reporting per ethical and regulatory requirements; Dr. Michael Mithoefer, Board Certified in Psychiatry, Emergency Medicine, and Internal Medicine and Dr. Julie Holland, psychiatrist and editor of *The Pot Book:* A Complete Guide to Cannabis.

This multi-site study will be conducted at Johns Hopkins University, the Private Practice offices of Dr. Suzanne Sisley, and supported by PIs at the University of Pennsylvania and the University of

Colorado at Denver School of Medicine. Each Site PI will have adequate staff to support the study activities and will be responsible for oversight and ensuring compliance of their respective sites with the study protocol and all applicable requirements. The Coordinating PI, Marcel Bonn-Miller, Ph.D., will be responsible for oversight of the site PIs. Dr. Riggs will serve as the Senior Scientific Advisor for the study. MAPS will be responsible for project management, data monitoring and storage, drug accountability, and ensuring regulatory files are created and maintained per Good Clinical Practice (GCP) requirements. VA-trained independent raters, not part of any site team or MAPS, will be responsible for administering the primary outcome measure (CAPS-5) at the primary and secondary end points.

MAPS is the Coordinating Center and FDA sponsor, with responsibility for ensuring compliance with the highest standards of clinical research, study protocol, and federal regulations across sites. MAPS will design all study documents ensure consistency and compliance with regulatory requirements. As the Coordinating Center, MAPS will develop and implement the Monitoring Plan, multicenter randomization system linked to Schedule 1 drug accountability, provide a centralized Title 21 CFR-compliant Electronic Case Report Form (eCRF) database to collect study data, and will manage the overall project budget. MAPS will manage enrollment targets and facilitate discussions with Medical Monitors and Site PIs about inclusion/exclusion, deviations, and safety. The study will be managed in line with the Phase 2 Marijuana Clinical Development Plan.

The Coordinating PI and MAPS project manager will visit all sites to ensure site readiness and training prior to study commencement. Each site will be equipped with laboratory space for conducting patient interviews and laboratory assessments, and a dedicated indoor smoking chamber that allows for the administration of smoked cannabis. All marijuana will be packaged at the Johns Hopkins research pharmacy and the required amount will be shipped to the Arizona site for storing and dispensing according to DEA requirements. All Investigators and Study Coordinators will attend the central Investigator Meeting with the Medical Monitors and Sponsor staff for training on the protocol, procedures, safety considerations and infrastructure. The collaborative structure of this multi-site study will be established to ensure uniformity across sites. Throughout the study, the sponsor will meet regularly with the Investigators, and the study monitor will continuously monitor data remotely and conduct in person routine monitoring visits. All sites will complete remote data entry into a centralized FDA compliant electronic database. MAPS will ensure the database is FDA and IRB auditable at any time. All key personnel will be involved in final data clean up and database lock. A qualified statistician will perform data analysis with input and review from key personnel. Close out visits will be preformed at each site and the sponsor will manage the Final Clinical Study Report process to ensure reporting as required by FDA. The publication plan will be managed by the Coordinating Investigator to ensure timely dissemination of study data.

C. Research Design and Methods

Overview: The proposed Phase 2 randomized, placebo-controlled, triple-blind, crossover, multi-site study will assess the safety and efficacy of 4 types of smoked marijuana to manage chronic, treatment-resistant PTSD symptoms among 76 veterans in an outpatient setting. Ad-lib self-administration will be permitted up to 1.8 grams daily. Stage 1 will provide information about the efficacy of active marijuana versus placebo. Nineteen participants will be randomized to one of four marijuana types, each containing different ratios of THC to CBD, and obtained through the NIDA drug supply program: High THC, High CBD, THC/CBD or placebo. Stage 2 conditions include High THC, High CBD, and THC/CBD with participants randomized to a different

condition than assigned in Stage 1. Stage 2 will permit a within-subjects comparison of symptom change as a function of marijuana potency, including differences in personal preference (by self report). To discourage the risk of diversion of unused marijuana and encourage participant use of marijuana in a naturalistic ad-lib manner, unused marijuana from Stage 1 and/or 2 will be offered to participants in an optional Stage 3 study period lasting up to 2 months. Long-term outcomes will be assessed at six months after end of Stage 2. Study duration for each participant is eight months.

Authorization: MAPS has opened IND #110513 for marijuana with the FDA. The initial protocol received approval by the FDA's Division of Psychiatry Products and FDA's Controlled Substances Staff. There are no pending comments on the initial design of the study, which was placed on a clinical hold pending receipt of information from NIDA about the marijuana that will be used in the study. The initial protocol has also been approved by the Public Health Service (PHS) for purchase of marijuana from NIDA, after the PHS determined that the originally proposed investigator Dr. Sisley is qualified and the proposed research has merit. The University of Arizona Institutional Review Board (IRB) also approved the initial protocol. A protocol amendment to add an additional site at JHU, to change the location of the study in Arizona, and to implement some of the optional PHS recommendations about design elements will be re-submitted to the FDA, PHS, and each site IRB for proper regulatory and ethical approvals prior to initiating the study. DEA approval customarily comes after all the other approvals have been obtained. NIDA's approved source is currently growing requested marijuana for the study and the manufacturing information will be submitted to FDA upon receipt, currently projections anticipate availability in April –June, 2105. We understand that should this grant request be approved, it would be contingent on our obtaining all the required regulatory approvals.

Protection of Human Subjects: FDA submission and IRB applications specific to each site will be submitted upon completion of the protocol amendment. Site staff will receive HIPAA and GCP training; all safety data will be monitored and reviewed by the sponsor Medical Monitor and Coordinating PI. All sites will use an FDA and IRB-approved Informed Consent and will follow GCP requirements for consenting. The Site PI, Independent Rater, and/or designated Sub-I will be responsible for clinical evaluation and introductory sessions intended to screen out any participants that satisfy exclusion criteria (see Data Safety and Monitoring section for exclusion criteria). MAPS has developed an IRB-approved safety plan for responding on a 24-hour basis to any psychological crisis, with management of participants who experience sequelae and appropriate referral in consultation with investigators and medical staff at each site.

Measurements (clinical/laboratory, surveys, questionnaires):

Primary Outcome Measure: The Clinician-Administered PTSD Scale based on DSM-5 (CAPS-5) is a semi-structured clinical interview administered by a blinded Independent Rater and is used to assess PTSD symptom severity and diagnostic status of PTSD. The CAPS has been a gold standard measure of PTSD symptoms. The previous version, CAPS-4, was used as the primary outcome measure to obtain FDA approval for Zoloft and Paxil as medications for PTSD

Secondary Outcome Measures: The PTSD Checklist is a 20-item self-report questionnaire in which respondents indicate the presence and severity of PTSD symptoms, derived from the DSM-5 symptoms of PTSD and an index of overall PTSD symptom severity. The Inventory of Depression and Anxiety is a 64-item self-report questionnaire of depression and anxiety symptoms. The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire of self-reported sleep quality over the preceding month. The PSQI-Addendum is a 7-item addendum for the PSQI that assesses disruptive

nocturnal behavior specific to PTSD. For Actigraphy (ACT), the wActiSleep+Monitor actigraphy device will be used as a noninvasive objective laboratory assessment that provides accurate and reliable measurements of sleep and wakefulness. The Inventory of Psychosocial Functioning is an 80-item questionnaire that that was developed for use among individuals with PTSD. The Drug Effect Questionnaire (DEQ) is a 15-item VAS questionnaire that participants will use to report subjective drug effects during marijuana self-administration sessions in the laboratory.

Process Measures: The Daily Substance Use Diary will be used to track daily use of marijuana and substances including other drugs, alcohol, and tobacco as an electronic data capture form completed on a mobile wireless device. Weight of daily marijuana usage will be measured in the laboratory to support these data. The Long-Term Follow-Up (LTFU) questionnaire is a sponsor-developed self-report questionnaire 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 the final Stage 2 visit. Blood and urine cannabinoid levels will be analyzed using a combination of qualitative EIA rapid test kits and quantitative analysis via GC/MS or LC/MS/MS in order to confirm compliance with the protocol (e.g. use of assigned marijuana type and abstinence during washouts). Biomarkers of inflammation in blood will be assessed in duplicate with appropriately sensitive, specific and validated enzyme-linked immunosorbent assay (ELISA) for CRP, IL-1β, and IL-6.

Safety Measures: The Cannabis Use Disorders Identification Test-Revised is an 8-item self-report questionnaire used to assess problematic marijuana use within the past 6-months. The Marijuana Withdrawal Checklist (MWC) will be used to assess the presence of marijuana withdrawal symptoms. The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-administered interview of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial. The Experiences with Self-Administration of Marijuana Survey (ESAMS) is a self-report measure of perceived adverse events that occur during self-administration of marijuana. As ongoing clinical measures of safety, adverse events, concomitant medications and therapy will be monitored and collected in the eCRF. Vital signs will be measured in the laboratory on a weekly basis.

Site Selection, Recruitment & Subject Eligibility*:* The two sites for this study were selected based on site experience, and ability to recruit diverse participants. Ability to recruit and appropriateness of subject population was assessed based on the demographic data presented in Table 1.

Table 1. Demographic Data on Veterans For Sites

Site	N	Mean Age	Married	Female	Black	White	Asian	Hispanic	American Indian	OEF/ OIF
JHU	4494	54	46%	11%	43%	51%	1%	2%	0%	20%
AZ	8869	52	51%	9%	7%	79%	2%	13%	2%	26%

In addition, the sites are located in medical marijuana states. If participants found marijuana to be useful in managing their PTSD symptoms during the study, and chose to obtain medical marijuana afterwards, residing in a state where medical marijuana is legal with physician recommendation would reduce their risk of arrest and/or incarceration after the study.

About 150 veterans with chronic, treatment-resistant PTSD will be recruited through printed ads, Internet ads, referrals from other psychiatrists, psychotherapists or physicians, and through word of mouth to ensure enrollment and retention of 76 participants through the primary endpoint. Eligible participants may either be marijuana naïve or current marijuana users, as long as they are willing

and able to stop using non-study marijuana for two weeks prior to Baseline and, if enrolled, through the end of Stage 3. Only participants with stable medication or therapy for a period of at least 1 month will be enrolled. Participants must be able to give adequate informed consent and be able to attend all required visits. Participants must pass an initial urine drug screen for opiates (unless prescribed), methamphetamine, cocaine and amphetamines at the start of screening. Participants' will received a non-coercive amount of compensation for time/effort required to perform assessments but not for the treatment. Participants must have no contraindications for study participation and meet all protocol inclusion and exclusion criteria at baseline.

Subjects and Procedures: After an initial phone screen, potential participants will have an in-person visit for the informed consent process. Participants will undergo initial screening based upon study inclusion/exclusion criteria (see Measurement section, above). Upon confirmation of initial eligibility, potential participants who test positive for active marijuana use will be required to stop using for a period of two weeks. Compliance will be assessed as a condition of enrollment by pre and post blood and urine cannabinoid analysis. The primary method for determining compliance will be qualitative urine cannabinoid screening at the end of the 2-week period. Those who have a negative screen will be considered compliant. For those who qualitatively still test positive (likely for individuals who use marijuana daily prior to study initiation), we will use algorithms developed by Huestis and colleagues that can reliably differentiate new marijuana use from residual cannabinoids between 2 time points of a defined duration [27]. Withdrawal symptoms and problems associated with marijuana use will be monitored in candidates using marijuana prior to the study to assess potential substance use disorders at screening. After the washout, a blinded Independent Rater will assess potential participants via telemedicine for DSM-5 defined PTSD of at least moderate severity with the CAPS-5.

After randomization, at the beginning of Stage 1 and Stage 2, participants will have two four-hour introductory marijuana smoking sessions on consecutive days in order to obtain systematic prospective data on the subjective and physiological effects of smoked marijuana in a controlled setting, and to assess and manage the risk of anxiety reactions that may occur during marijuana self-administration later in the study. The two introductory sessions will provide training on self-administration procedures under observation and be monitored for safety. Participants will learn how to record their marijuana use with a portable tablet supplied by the study site to study use patterns and as a means to prevent diversion. Participants will report subjective drug effect ratings using the DEQ and vital signs will be obtained at specified time points for 3 hours after smoking. During these sessions, participants will receive information about what to expect after smoking marijuana and discuss methods for documenting and managing any side effects. This will include information about community support, breathing strategies, as well as what rescue psychotherapy or medications are available for participants to use if needed. Participants who have a persisting anxiety reaction during these supervised sessions can choose to not continue in the study, or may be withdrawn from the study based on the clinical judgment of the Investigator and medical team.

Upon completion of the second introductory session, study staff will provide participants with a lockable box and combination for secure storage of study drug, the Actigraphy wristwatches for objective measures of sleep, and the portable tablet for completing electronic daily diaries, self-report forms, and video recording. Participants will provide study staff with the contact information of a community observer, who will provide an independent opinion regarding the subject's substance use, self-administration of study marijuana, and the likelihood of diversion. Weekly marijuana will be provided in seven individually labeled packages of 1.8 grams per day.

The active phase of the study encompasses Stage 1 (3 weeks), Cessation 1 (2 weeks), Stage 2 (3 weeks), and Cessation 2 (2 weeks). There will be weekly in-person visits during each of the three weeks of self-administration for Stage 1 and Stage 2 to monitor participant well-being, assess adverse events and marijuana use, and self-report records. At the start of each week of self-administration, prior to receiving the next week's supply, there will be a urine drug screen, and measurement of vital signs. Any unused marijuana from each weekly allotment will be returned to the investigator or designee to be weighed and accounted for at the end of the week prior to receiving the next weekly supply. Participants of childbearing potential will be required to complete weekly pregnancy testing, in addition to use of effective contraception. Using the Daily Substance Use Diary, participants will record estimated amount smoked, time, frequency, and route of marijuana self-administration, as well as concomitant use of nicotine, alcohol, or other drugs. The ESAMS will be completed daily after self-administration to capture side effects. Participants will be required to video record each self-administration, and review of video recordings to confirm use by subject will be required before receiving the next weekly supply. The site staff will initiate a brief daily phone contact for the first week of the study and weekly during the active phase of the study to monitor for safety. Participant suicidal ideation will be assessed weekly with the C-SSRS, and daily if results are above a zero and indicate development of suicidal ideation. Weekly evaluations will include the PCL-5, IDAS, IPF, CUDIT-R, and PSQI. During each evaluation, Actigraphy wristwatch data will also be downloaded (see Measures, above). Study staff will verify participant identity, safety, and compliance through review of self-report forms and video recordings, as well as telephone contact reports. Analysis of blood/urine cannabinoids will be conducted before and after self-administration and cessation periods. At Baseline and end of Stage 1, Cessation 1 and end of Stage 2, additional blood samples will be collected for analysis of inflammation markers.

At the end of Stage 1, primary endpoint measures will be administered. The independent rater will assess symptoms of PTSD on the CAPS-5 via telemedicine and self-reported symptoms of anxiety, depression, withdrawal, sleep quality, and psychosocial functioning will be assessed. At the conclusion of these assessments, the two-week cessation period will begin. An identical assessment battery and procedure will occur at Stage 2 baseline and at the end of Stage 2. In Stage 2, participants will undergo the same sequence of events and procedures described for Stage 1.

During the optional Stage 3, participants who choose to receive unused marijuana from Stage 1 and/or Stage 2 via weekly supply will continue to video record smoking of the remaining marijuana and complete the Daily Substance Use Diary, ESAMS, and CSSRS to monitor safety. Participants will continue weekly pregnancy testing, in addition to use of effective contraception. Stage 3 may last up to two months, if any marijuana is remaining at this time it will be accounted for and retained by the site for final accountability and disposal per DEA standard procedures.

There will be a long-term follow up assessment conducted via telemedicine six months after the end of Stage 2. Participants will complete the long-term follow-up questionnaire concerning their mental health, substance use, and changes in PTSD therapies and medications. An Independent Rater will administer the CAPS-5. Participants will complete the PCL-5, PSQI, IDAS, IPF, CUDIT-R, C-SSRS, MWC, and 1 week of actigraphy monitoring.

Randomization and Blinding: To achieve sufficient statistical power, and account for dropouts about 116 subjects will be randomized in a 1:1:1:1 ratio across participating sites and the four groups High THC, High CBD, THC/CBD, or Placebo treatment groups based on sequential order of enrollment into the study. The assigned randomization code will correspond to a blinded

treatment number (kit number). Randomization and enrollment will halt when 76 subjects complete stage 1 (N=19 per group). In order to maintain the blind for participating subjects, site staff, independent raters, and sponsor staff, a central electronic database will be utilized for randomization based on validated computer-generated lists. The Stage 1 randomization list will utilize blocks to balance treatment assignments. Stage 2 randomization will utilize multiple validated randomization lists that re-randomize subjects in a 1:1 ratio to new treatment assignments excluding the previously assigned Stage 1 dose and the placebo condition.

Table 1. Subject Distribution by Potency and Stage

Stage 1: N= 76 (up to 116) Subjects randomized 1:1:1:1 to following 4 dose arms				
	High THC	High CBD	THC/CBD	Placebo
Stage 2: Subjects re-randomized to following dose arms				
Stage 1 arm:				
Placebo	High THC	High CBD		
High THC		High CBD	THC/CBD	
High CBD	High THC		THC/CBD	
THC/CBD	High THC	High CBD		

Intervention, Dose Selection: Four types of marijuana obtained through the NIDA Drug Supply Program, that vary in ratios of THC to CBD, will be used: High THC, High CBD, THC/CBD, or placebo. We are requesting concentrations of 12-15% for "High" and <2% for "Low," but actual potency will be determined once the marijuana is actually grown and harvested by NIDA. *Ad-lib* self-administration will be permitted up to a maximum of 1.8 grams/day.

The doses of marijuana (excluding placebo) were chosen because they contain a range of THC and CBD ratios and potencies generalizable to what many veterans are currently using to manage PTSD symptoms in non-clinical settings in states with legalized medical marijuana. The final doses and potency to be tested are subject to availability through the NIDA Drug Supply Program. Prior to the study start laboratory testing of the marijuana will be completed to verify chemical composition of each potency group. The active doses are expected to produce all the commonly reported subjective effects of marijuana. The physiological effects are expected to be tolerable based on previous observational studies in the literature. The placebo is expected to produce minimal side effects, without the range of psychological and subjective effects seen in active doses.

Statistical Analysis: Bonnie Dumas PhD, Assistant Professor at the Medical University of South Carolina College of Nursing, will serve as an independent biostatistician for the study. Key Personnel, MAPS, and the biostatistician will agree on a Statistical Analysis Plan at the beginning of the study. The biostatistician will perform an ITT analysis using repeated measures Analysis of Covariance (ANCOVA) analysis to compare demographics and all available data from weekly assessments from all subjects who are randomized, even if they withdraw from the allocated treatment prior to the primary endpoint [2]. Distribution of treatment dropouts will be examined by condition and if unequal, we will control for group assignment.

Briefly, the sponsor will judge the clinical and statistical significance of the study based on the primary analysis of observer-blind CAPS-5 data collected at Baseline and end of Stage 1 using ANCOVA with marijuana potency as a between-subject factor and time of assessment as a within-group factor. A similar secondary analysis will also be performed with Stage 2 data using Stage 1 data as a covariate for each outcome measure if effects of marijuana potency are detected in Stage 1. Effect size will be estimated based on all outcome measures using Cohen's techniques. The

biostatistician will conduct secondary analyses of weekly assessments of PCL-5, PSQI, IDAS, IPF, CSSRS, MWC, CUDIT-R, DEQ and ACT scores using repeated measures ANCOVA. Statistical significance will be determined based on $\alpha < .05$ for all tests other than the PCL-5, which will be a secondary measure for self-reported PTSD symptoms intended to support the CAPS-5.

Quantitative levels of THC, CBD and their metabolites will be assessed in order to ascertain whether participants were compliant with only using the marijuana assigned to them during the study. Correlational analyses will also be conducted between biological cannabinoid levels and clinical outcomes to determine whether there is a dose-effect relation between cannabinoid exposure and clinical response.

Prognostic value of CRP, IL-1β and Il-6 will be examined by two regression analyses, one between biomarker values gathered at Baseline and the primary endpoint CAPS-5 global severity score, and another regression analysis between biomarker values collected after two weeks of cessation and the CAPS-5 global severity score and at the end of Stage 1.

Qualitative safety analyses will examine daily ESAMS and Substance Use Diaries by summary tables listing maximum severity and duration, as well as concomitant medications/therapies and adverse events with frequencies and percentages tabulated overall and by potency group.

This pilot RCT is the first study of its kind intended to gather estimates of effect size of marijuana for PTSD. In the absence of published effect sizes of marijuana for PTSD, possible effect sizes were estimated to be 0.4 for a between-subject comparison, based on a recent meta-analysis conducted with the National Center for PTSD [1], which found an effect size of 1.64 (confidence interval 1.13-2.16) for FDA-approved PTSD medications and 1.20 for placebo treatments (confidence interval 0.98 -1.45). Thus in the proposed study, N=76 with 19 subjects randomized to each group will provide approximately 82% power to detect these or greater differences between groups on the same primary outcome measure used to obtain FDA approval for PTSD medications.

Data Safety and Monitoring: Medical monitors will have oversight of all safety data; the Medrio database will be used for Serious Adverse Event (SAE) tracking and the Electronic Patient Reported Outcome (ePRO) will be used for daily symptom reporting. These validated clinical data systems will provide centralized access to review safety data in real-time. The sponsor will complete all required safety submissions to the FDA and support the sites in any reports to IRBs. In order to minimize risk to participants the following exclusion criteria have been set. In order to manage the safety risks of participants enrolled in the study the following individuals are not eligible to be enrolled:

1. pregnant, nursing, or of child bearing potential; not practicing effective means of birth control.
2. history or current primary psychotic disorder, bipolar affective disorder type 1, positive family history (first degree relative) of psychotic disorder or bipolar affective disorder type 1.
3. history of, or current of Axis 2 Personality Disorders Cluster;
4. dissociative identity disorder or an eating disorder with active purging, evidence of significant, uncontrolled hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, gastrointestinal, or neurological disease.
5. any allergies to marijuana or contraindication for smoking of marijuana.
6. 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. at initial screen -positive urine drug screen for opiates (unless prescribed), methamphetamine, cocaine and amphetamines; meets DSM-5 criteria for substance abuse/dependence (other than caffeine or nicotine) in the past 60 days;
8. at 2-week baseline meets criteria for cannabis use disorder (5 of 11 DSM-5 criteria) and continued marijuana use confirmed by blood or urine;
9. unable to attend face-to-face visits;
10. unable able to give adequate informed consent,

Documentation of Adverse Effects: The safety of participants will be assured during and after the experimental sessions by assessing physiological effects, AEs, and suicidal ideation. Daily information on safety and tolerability will be collected during the active part of the study. Withdrawal symptoms and problems associated with marijuana use will be monitored throughout the treatment period. Serious Adverse Events (SAEs) will be collected through termination. All AEs will be collected during drug administration through the two-week follow-up after Stage 2. Events requiring medical attention will be collected from the two-week follow-up after Stage 2 through the subject's last 6-month follow up. Events related to planned treatments or physician visits for baseline conditions collected in the Medical History will not be collected unless there is an exacerbation of the condition. Any AE leading to withdrawal from the protocol will be collected throughout the study. All AEs related to changes in psychiatric status will be collected throughout the study.

Benchmarks of success: The proposed study will be successful if the following milestones are achieved: In the first year, completion of the Investigator Meeting, start of screening potential participants at each site, enrolling the first participant at each site, first completion of the primary endpoint. In year 2, completion of enrollment, completion of all primary endpoints and first participant completion of the 6-month follow-up. In year 3 completion of all 6-month follow-ups, database lock, completion of the Final Clinical Study Report, and a scientific paper about the results accepted in a peer-reviewed scientific journal. This study will provide clear benefit for Colorado's veteran and PTSD populations by supplying data from objective clinician-administered and laboratory-based measures of effects on PTSD and associated co-morbid symptoms, and has the potential to enhance Colorado's national leadership position in researching marijuana as a medicine for debilitating medical conditions.

D. Laboratory Testing:

Three laboratories will provide testing. Dr. Christopher Lowry at the UC Boulder will perform testing for biomarker analysis of inflammation markers with appropriately sensitive, specific and validated assays for CRP, IL-1β, and IL-6 (ELISA Kits: Human IL-1 beta/IL-1F2 Quantikine HS; Human IL-6 Quantikine HS, Human C-Reactive Protein/CRP Quantikine). Dr. Lowry has experience measuring inflammation markers in placebo-controlled clinical studies and will ensure that the clinical investigation adheres to GCP and the protocol. Friend Labs Inc. will conduct laboratory testing of blood/urine cannabinoids and potency of marijuana for its chemical composition at a College of American Pathologists (CAP) accredited laboratory with an appropriately sensitive, specific and validated assay. Potency of marijuana and cannabinoid profile will be tested using high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). LabCorp a CAP accredited national lab with standardized reference ranges will perform testing of medical eligibility at screening using the compressive metabolic profile, comprehensive thyroid panel and HIV test.

E. Budget: See attached