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Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: **H-50300**
Status: Approved
Initial Submit Date: 10/12/2023
Approval Period: 12/11/2024 - 12/11/2025

Section Aa: Title & PI

A1. Main Title

THE STARLIGHT PROTOCOL (STATE-FUNDED TRIAL ASSESSING RECOVERY AND LONG-TERM IMPACT OF GUIDED PSILOCYBIN FOR HEALING TRAUMA)

A2. Principal Investigator

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A3. Administrative Contact

None

A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

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A5. Funding Source:

Organization: TEXAS DEPARTMENT OF HEALTH;AIM YOUTH MENTAL HEALTH

A5a. Associated ESP2 funding proposal linked to this protocol:

A6a. Institution(s) where work will be performed:

BCM: Jamail Specialty Care Center
BCM: Baylor College of Medicine
The Menninger Clinic

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?

Yes

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?

Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?

The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,
- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

In recent years there has been increasing interest in investigating the use of psilocybin, a classic hallucinogen, as an adjunct to psychotherapy for the treatment of various psychiatric conditions. Recently completed trials have shown positive effects of this treatment among patients with depression and anxiety (Davis, Barrett, May, et al., 2021; Gukasyan et al., 2022; Goodwin et al., 2022; Goodwin et al., 2023; Griffiths et al., 2016; Grob et al., 2011; Kiraga et al., 2022; Xi Li et al., 2023), obsessive compulsive disorder (Moreno et al., 2006) and substance use disorders (Bogenschutz et al., 2015; Bogenschutz et al., 2022; Johnson et al., 2014, 2017; van der Meer et al., 2023). Results from these studies demonstrated that psilocybin-assisted therapy is safe, has a minimal adverse event profile with no documented serious adverse events, and data revealed robust improvements in mental health symptoms in the short- and long-term and provided foundational evidence suggesting these treatments could be effective in the treatment of individuals with symptoms related to a cluster of mood, substance use, and anxiety disorders (Hodge et al., 2023; MacCallum et al., 2022; Schlag et al., 2022). This is particularly relevant for the treatment of PTSD as the combination of mood, anxiety, and substance use symptoms represent several core aspects of the cluster of PTSD symptoms (Flory & Yehuda, 2015, 2022). We are also investigating the effect of psilocybin-assisted therapy on PTSD symptom severity. The results should provide information about clinical trends that may be compared with previously published depression research that utilized psilocybin as a treatment (e.g., Bogenschutz et al., 2022; Sloshower et al., 2022; von Rotz et al., 2023).

Consistent with current evidence supporting the notion that psilocybin-assisted therapy may be effective in treating PTSD, a recent open label trial of psilocybin-assisted group therapy for demoralization in long-term AIDS survivors showed a clinically meaningful change in PTSD symptom severity, as measured by the PTSD Checklist-5 (PCL-5), from baseline to 3-month follow-up with a large effect size (Anderson et al., 2020). However, this study was not designed specifically to address symptoms of PTSD, nor did it focus on the broader population of people with this diagnosis. Furthermore, no study to date has focused on examining the safety and efficacy of psilocybin-assisted therapy among United States Military Veterans for any psychiatric indication, a population with substantial burden of mental health problems compared to the general population. For example, despite inherent resiliencies and specialized training, members of the armed forces are often exposed to a number of military deployments and intense combat incidents, which are associated with higher risk of PTSD compared to the civilian population (Hanwella & de Silva, 2012; Hing et al., 2012). Additionally, there has been an alarming increase in the incidence of suicides in Veterans, set in the context of limited effective treatment methods for this unique population (Hing et al., 2012; Rocklein Kemplin et al., 2019) Although several pharmacological and psychotherapy interventions have been developed to treat PTSD (Ravindran & Stein, 2009; Watkins et al., 2018), these treatments are difficult to complete, challenging to access, and are lacking in efficacy for many Veterans (Hertzberg et al., 2000; Krystal et al., 2017; Steenkamp et al., 2015). Furthermore, there is emerging evidence that standard pharmacologic treatments are not as effective in Veterans with PTSD as they are in civilians (Hertzberg et al., 2000; van der Kolk, 2014), and are no longer recommended as a front-line treatment (VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, 2017). Although there is encouraging preliminary data on the safety and efficacy of psilocybin-assisted therapy from a variety of patient populations, more research is needed to establish safety and efficacy of this treatment among Veterans broadly speaking and among with PTSD specifically. Not only could this novel treatment help ameliorate the burden of PTSD in this population, it could potentially reduce the risk of suicides among Veterans and reduce the devastating impact of this mental health crisis in families and communities across the US.

PTSD and increased risk for suicide: Suicide exerts a heavy burden on society and is amongst the top three leading causes of mortality in the US for individuals aged 15 to 44 years (National Institute of Mental Health, 2022) accounting for over 700,000 annual deaths globally (World Health Organization, 2021). Veterans (Pompili et al., 2013) are at particularly high risk of suicide, compared to civilians. Among young adults, Veterans are at 7x greater risk than civilians for suicidal ideation (Logan et al., 2016), and ~22 Veterans die from suicide every day (Kemp & Bossarte, 2012). Further, Veterans and other trauma-exposed individuals with PTSD are at increased risk for suicide (Jakupcak et al., 2009). A recent study examining 4,069 Veterans found that PTSD and adverse childhood experiences were the strongest predictors of suicidal thoughts and behaviors (STBs) (Nichter et al., 2021). Despite this dire state, current treatment options for STBs are extremely limited. Recreational psilocybin and other serotonergic agonist drug use decreases odds of STBs (Jones & Nock, 2022; Zeifman et al., 2019). Evidence from recent randomized controlled clinical trials of MDD found that PAT decreases suicidal ideation up to 2 months after conclusion of treatment (Davis et al., 2021). Yet, the effectiveness, feasibility, and tolerability of psilocybin-assisted therapy for STBs also remains unstudied to date in any patient population.

With critical importance to both PTSD and STBs, psilocybin-assisted therapy's broad range of effects highlight the potential for the involvement of transdiagnostic factors. Psilocybin-assisted therapy may reduce very specific symptoms of MDD, anxiety, and perhaps PTSD also may foster improved cognitive flexibility and generation of alternative coping plans outside of suicide, including social support(Hausman et al., 2020). Interpersonal connectedness is amongst the most critical factors in mental health risk, including PTSD and STBs (Watts et al., 2017). Interpersonal conflict, criticism, rejection, and thwarted belongingness (Chu et al., 2017; Hagan & Joiner, 2017; Nock et al., 2009) are often cited as a cause for suicide attempts (Burón et al., 2016) per self-report and 'psychological autopsy' studies in individuals who died by suicide (Foster, 2011), whereas connectedness and social support are protective against STBs in civilians and Veterans (Klonsky & May, 2015; Pietrzak et al., 2017). Interpersonal functioning is a potentially powerful modifiable factor. Social cognitive deficits, particularly mentalizing, contribute to interpersonal difficulties (Levi-Belz & Lev-Ari, 2022). Mentalizing is the forming of mental models of our own and others minds needed for intimate and gratifying relationships (Allen et al., 2008; Luyten et al., 2020). Mentalizing failures can increase social stressors due to communication difficulties, impair affect regulation strategies like reappraisal, and reduce access to stress-buffering social networks, increasing STBs (Doba et al., 2022; Li et al., 2020). Interpersonal factors are potentially modifiable with psilocybin-assisted therapy. Profound psilocybin-induced psychedelic experiences may foster interconnectedness transcending the interpersonal to establish a secure and trusting connections to something larger than oneself (Stauffer et al., 2020). Research suggests therapeutic changes in x psilocybin-assisted therapy are partly attributable to increased interpersonal connectedness (Watts et al., 2017),trust, safety, belonging, and dissolution of sense of self, and improved mentalizing (Pokorny et al., 2017) (Agin-Liebes et al., 2021; Strumila et al., 2021) (Mason et al., 2019). These findings have implications for psilocybin-assisted therapy's enhancement of affiliative factors (Blatchford et al., 2021) impaired in individuals with PTSD at perhaps at elevated risk for STBs.

** Please see attached document in Section S (clean - RFC sub - EMG STARLIGHT - LAA - v0004 - 20230829) for additional background information supporting this protocol as reviewed and approved by the FDA for IND 167280.

Section D: Purpose and Objectives

Although there is encouraging preliminary data on the safety and efficacy of psilocybin-assisted therapy from a variety of psychiatric patient populations, more research is needed to establish safety and efficacy of this treatment among Veterans with posttraumatic stress disorder (PTSD), a signature injury of the wars in Iraq and Afghanistan and a operational priority area for the VA. Not only could this novel treatment help ameliorate the burden of PTSD in the Veteran population, it could potentially reduce the risk of suicide and reduce the devastating impact of this mental health crisis in families and communities across the US. Therefore, the principal investigator for this study plans to build upon the psilocybin-assisted therapy intervention used in prior completed trials such as those at Johns Hopkins University (i.e., Davis, Barrett, May, et al., 2021) to conduct an open-label trial of two psilocybin administration sessions combined with psychotherapy to investigate the safety, tolerability, and clinical efficacy of psilocybin-assisted therapy for the treatment of PTSD in US Veterans. Primary objectives: 1. Investigate the safety of psilocybin-assisted therapy among Veterans with PTSD. 2. Investigate the effect of psilocybin-assisted therapy on clinician-rated PTSD symptom severity.

Secondary objectives: 1. Investigate the effect of psilocybin-assisted therapy on self-reported PTSD, depression, and anxiety. 2. Investigate the effect of psilocybin-assisted therapy on quality of life and psychological flexibility.

Exploratory objectives: 1. Investigate the effect of psilocybin-assisted therapy on functional connectivity networks using resting-state functional magnetic resonance imaging (fMRI). NOTE: PARTICIPATION IN THE MRI SESSIONS IS ENTIRELY OPTIONAL AND WILL NOT IMPACT A PARTICIPANT'S ENROLLMENT OR ENGAGEMENT IN THE STUDY IN ANYWAY. FOR THOSE WHO ELECT TO PARTICIPATE, SCANS WILL BE CONDUCTED UNDER A SEPARATE PROTOCOL (BCM H-48748).

Primary Endpoint: Safety as measured by the Columbia Suicide Safety Rating Scale, Adverse Event Reporting Form, and Clinician Administered PTSD Rating Scale for DSM 5 (CAPS-5)

Secondary Endpoints: Clinical Efficacy as measured by the PTSD Checklist 5 (PCL-5), Quick Inventory of Depression Severity (QIDS), Generalized Anxiety Disorder-7 (GAD-7), Brief Inventory of Quality of Life, and Acceptance and Action Questionnaire II

Exploratory Endpoints: Functional connectivity changes pre/post treatment as measured by state-of-the-art neuroimaging analysis methods *optional scans conducted under a separate protocol (H-48748)

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Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:
Both

Age:
Adult (18-64 yrs)

Ethnicity:
All Ethnicities

Primary Language:
English

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?
Mentally ill

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Eligible participants will receive full explanation of the study protocol, as well as discussion of the risks, benefits, costs, and time commitments. Patients will be given a written informed consent document detailing the study and any questions will be answered by one of the investigators or study team. Individuals will be informed that they may withdraw consent at any time without jeopardizing the clinical treatment to which they would otherwise be entitled.

Individuals will not be enrolled who are: children, prisoners, terminally ill, cognitively impaired, pregnant, or breastfeeding. Participants will be judged informally on their mental and emotional competency and capability to provide informed consent by trained research staff, with any questions about capacity being fully ascertained by study clinicians via clinical interview prior to beginning procedures.

The study includes careful screening to help ensure safety and appropriateness for participation. The design of the trial includes preparation and integration sessions with emphasis on set and setting, meaning we will work closely with participants to help them build comfort and trust with their therapy team, provide close monitoring and support throughout the trial. They are able to maintain SSRI medication and engagement in stable psychotherapy, which is important for safety and reduced AEs.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:
u) Drug, Phase II, Single Center

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This is an open-label trial evaluating the safety, efficacy and durability of psilocybin drug administration sessions paired with preparatory (pre-dosing) and integration (post-dosing) psychotherapy among a sample of military Veterans diagnosed with PTSD who have not experienced amelioration in symptoms following prior medication and psychotherapy treatment (i.e., have treatment resistant symptoms). Across stress- and trauma-related mental health concerns (e.g., depression, PTSD) there is no standardized definition or consensus for what constitutes treatment resistance. In depression, generally the term treatment-resistant depression or TRD, is used when one (Fava, 2003) or more (often two or more; Berlim & Turecki, 2007;) standard pharmacologic antidepressant treatment trials of appropriate dosage, duration, and compliance fail to produce significant clinical improvement for a patient. While the definition of TRD is subject to significant debate due to the heterogeneity of the condition, diversity of symptoms, and a lack of specific and validated quantifiable biomarkers, it is loosely defined as failure of two or more adequate therapeutic trials to provide at least moderate symptom control (Gaynes et al., 2018; Jaffe et al., 2019; Fountoulakis et al., 2019). More recently it has been suggested the included of psychotherapy trials should also be considered in decisions about refractory symptoms. Given the known limitations of approved pharmacologic intervention as well as psychotherapeutic interventions, we argue that we should aim to be as inclusive and 'early-on' in intervention as possible. We do not see the benefit in having so many novel, especially novel rapid-acting interventions to include ketamine/esketamine to be considered only as an option for those with severe symptoms and treatment resistance. What this means in reality is that patients will have struggled for months, years, and sometimes decades before they are offered such interventions. We plan to study psilocybin-assisted therapy among Veterans who have tried one or more standard and accepted interventions (e.g., SSRIs or trauma-focused therapy) and not found clinical benefit. Secondarily, we will examine the effect of psilocybin-assisted therapy on PTSD severity, PTSD related cognitive processes and functional outcomes, depression, anxiety, suicidal ideation/behaviors, social support, and several self-report measures of various mental health symptoms. The study will also include participant and monitor ratings of subjective drug effects during and after each drug session as well as scales exploring possible psychological mechanisms of psilocybin therapy and expectations/expectancy bias. Participants will complete all study visits including the long-term follow up assessments through 6 months post-intervention. We will enroll medically stable participants with a diagnosis of PTSD as defined by a DSM-5 diagnosis based on a Clinician Administered PTSD Scale-5 (CAPS-5) total severity score ≥31 at baseline following unsuccessful adequate trials of pharmacologic and/or psychotherapeutic interventions.

The exploratory aim will examine changes in intrinsic connectivity networks pre- to post-treatment and will also examine the durability of these effects through follow-up visits. As above, these MRI sessions are fully optional and do not impact an individual's participation in the intervention aims. Further, these MRI sessions are conducted under a separate protocol (H48748). Using standard connectome fingerprinting methods we will evaluate changes in network connectivity.

Inclusion Criteria:

• Be a United States Military Veteran • 21 to 64 years old • Have given written informed consent • Have at least a high-school level of education or equivalent (e.g. GED). • Have a current DSM-5 diagnosis of Posttraumatic Stress Disorder • Have a CAPS-5 total severity score of ≥31 at baseline • No MAOI antidepressant medications for approximately 5 half-lives prior to baseline assessment and enrollment – SSRIs will be allowable so long as participants are on a stable regimen (medication and dosing) for a period of 3 months. • Concurrent psychotherapy is allowed if the type and frequency of the therapy has been stable for at least two months prior to screening and is expected to remain stable during participation in the study. • Be medically stable as determined by screening for medical problems via a personal interview, a medical questionnaire, a physical examination, an electrocardiogram (ECG), and routine medical blood and urinalysis laboratory tests • No use of hallucinogens in the past 3 months and no history of regular or frequent use of hallucinogens (e.g., microdosing, attending regular retreats either outside the US or in the 'underground' within the country, regular psychedelic church attendance, etc.)

Exclusion Criteria:

General medical exclusion criteria: • Individuals who are pregnant (as indicated by a positive urine pregnancy test assessed at intake and before each drug session) or nursing; individuals who are of child-bearing potential and sexually active who are not practicing a highly effective means of birth control (i.e., implants, injectables, combined oral contraceptives, progestin containing IUDs, or vasectomized partner). • Individuals with partners of childbearing potential who are sexually active and not practicing a highly effective means of contraception (i.e., condom with spermicidal foam/gel/film/cream/suppository). • Cardiovascular conditions: coronary artery disease, stroke, angina, uncontrolled hypertension, a clinically significant ECG abnormality (e.g., atrial fibrillation), prolonged QTc interval (i.e., QTc > 450 msec), artificial heart valve, or TIA in the past year • Systolic blood pressure (SBP) > 139 mm HG; diastolic blood pressure (DBP) > 89 mm HG; heart rate (HR) > 90 bpm. • Epilepsy with history of seizures • Insulin-dependent diabetes; if taking oral hypoglycemic agent, then no history of symptoms of hypoglycemia

Psychiatric Exclusion Criteria: • Current or past history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I or II Disorder • Current or history within six months of meeting DSM-5 criteria for a moderate or severe alcohol, tobacco, caffeine, or other drug use disorder; if a regular smoker, they must agree to use a nicotine patch on the day of dosing (can be coordinated with study team medical personal) as smoking will not be allowed on these sessions • Have a first or second-degree relative with schizophrenia spectrum or other psychotic disorders including substance/medication-induced or due to another medical condition, or Bipolar I or II Disorder • Risk for acute suicidality as determined by clinician judgment and/or the following: (a) at screening, the participant scores "yes" on Suicidal Ideation Items 4 or 5 of C-SSRS within 6 months prior to screening; (b) at baseline, the participant scores "yes" on Suicidal Ideation Items 4 or 5 since the screening visit; and/or (c) At screening, the patient has had 1 or more suicide attempts (regardless of medical outcome) within 2 years prior to screening. • Has a psychiatric condition which precludes the establishment of therapeutic rapport as evidenced by long-term patterns of unstable relationships, history of significant stress-related paranoia, and identity disturbances • History of a medically significant suicide attempt • Current MAOI antidepressant use

F2. Procedure

To be screened for the study, all participants must be willing to sign a release of information form allowing study personnel to communicate with current or previous mental health or medical providers. This communication may be used to confirm current or past treatments including psychiatric medication, to evaluate appropriateness of the participant for the study and to facilitate communication with the provider throughout and at the end of the study as needed.

A preliminary remote screening will be completed prior to informed consent in order to determine obvious exclusions from the study protocol. During this time the study team will also inquire about the individual's interest and ability to complete the MRI sessions under protocol H-48748 and will evaluate for safety for those who would like to participate. For those who would like to be scanned, a safety pre-screening questionnaire will be administered to determine suitability for MRI, to identify issues for which the prospective participant must provide medical information so the study physician can determine MRI safety prior to scheduling a baseline scan. If for any reason individuals do not want to or are not able to complete the scans, this will not impact their ability to complete the intervention portion of the study in anyway and also will not delay their participation.

All screening procedures will take place under BCM approved core screening and scanning protocol (H-48748), which supports a streamlined and consistent approach to screening and reduces participant burden within the PI's research program. Screening for this trial includes physical and psychiatric history, diagnostic interviewing, ECG, routine labs, and a physical evaluation including careful review of medication usage/history and potential MRI contraindications and safety (for those who opt-in to this portion). Routine laboratory studies will include a comprehensive metabolic panel (e.g. electrolytes, hepatic and renal function tests), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and urinalysis. Additional tests will be requested as clinically indicated.

After being determined eligible and enrollment into the trial, participants will begin preparation therapy for a total of 4 hours of contact time (planned to schedule for two days in one week, e.g., Monday and Thursday sessions) before the first psilocybin dosing day. At least one of these sessions will be in-person, though the option for virtual/remote sessions is available as needed. Both monitors will be present throughout the dosing day and a study physician will be available for any medical issues, emergencies and monitoring. Participants will be carefully evaluated for discharge after dosing to ensure safety and will be released to a friend or family member as they will not be allowed to drive on their own. Two post-psilocybin integration therapy sessions visits will follow Psilocybin Sessions 1 and 2 for four total integration sessions. Within 48 hours prior to dose 2, staff will reach out for a brief check-in and limited preparation session, addressing any questions/concerns and reviewing goals, expectations, etc. This is expected to be no more than ~30 minutes. The second dosing day and post-dose integration sessions will be identical in format to the first dose. Virtual follow-up visits will occur at 1, 3 and 6 months post-treatment to evaluate ongoing safety and durability of any noted therapeutic effects. The lead facilitator will be a licensed clinician with graduate-level professional training and clinical expertise in psychotherapy and will be licensed to practice independently (e.g., MD, PhD, MSW, PCPC, LMFT, Psychiatric NP). The second monitor must have at least a bachelor's degree and at least one year of clinical experience in a mental health care setting. Further, a BLS-certified physician will be on call for the ~8 hour of the dosing visit and able to reach the clinical dosing site within 15 minutes in the case of a physiological or psychiatric emergency. at least one will have a PhD or MD and both will be knowledgeable in the treatment of PTSD). For those who opt-in and are eligible for the MRI sessions (completed under protocol H-48748), these will be completed at baseline (prior to any intervention), ~ next day/24-hours post-dose 1 and 2, ~ 1 week post-dose 1 and 2, and at the follow-up visits.

Following preparation therapy, each participant will have a low dose (15 mg) psilocybin session to establish basic skills with session format, psilocybin effects, and continue to build rapport with session facilitators. This dose and higher doses have been well tolerated by psilocybin-naïve participants in previous and ongoing studies (R. L. Carhart-Harris et al., 2016; Davis, Barrett, May, et al., 2021; Griffiths et al., 2006, 2016; NCT03866174). Given the potential intensity of the psilocybin and the reality of experiencing significant trauma memories, the purpose of the first psilocybin session is to familiarize participants with the drug effects that may be encountered at a higher dose of psilocybin. The first psilocybin session will also allow for assessment of both the suitability of each participant to the study procedures and drug effects, and the safety of administering a higher dose to each participant. Within ~24 hours after the psilocybin session, participants will return for a 1-2 hour follow-up therapy session to assess safety, discuss the psilocybin session, and prepare for the high dose session. For those who are completing MRI sessions, they will complete a post-dose 1 scan at this time as well (~next day to dose). The next psilocybin session will utilize a high dose (25mg) and take place approximately 2 weeks after the first psilocybin session. Following this session, participants will again meet with therapy facilitators within ~24 hours to discuss the psilocybin session and to plan for concluding therapy. Outcomes will be assessed at baseline (prior to preparation therapy) and at 1, 3, and 6-months after the second psilocybin session. Therapy visits will be included at each primary outcome assessment time point and additional safety assessments will be conducted via telephone and video conferencing between in person visits at 2 and 3 weeks following the final psilocybin session, with options for telephone and video conferencing visits in between in-person visits. Clinical outcome measures will be assessed at baseline and throughout the study, as described below.

Psilocybin will be provided by Usona Institute in opaque gelatin capsules and will be administered with approximately 100 mL water. During the initial stages of the psilocybin session, participants will be encouraged to lie on bed, wear eyeshades and listen to a program of music through headphones, consistent with other psilocybin studies. The peak effects will be determined by asking the participants to provide a verbal rating of the intensity of subjective effects on a rating scale from 0 to 10, with 0 equaling "no effects" and 10 equaling "extremely intense effects". They will complete other MRI sessions at T+2h and T+6h. Participants and monitors will complete the Mystical Experiences Questionnaire (MEQ-30) and Altered States of Consciousness (5D-ASC) to evaluate psychedelic effects. Vital signs will be assessed at least prior to psilocybin administration, hourly for the first 3 hours thereafter, and before discharge.

A brief description of the visits is presented here:

Days ~-30: Screening: As detailed above, this will be completed via phone/zoom, internet survey, and in-person visits to complete a comprehensive medical and psychiatric evaluation.

Day 1: Preparation session 1 – This can be remote or in-person depending on need and preference. At least one of these sessions will be conducted in person.

Day 2: Preparation session 2, same as above.

*For those who are completing MRI sessions (administered under H-48748), these will be conducted during the week prior to the first dosing session. While all MRI procedures are further detailed in the separate protocol, briefly, participants will present to CAMRI at Baylor Main Campus. They will complete urine drug and pregnancy (if applicable) tests and, if both show a negative result, will complete the MRI.

Day 3: Psilocybin dosing day 1 – The participant will present to Baylor Main Campus in the morning (likely between 8 and 9 AM). They will complete a urine drug and pregnancy test as well as some pre-dose behavioral measures. The study physician will see them and confirm their safety and appropriateness for the dose, checking vital signs, etc. The participant will then be given a 15 mg oral dose of psilocybin, to be taken with a small amount of water. They will be monitored throughout the entire session (estimated to be approximately a 10 hour day). As above, the facilitators will be present in the room throughout the day. Further, a BLS-certified physician will be on call for the ~8 hour of the dosing visit and able to reach the clinical dosing site within 15 minutes in the case of a physiological or psychiatric emergency. Further the Challenging Experiences Questionnaire (CEQ) and Psychological Insight Questionnaire (PIQ-6) will be administered to the participant and monitor evaluate potential psychedelic effects. Participants will be medically assessed for discharge (evaluation of medical and psychiatric stability/safety, effects of psilocybin have subsided, and confirmation of appropriate transportation). If participants report or demonstrate any physical or psychiatric health criteria that are deemed unsafe or concerning they will not be discharged until these have resolved. If these do not resolve in a short period of time, appropriate elevated care will be sought including transfer to a medical facility. The following criteria would be required prior to discharge: (1) Vital signs are stable and possible adverse effects (e.g. sedation, dissociation) have subsided. (2) The Participant has a willing and able adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and documented. (3) The Participant agrees not to drive or operate heavy machinery/equipment and not to make major financial or legal decisions for the remainder of the day in which psilocybin is administered. Note, the study team will help to arrange transportation for participants as needed. Rescue Medications Available During Dosing: In the unlikely event that a participant requires medication management for anxiety, the study physician may use a benzodiazepine, e.g., Diazepam or Lorazepam

The use of rescue medications to control symptoms will be at the judgment of the study physician. The study will supply the rescue medications, which will be obtained locally. The date and time of medication administration, reason for administration, as well as the name and dosage regimen of the rescue medication will be recorded on the Concomitant Medications log. Use of psychotropic agents (e.g. diazepam) will be on a single dose/time limited basis and hence will not fall under the study exclusionary criteria regarding chronic use of these agents prior to enrollment.

In the unlikely event of a medical or psychiatric emergency that cannot be safely managed by staff with reassurance or pharmacological intervention, the study physician will determine if the participant can be safely escorted by medical staff to the nearest emergency department, or if 911 needs to be called for transport.

Dose 2 will take place ~ 2 weeks after the first dose.

** Please see attached document in Section S (clean - RFC sub - EMG STARLIGHT - LAA - v0004 - 20230829) for additional background information supporting this protocol as reviewed and approved by the FDA for IND 167280.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 18 Worldwide: 18

Please indicate why you chose the sample size proposed:

No prior investigations of the effects of psilocybin on PTSD symptoms have been published to date. Because this trial has a primary objective of establishing the safety of this treatment approach among this population, and based on effect sizes in prior laboratory studies of psilocybin for other clinical populations (Davis, Barrett, May, et al., 2021; Griffiths et al., 2016), we believe that a sample size of N = 18 will provide sufficient power to detect a moderate effect size of pre- and post-psilocybin changes. If the data suggest possible efficacy, these data should be sufficient to conduct a power analysis for a subsequent, larger randomized controlled trials.

We expect to consent up to 72 volunteers at BCM (some of whom will not pass the in-person screening), in order to achieve 18 individuals who enroll in the study and subsequently complete both psilocybin sessions and the final follow-up assessment. Volunteers will be United States Military Veterans, all branches of service are welcome and enrollment with the VA is not a requirement as we recognize some Veterans do not want to engage with this organization. We will attempt to reflect recent data from the 2019–2020 National Health and Resilience in Veterans Study (NHRVS), which showed that 26.7% of US Veterans with past month PTSD were female and 34.8% were non-white (Wisco et al., 2022). Extrapolating from this analysis, we expect to recruit ~13 male participants, 5 female participants, 12 white, and 6 non-white participants. Participants will be recruited primarily from the greater metropolitan Houston region, which is a very large and very diverse city with a large Veteran population. Participants may or may not have used hallucinogens in the past. The investigator is aware that many Veterans (and non-Veterans) have been seeking these interventions outside the US where they are unregulated and also sometimes within the US in 'underground' settings. These individuals will not be penalized and excluded, though very recent or regular and frequent use would be exclusionary from a safety perspective.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

For primary and secondary measures assessed at baseline and follow-up (C-SSRS, CAPS-5, PCL-5, DSPS, PGI-X, PHQ-9, STAI, SRS, B-IPF, Tellegen Absorption Scale, Acceptance and Action Questionnaire, Big Five Inventory, etc.), repeated-measures ANOVAs will be used with post-hoc comparisons, will be conducted to test for differences from baseline and the follow-up visits. Planned comparisons from baseline to one month post final psilocybin session will be conducted for primary outcome measures. These longitudinal outcome measures will be regressed on measures of acute and persisting psilocybin effects to examine whether such effects appear to be predictive of clinically relevant outcomes. The acute and persisting effects measures are: Within-Session Monitor Rating, Mystical Experience Questionnaire, Challenging Experience Questionnaire, Next-Day Monitor Rating Form, Next-Day & Psychological Insight Questionnaires, Persisting Effects Questionnaire, Monitor Rating of Enduring Effects.

Primary Endpoints: 1) Psilocybin-assisted therapy will be safe to administer among Veterans with PTSD as indicated by no statistically significant increases in mean ratings of suicidal ideation on the C-SSRS from Baseline through 1m post psilocybin session two. a. Ratings of suicidal ideation on the C-SSRS will be included from baseline, one day post psilocybin session one, one day post psilocybin session two, and one month post psilocybin session two. a. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of suicidal ideation from baseline through one month post psilocybin session two. b. Data will be presented with F-tests using an alpha (p-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

2) Psilocybin-assisted therapy will be safe to administer among Veterans with PTSD as indicated by no serious adverse event reporting related to administration of psilocybin. a. Descriptive analysis of adverse event reporting longs will be conducted to determine if any serious adverse events have been reported related to psilocybin administration.

3) We will find statistically significant decreases in PTSD symptom severity from baseline to 1 month after final psilocybin session as measured by the Clinician Administered PTSD Scale-5 (CAPS-5). a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit four, and one month post psilocybin session two. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptoms severity from baseline through one month post psilocybin session two. b. Data will be presented with F-tests using an alpha (p-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

4) We will find statistically significant decreases in PTSD symptom severity from baseline to 1 month after final psilocybin session as measured by the self-report PTSD Checklist for DSM-5 (PCL-5). a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit four, and one month post psilocybin session two. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptoms severity from baseline through one month post psilocybin session two. b. Data will be presented with F-tests using an alpha (p-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

Secondary Endpoints:

1) We will find statistically significant improvements in depression, anxiety, quality of life, etc. from baseline to 1 month after final psilocybin session as measured by the self-report measures. a. Mean ratings of will be included from baseline, preparation visit four, and one month post psilocybin session two. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings from baseline through one month post psilocybin session two. b. Data will be presented with F-tests using an alpha (p-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

In this study, we will use oral psilocybin provided and manufactured by the Usona Institute, a non-profit organization which conducts and supports biochemical and clinical research to further the understanding of psilocybin. The attached Investigator¿s Brochure (Psilocybin Investigator¿s Brochure, 2021) provides an in depth analysis of 8 clinical trials examining the safety and preliminary of efficacy of psilocybin. In total, 579 oral doses of psilocybin were administered in these studies, with 290 participants receiving at least one dose and 14 participants receiving 4 doses. Doses ranged from very low dose to a high dose, corresponding to 3.15 mg to 42 mg respectively. Data collected from these studies demonstrated that psilocybin was safe and well tolerated and that most adverse events resolved within 24 hours. Overall, the most commonly reported adverse events were psychological in nature and included acute anxiety and the induction of negative emotional states. Acute adverse reactions, characterized by strong dysphoria and/or panic, occurred transiently and only in the two highest dose conditions in a small proportion of subjects (5-8%). The rates of prolonged psychiatric symptoms of any kind are estimated by Usona to be between 0.08-0.09%. The most common physiologic adverse effects included transient cardiovascular side effects (increased blood pressure and heart rate), nausea and headaches. Presented below are additional details related to the known acute and prolonged adverse effects associated with psilocybin. Several of these domains are expanded upon in the Investigator¿s Brochure (attached). Following the sections directly related to psilocybin, we describe the risks associated with the non-drug aspects of this proposed study. Psilocybin Pharmacology: Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is most accurately characterized as a prodrug, and is dephosphorylated by hepatic first pass metabolism into the 5-HT2A, 5-HT1A, and 5-HT2C receptor agonist psilocin (Nichols & Presti, 2004), with subjective effects lasting between 4 and 6 hours (Passie et al., 2002). Thus, when discussing psilocybin¿s effects throughout this document, it is understood that psilocin is the active constituent. Psilocybin has about a 50% oral bioavailability as measured by plasma psilocin levels (Hasler et al., 1997). Psilocin has a half-life of 2-3 hours and is detectable in plasma within 20 minutes of psilocybin ingestion. Following an oral dose, onset of subjective effects occurs within one hour, peak at about 2 hours, and resolve at 4-6 hours. Psilocybin and its analogues (psilocin, CEY-19, and CZ-74) are all psychoactive indoles with side-chains that place them within the general class of tryptamines. These compounds are analogues of hydroxytryptamine (5-HT, serotonin, a naturally-occurring neurotransmitter). The psychopharmacological mechanism of psilocybin and its analogues is similar to LSD and mescaline in that all these compounds seem to act as post-synaptic agonists at 5-HT2A and 5-HT2C receptors (Sanders-Bush & Mayer, 2006). In healthy human participants psilocybin increased thyroid stimulating hormone, adrenocorticotropic hormone, and cortisol, and moderately elevated blood pressure (Hasler et al., 2004). Psilocybin subjective effects in healthy participants were blocked by the 5-HT2A antagonist ketanserin as well as by the mixed 5-HT2A/D2 antagonist risperidone (Vollenweider et al., 1998). Studies using positron emission tomography (PET) showed that psilocybin increased frontal glucose metabolism in healthy participants, suggesting that the behavioral effects of psilocybin involve the frontal cortex (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1998). However, a recent fMRI imaging study by Carhart-Harris et al. (R. L. Carhart-Harris et al., 2012) showed that intravenous administration of a low dose of psilocybin decreased brain activity and neural connectivity in some of these same brain regions. Whetherthese differences are due to the difference in route of administration, imaging technologies or some other factors in presently unknown. Other PET studies have focused on the interaction between 5-HT2A and D2-dopamine receptors during acute psilocybin administration. Vollenweider and colleagues (Vollenweider et al., 1998) found that psilocybin increased dopamine release in the caudate nucleus and the putamen, suggesting that stimulation of 5-HT2A receptors by psilocybin modulates striatal dopamine, which in turn may underlie some of the behavioral and psychological effects of psilocybin. Other brain-imaging results have suggested psilocybin-related changes in 5-HT2A receptor density in the medial prefrontal cortex, insula and anterior cingulate (Hasler et al., 2009) , although the full data from several recent studies have not yet been published (see Table 1 in Studerus et al., 2011). Psilocybin Toxicology: Animal studies suggest very low levels of general medical toxicity. The LD50 in rodents is approximately 2,000 to 3,000 times the usual human dose on a mg/kg basis (Tyl¿ et al., 2014; Usdin, 1972), comparing favorably with drugs such as aspirin and caffeine. Additionally, two GLP-compliant genotoxicity studies, which utilized psilocybin prepared through Usona Institute¿s current manufacturing process, were negative for toxicity (Psilocybin Investigator¿s Brochure, 2021). In a review of the pharmacology of psilocybin in humans, Passie et al. (2002) concluded that psilocin, the active metabolite of psilocybin, exhibits low toxicity and is physiologically well-tolerated. Recent analysis has demonstrated a largely benign safety profile for psilocybin (Amsterdam et al., 2011; Roscoe & Lozy, 2022), with independent analyses finding that psilocybin exhibits the least risk of harm to self or others when assessed relative to other commonly abused drugs (R. L. Carhart-Harris et al., 2013; Gable, 1993, 2004; Nutt et al., 2010; van Amsterdam & van den Brink, 2010). Nevertheless, users may acutely experience moderate to severe disorientation, anxiety, or fear responses (Carbonaro et al., 2016; R. R. Griffiths et al., 2006, 2011), a risk shared with LSD and the other hallucinogens, and which have been managed successfully in several clinical trials (e.g., Davis et al., 2021). Clinical research with psilocybin has increased substantially over the past several years, with publication of 7 distinct prospective studies (including reports on long-term follow-up outcomes) and several scholarly reviews in 2017 alone. There have also been several ancillary publications based on secondary outcomes and qualitative analyses of previously published psilocybin studies in recent years. The results of these studies provide further support that psilocybin exhibits low toxicity, is physiologically well tolerated, and can be safely administered in clinical studies to appropriate screened and prepared volunteers. Most notably, this safety profile was demonstrated at high doses of psilocybin in a pharmacokinetic study (Brown et al., 2017) that administered doses of up to 0.6 mg/kg (the highest dose in the Hopkins laboratory¿s studies has been 30 mg/70 kg, or 0.43 mg/kg). That study reported that ¿no serious physical or psychological events occurred during or within 30 days of any dose.¿ Physiological Adverse Effects: Clinical data show psilocybin to have a safe physiological profile. Psilocybin and related hallucinogenic compounds were investigated in humans in numerous clinical research studies in the 1950s and 1960s. The incidence of adverse effects in these early studies was very low, especially when participants were carefully screened, prepared, supervised, and followed up (Bergman, 1971; S. Cohen, 1960; Strassman, 1984). More recently, several research studies have demonstrated physiological safety (R. R. Griffiths et al., 2006, 2011; Hasler et al., 1997, 2004; Studerus et al., 2011). In general, minor adverse physiological effects that may beassociated with psilocybin administration are dizziness, nausea, vomiting, incontinence, and muscle twitching. In addition, recent data indicate that psilocybin can cause transient headaches of mild to moderate severity (i.e., not severe) usually starting about 7 hours after administration (Johnson et al., 2012; Studerus et al., 2011). Physiological effects of psilocybin also include moderately increased heart rate and blood pressure. In a 2006 study (R. R. Griffiths et al., 2006), the mean increase in heart rate following administration of psilocybin 30 mg/70 kg was 19.8 beats per minute, the mean increase in systolic blood pressure was 31.4 mm Hg, and the mean increase in diastolic blood pressure was 17.9 mm Hg. In a dose-effect study (R. R. Griffiths et al., 2011), the mean difference in heart rate between placebo and the highest dose (30 mg/70 kg) was 8.2 beats per minute, the mean difference in systolic blood pressure was 20.5 mm Hg, and the mean difference in diastolic blood pressure was 11.3 mm Hg. As described below in Section 8b (Steps taken to minimize risks), we will implement medical emergency procedures and cardiovascular monitoring procedures similar to those that have been used in past studies with psilocybin (R. R. Griffiths et al., 2006, 2011). Hypertension comorbid to PTSD is often evaluated as a psychosomatic disorder (Persu et al., 2018). In a 2018 study of 3846 US military casualties, severity of initial injury and duration of PTSD appeared to independently contribute to the risk of hypertension, showing a correlation between the chronicity of PTSD and subsequent development of high blood pressure (Howard et al., 2018). In other studies, PTSD patients with comorbid hypertension who were treated with the hypertension medication Prazosin showed a reduction in various PTSD symptoms (Raskind et al., 2016; Zhang et al., 2020). Evidence supports psychological interventions alleviate essential hypertension seen in patients with PTSD and other anxiety-like syndromes (Casiglia & Tikhonoff, 2018; Linden & Moseley, 2006; Xue et al., 2020). Thus, despite the transient blood pressure changes common to psilocybin sessions, we do not anticipate an increased risk of chronic hypertension developing in this population. Behavioral and Psychological Adverse Effects - Acute: We will adhere to the gold standard of safety procedures used in trials of psilocybin-assisted therapy for other stress- and trauma-related concerns, such as the depression trials conducted at Johns Hopkins Center for Psychedelics and Consciousness Research (Davis, Barrett, May, et al., 2021; Johnson et al., 2008). Since their establishment in 2000, psilocybin doses of 20 mg/70 kg or higher have been administered to more than 300 volunteers in more than 440 sessions. These procedures also reflect changes made over the years to protect patient and staff safety in any instance of patient disorientation or setting disturbance. The clinical safety of psilocybin has been extensively studied, both as a single agent and as adjunctive treatment in adult populations. Psilocybin is administered orally, and has been studied in open-label, and double-blind, controlled trials. Dosing regimens have ranged from 0.014 mg/kg to 0.6 mg/kg (~50mg in 80kg person), administered as either a single dose, or multiple doses weeks apart. Adverse event data from previous clinical trials has been used to evaluate the physiological profile of psilocybin. The investigator brochure for psilocybin summarizes the adverse event data collected from controlled clinical trials utilizing psilocybin in conjunction with cognitive enhancement therapy across multiple subpopulations.

** Please see attached document in Section S (clean - RFC sub - EMG STARLIGHT - LAA - v0004 - 20230829) for additional background information supporting this protocol as reviewed and approved by the FDA for IND 167280.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?
Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H â€" Data and Safety Monitoring Plan' as an attachment in Section S.

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?
No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

If hypotheses are confirmed, participants may benefit from partial to substantial relief of treatment-resistant PTSD symptoms. Although a significant body of research (as outlined in section 2.2 Background) has suggested that psilocybin may produce positive effects in the treatment of PTSD, no such benefit from the sessions can be promised. However, given the chronicity and severity of PTSD in this population and the fact that PTSD disrupts all aspects of life, including social, occupational, and interpersonal functioning, even small decreases in symptom severity and frequency would be significant. Additionally, as part of this protocol, participants will undergo at least 8 non-drug, therapeutically oriented sessions with trained psychiatrists, psychologists, and session facilitators. Participants may benefit from the general review of life values and direction that will occur in these meetings over a period of several months. Further, the behavioral activation possible from attending both remote and in-person study visits may also have some therapeutic benefit, though this cannot be guaranteed. Finally, society and the Veteran population may benefit greatly from advanced understanding of the potential of psilocybin-assisted therapy for PTSD in Veterans and generally in the identification and development of a novel rapid and sustained PTSD medication.

Describe potential benefit(s) to society of the planned work.

There is a tremendous need to identify a fundamentally novel intervention that offers: (1) rapid acting and robust effects in reducing PTSD symptoms that may alleviate the need for more resource-intensive care and (2) effectiveness in patients not achieving adequate benefit from existing interventions (e.g., SSRIs and trauma-focused talk therapy). Mounting evidence suggests the integration of the targeted use of certain psychoactive substances within a psychotherapeutic treatment may have the potential to address some of these challenges. The rationale behind this approach is that these drugs can catalyze the psychotherapeutic process, for example, by increasing the capacity for emotional and cognitive processing through pharmacologically diminishing fear and arousal, by strengthening therapeutic alliance through increased trust and rapport, or by targeting processes of fear extinction and memory consolidation. Additionally, from a neuroscience perspective, there is a rapid and robust increase in functional connectivity, which supports a "rewiring" of the brain or opportunity to 'reprocess' thoughts/memories/beliefs and gain insight, which may be helpful in positive clinical outcomes.

There is great reason to suspect psilocybin-assisted therapy may provide effective, safe, and well-tolerated intervention for individuals with PTSD.Over the past 15 years, research has shown that psilocybin, a serotonin 2A (5-HT2A) receptor agonist with secondary effects on glutamate neurotransmission, can safely and reliably occasion personally meaningful experiences that are associated with lasting increases in personal well-being, life satisfaction and positive behavior change in healthy adults. Among patients with mental health problems, recently published trials have demonstrated that psilocybin has rapid, substantial and sustained efficacy in reducing symptoms of depression and anxiety in people with a life-threatening cancer diagnosis (Griffiths et al., 2016; Ross et al., 2016), in treating symptoms of major depression in a sample of patients who are treatment-resistant to conventional antidepressants (R. L. Carhart-Harris et al., 2016), and recently in a sample of patients with major depressive disorder (MDD) (Davis, Barrett, May, et al., 2021). Moreover, psilocybin has lower abuse liability and toxicity than other behaviorally potent glutamate-modulators (e.g., ketamine; (Gable, 1993, 2004) and is generally not associated with long-term perceptual, cognitive, or neurological dysfunction (Studerus et al., 2011) or other adverse effects (Roscoe & Lozy, 2022), and use of hallucinogens has been shown to reduce the probability of experiencing significant psychopathology in population-level samples (Hendricks, Johnson, et al., 2015; Hendricks, Thorne, et al., 2015). Finally, the use of hallucinogens has been linked to modest increases in executive function, and no deficits in cognitive function (Aday et al., 2020; Bouso et al., 2015). Thus, research on psilocybin has demonstrated safety and tolerability, immediate and persistent mood effects, persistent cognitive effects, and combined serotonergic and glutamatergic effects of this drug.

The potential for discovering a new intervention with potential for rapid and robust improvements in PTSD and related symptom clusters (depression, anxiety, suicidal thoughts and behaviors, addiction) is incredibly important and incredibly exciting. Further, there is a great deal of 'hype' around these interventions and further understanding of how and for whom there interventions may be useful and appropriate, the challenges and limitations, and issues concerning indications, modalities of therapy, etc. are critical to moving ahead thoughtfully to improve and save lives of those struggling with stress- and trauma-related mental health concerns.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

Yes, without doubt the potential benefits outweigh the risks of this intervention. Psilocybin and psilocybin-assisted therapy have demonstrated safety and tolerability in multiple patient populations and has very low abuse potential. Given the urgent need for expanded treatment options for individuals struggling with PTSD and related concerns, it is vital we explore this intervention. We have multiple measures in place to limit the risks involved (which are fairly minimal to begin). Regardless of the findings of this trial (supporting the hypothesis of effective and safe treatment or perhaps in opposition to the hypothesis), they are vital to our understanding of the potential of this intervention for PTSD. Psilocybin-assisted therapy is in the FDA drug development pipeline and expected to have FDA approval within a couple of years. It is also vital that we have some further understanding of the potential benefits and limitations for various indications as it is quite likely this would be prescribed in an off-label fashion (currently being reviewed for treatment resistant depression and major depressive disorder).

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?
No

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
No

J2. Consent Procedures

Who will recruit subjects for this study?
PI
PI's staff
Third Party:

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

The study team will employ a multimodal enrollment strategy to help ensure enrollment targets are met. Participants may be recruited through means including: word of mouth, contact with community-based service groups and clinics, posted flyers at relevant sites, public advertisements (e.g., print, newspaper, billboards, bus ads), and via online advertisement including social media (e.g., facebook, twitter, Instagram), recruitment and marketing services (e.g., Trialfacts/Rewards for Research), digital media (e.g., TV, online radio, podcasts), and news releases.

Whenever recruiting on social media we will not interact with people online, will lock comments any time that option is available, and will also post a conspicuous note alongside the flyer or other content saying that social media is not a secure medium and people should not disclose personal information in response to our post. Rather, the person should follow the link to securely request that we contact them.

Staff from referring studies will provide participants with our study & contact information. Alternatively, if allowable under past consents or at a person's request, a clinician or P.I. may provide their name & contact information to us to contact the person. Under H-48748, a brief pre-screening for MRI suitability & study eligibility may be conducted by staff prior to informed consent. Responses & any MRI contraindications will be retained along with full name & contact information. No elements of dates related to subject's age will be retained from pre-screening, but the date of pre-screening will be recorded. Assent for this procedure will be obtained by asking the individual for permission to ask them brief questions about their medical history to help determine MRI safety and study eligibility.

Children, prisoners, individuals who are pregnant, & mentally disabled persons will not be included in this study. Further, we shall exclude individuals who lack the intellectual capacity to consent freely & to understand the written details of the consent form. All participants who volunteer to participate will be informally judged both mentally & emotionally competent & capable of providing informed consent by trained research staff, with any questions about capacity being fully ascertained by study clinicians via clinical interview prior to beginning procedures.

For in-person visits, consent process will take place in a private room. If participant wishes, a representative may be present. Consent will be read aloud, or the prospective participant will read alone. The participant will be given time to ask questions & decide if they really wish to participate. They will be given contact information for the PI & study coordinator. The participants will be asked if they understand all the possible risks & discomforts that may be associated with participating & will be asked to briefly summarize their understanding of the elements of the protocol (e.g., specific procedures & time requirements, compensation, confidentiality, risks & potential discomfort, etc). Actual consent will not be obtained until the consenting staff & the participant are satisfied that they are fully informed. If a wet signature is obtained on paper, that document will be scanned and stored by the study team in electronic form. The original paper will not be retained.

Remote consents may be easily collected in similar fashion. All consent procedures are the same except: 1) participant & staff will meet by remote means (e.g., secure Zoom conference). 2) Rather than a wet signature, DocuSign may be used to collect informed consent signature.

Are foreign language consent forms required for this protocol?
No

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?
Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes

Specific information concerning alcohol abuse:
Yes

Specific information concerning drug abuse:
Yes

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
Yes

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
Yes

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
Yes

Identifiable biospecimens
No

Will identifiable biospecimens be stored for future research?
NA

If yes, is the storage of biospecimens optional for subjects?
NA

Will identifiable private information be stored for future research?
NA

If yes, is the storage of information optional for subjects?
NA

Questionnaire, Survey, and/or subject diary
NA

Other:
No

At what institution will the physical research data be kept?

Every effort will be made to maintain the confidentiality of the physical study records, which will be maintained at BCM.

All data is stored within the BCM REDCap. Any physical data relating to the study will be stored at BCM Main Campus in our secured offices, closely monitored in a restricted access building and in a restricted badge access only office space in a locked office.

How will such physical research data be secured?

Secure storage, closely monitored or locked at all times. Additionally, all records will be coded, and PHI and non-PHI data will be stored separately to avoid linking the two.

At what institution will the electronic research data be kept?

Every effort will be made to maintain the confidentiality of the electronic study records, which will be maintained at BCM.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
No

Such electronic research data will be secured via Other:
Yes, (describe below):
PHI data will be password-protected, encrypted, and/or otherwise access-restricted on machines housed within the BCM network.

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.

De-identified data may be transmitted by various secure means, such as: encrypted email, file sharing through University Box accounts, transfer over direct computer-to-computer connections (SSH tunnel, physical connection), or using SSL-encrypted portals such as Baylor College of Medicine instance of REDCap (https://redcap.research.bcm).

Will you obtain a Certificate of Confidentiality (COC) for this study?
Yes

Please further discuss any potential confidentiality issues related to this study.

As with any clinically-related study, personal information will be collected and there is always a possibility of confidentiality issues. However, we believe that the possibility of problems arising from this type of research is extremely small. Precautions will be taken to minimize this risk.

Will information about the subject's participation be included in subject's medical records?
No

Please further discuss any potential confidentiality issues related to this study.

As with any clinically-related study, personal information will be collected and there is always a possibility of confidentiality issues. However, we believe that the possibility of problems arising from this type of research is extremely small. Precautions will be taken to minimize this risk.

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

Other than travel to and from the study site for study visits, there are no costs to participants associated with participation – there is no cost to participants (or their insurance) for the treatment. Furthermore, travel costs can be reimbursed. Additionally, costs for food, lodging, parking, child care, pet care, or other costs associated with participation in the study will be reimbursed.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
1000

Distribution Plan:

Participants will be paid $200 for completion of all remote and in-person screening procedures (under 48748). Each preparation and integration session will be compensated at a rate of $50; each dosing session at $250; and each follow-up visit $20. An additional $200 will be offered to those who complete the entire study as a recognition of their time and investment in the study that may include taking time away from work, requiring child/dependent care, pet care or other support with financial implications and we want to fairly compensate them. If they complete some but not all of the procedures, they will be paid for what they have completed. We may provide reimbursement for travel, parking, food, child/dependent or pet care, or lodging costs related to study visits. Payment will be issued via ClinCard; however cash or check may be used to issue payment if ClinCard is unavailable.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

SAMPLE: Urine

What is the purpose of the sample collection?
A urine sample will be collected for drug and pregnancy testing prior to drug dosing.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Other: research team

Will the sample be stripped of identifiers?
Yes

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

If sample will be banked for future use:

Where will the sample be banked and for how long?

Does the banking institution have an approved policy for the distribution of samples?

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

Results will be revealed to the study PI and to the participant if positive, as these would be exclusionary for continued participation (e.g., positive drug use or pregnancy).

Please identify all third parties, including the subject's physician, to receive the test results.

It is not expected any third parties would receive test results.

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)
Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?
No

O1. Current Drugs

Drug : psilocybin

Is this study placebo-controlled?
No

Will the research involve a radioactive drug?
No

Section P: Device Studies

Does this research study involve the use of ANY device?
No

Section Q: Consent Form(s)

You are invited to participate in a research study designed to learn more about the safety, tolerability, and potential clinical benefit of Psilocybin-Assisted Therapy for the treatment of PTSD in US Veterans.

Section R: Advertisements

Mode of Advertising: Other: study flyer

Mode of Advertising: Other: study flyer

Exact language of Advertisement:

PSYCHEDELIC RESEARCH SEEKING VOLUNTEERS FOR A STUDY INVESTIGATING THE POTENTIAL OF PSILOCYBIN-ASSISTED THERAPY FOR VETERANS WITH PTSD YOU MAY BE ELIGIBLE IF YOU ARE: are a U.S. Veteran with PTSD who is 21-64 years old COMPENSATION: You will be compensated for your time in the study, about 8 weeks TO GET A CALL FROM OUR TEAM: complete the brief pre-screening at https://redcap.link/starlight or scan code