Psilocybin-assisted Cognitive Behavioral Therapy for Depression

Study Protocol

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Study Protocol

Objective: To determine (1) acceptability and initial feasibility of psilocybin as an adjunct to cognitive-behavioral therapy (CBT) for major depressive disorder and (2) determine the effect of psilocybin treatment combined with CBT.

Principal Investigators:
Marc J. Weintraub, PhD; Assistant Professor of Psychiatry; UCLA Semel Institute (760 Westwood Blvd., #A8-259, Los Angeles, CA 90095); mjweintraub@mednet.ucla.edu. Dr. Weintraub is a licensed clinical psychologist with expertise in the conduct of clinical trials for mood and psychotic disorders. Dr. Weintraub will be responsible for the review and evaluation of information relevant to the safety of the trial. He will also oversee the coordination of the clinical trial, serve as a clinician in the study, manage the study data, and lead the analysis and presentation of the study data.

David J. Miklowitz, PhD; Distinguished Professor of Psychiatry; UCLA Semel Institute. Dr. Miklowitz is a licensed clinical psychologist and the Director of the UCLA Mood Disorders Program. He has significant expertise in the conduct of clinical trials for mood and psychotic disorders. Dr. Miklowitz is the director of the Mood Disorder Clinic at the UCLA Semel Institute in which this study will be conducted. He will have several active roles in this study despite not leading psilocybin or CBT sessions. Dr. Miklowitz (along with Dr. Weintraub) will be responsible for the review and evaluation of information relevant to the safety of the trial. Dr. Miklowitz has significant expertise in the conduct of clinical trials for mood and psychotic disorders. As such, he will be integrally involved in the supervision and coordination of the psychosocial treatment portion of the study. Dr. Miklowitz will provide regular consultation on matters related to the treatment development portion of this study (e.g., assessing feasibility and acceptability of the CBT's integration with the psilocybin sessions). Dr. Miklowitz will also help oversee the screening and enrollment of study participants, collection and management of study data, and analysis and presentation of study data.

Sub-Investigators:
Ziva Cooper, PhD; Associate Professor of Psychiatry; UCLA Semel Institute. Dr. Cooper is a behavioral pharmacologist and the Director of the UCLA Cannabis Research Initiative.

Jessica Jeffrey, MD, MPH, MBA; Associate Professor of Psychiatry; UCLA Semel Institute. Dr. Jeffrey is a psychiatrist who serves as the Medical Director and lead psychiatrist of UCLA's Behavior Health Access.

Charles Grob, MD; Professor of Psychiatry; Harbor-UCLA Medical Center and UCLA Semel Institute. Dr. Grob is a psychiatrist and renowned expert in psychedelic treatment for psychiatric disorders.

Research Facility: UCLA Semel Institute – 760 Westwood Blvd, A Floor suite A800, Los Angeles, CA, 90095.

Institutional Review Board: UCLA Office of Human Research Protection Program, Box 951694, Los Angeles, CA 90095.

Specific Aims

The primary objectives of this clinical investigation are (1) to determine the acceptability and feasibility of joining psilocybin treatment with cognitive-behavioral therapy (CBT) for patients with depression, and (2) to determine the initial effect of psilocybin as an adjunct to CBT for major depressive disorder. Psilocybin will be administered orally in two doses during a 12-session CBT treatment to eligible study participants – a 10mg dose following the third session and a 25mg dose following the sixth session.

We hypothesize that psilocybin as an adjunct to 12 sessions of CBT will
(1) Be feasible and reviewed favorably by participants,
(2) Lead to improvements in depressive symptoms.

Background

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a natural product produced by numerous species of Psilocybe mushrooms. It is a tryptamine derivative, and in humans is rapidly enzymatically broken down to produce psilocin, which acts as a serotonin agonist (Carhart-Harris et al., 2014; Nichols, 2004). Psilocybin is classified as a Schedule I pharmacological substance by the DEA.

Psilocybin possesses a relatively low physiological toxicity and has not been shown to result on organ damage or neuropsychological deficits (Nichols, 2004). Psilocybin is not considered a drug of dependence or one that engenders compulsive drug seeking (NIDA, 2006). There is some concern that psychedelics can induce prolonged psychosis (Strassman, 1984). Based on clinical data from large trials in the 1950s, the rates were about 0.8-1.8 per 1000 patients (Cohen, 1960), which are lower than the base rate for psychosis in the general population. The most likely risks associated with this drug are anxiety, fear/panic, and/or paranoia (McCabe, 1977; Strassman, 1984). However, these side-effects tend to be experienced during the active phase of the psychedelic experience (up to 5 – 6 hours following administration) and then remit. Also, these symptoms are more likely to occur in individuals with a family history of bipolar disorder or psychosis. These family history attributes are exclusionary criteria for this study.

Psilocybin has an extensive history of use in humans. It has been used by indigenous cultures for centuries to millennia (Schultes et al., 2001). Early empirical work was done with the drug in the 1950s and 1960s, including investigating its potential therapeutic use in the treatment of cancer, substance dependence, and mental health difficulties (Grob et al., 1998). In more recent years, psilocybin has been studied in the context of mystical experiences (Griffiths et al., 2006). Psilocybin has been found to increase trait-levels of openness as well as engender feelings of connectedness and a greater sense of meaning and purpose (Griffiths et al., 2011; MacLean et al., 2011). In the general population, these perceptual and cognitive changes are strongly felt and endure for months following one administration (Griffiths et al., 2006).

Psilocybin research has also re-emerged as a potential therapeutic agent for mental health difficulties. Psilocybin has been tested in clinical trials for alcohol dependence (Bogenschutz et al., 2015), obsessive-compulsive disorder (Moreno et al., 2006), cancer patients (Grob et al.,

2011), and depression (Carhart-Harris et al., 2018). One recent trial has studied psilocybin in conjunction with psychotherapy (supportive therapy) for patients with depression (Davis et al., 2021). The data from recent trials of psilocybin in patients with depression suggest that one to two administrations of psilocybin produces antidepressant effects in individuals with major depressive disorder as well as treatment-resistant depression (i.e., individuals not responding to > 2 trials of antidepressants; Davis et al., 2021; Carhart-Harris et al., 2016).

Adjoining the psilocybin drug treatment is commonly a psychedelic-assisted therapy (PAT), which involves a supportive therapy that gives the participant freedom to experience the drug independent of clinical intervention by the drug monitor/therapist. The participant is encouraged to "collect experiences" and "dive deeply into the experience." The monitors will occasionally (e.g., once/hour) check with the volunteer to ensure that the individual is not experiencing significant distress or in need of support. Following the psychedelic experience, the participant might begin to reflect on and share the experience with the therapist in the latter hours of the drug session. Over the course of the following days/weeks, the therapist will assess the participant for safety as well as help the participant integrate these experiences with their pre-defined intentions for the psychedelic experience (Johnson et al., 2008; Davis et al., 2021).

As of yet, PAT is mostly unstructured and without a manualized format within the scientific literature. While PAT is considered useful in facilitating a positive response to psilocybin and reducing the likelihood of adverse events (Johnson et al., 2008), the details of the treatment are not clearly outlined or protocolized. Having a more protocolized psychosocial treatment that adjoins the psilocybin drug session can help to create a standardized treatment approach that can be more closely studied and optimized.

Cognitive behavioral therapy (CBT) is considered the gold-standard of empirically-based psychosocial treatments for depression (Cuijpers et al., 2013). Thus, CBT may serve as a useful, standardized foundation of psychosocial treatment to provide for patients with depression who are receiving psilocybin treatment. Additionally, psilocybin may help facilitate the uptake of CBT skills. Since psilocybin engenders greater cognitive flexibility and behavioral motivation (e.g., greater openness and social connectedness), it may help facilitate the uptake of CBT skills. Depressed individuals' negative beliefs and unhelpful behaviors can become quite fixed, which can make treatment progress slow. Together, psilocybin may be a helpful catalyst for the cognitive and behavioral changes that are sought in CBT, and CBT may help to solidify cognitive and behavioral changes that are spurred by the psilocybin experience.

This study seeks to build on the current approaches to psilocybin treatment by combining CBT with the already-established psilocybin + PAT approach to (1) test whether CBT can be feasibly and acceptably added to the current psilocybin treatment modality and (2) to work towards protocolizing the psychosocial treatment that adjoins psilocybin drug therapy.

GENERAL INVESTIGATIONAL PLAN:

This study is a preliminary, proof-of-concept pilot to determine feasibility of the treatment methods and effect sizes. The study design is a single-group, fixed dose trial whereby 30 eligible participants will undergo 12 sessions of CBT during which two doses of psilocybin will be administered– a 10mg dose following the third session and a 25mg dose following the sixth session. Participants will be followed for an additional 3 months following treatment

termination. Study procedures will follow previously established safety guidelines (Johnson et al., 2008).

We hypothesize that psilocybin as an adjunct to 12 sessions of CBT will:
(1) be feasible and reviewed favorably by participants, with minimal to no adverse effects;
(2) Lead to reductions in negative thinking, increases in engagement with the environment, and improvements in depressive symptoms over the 7-month study period.

Participants who are deemed to meet psychological and medical criteria for the study (see screening and testing procedures below) will proceed to the CBT treatment, The CBT protocol will include previously used psychedelic-assisted therapy (PAT) components, which help the patient prepare for the drug session, explore their personal drug experience after the drug session, and integrate this experience with their pre-determined intention for the drug session. Additionally, as a treatment development study, this study will allow for flexibility in the protocol so that the research team to optimize a psilocybin-based CBT, including the possibility of adding 1-3 booster sessions or reducing the treatment length by 1-3 sessions. The general structure of the CBT will contain the following.

- Therapy sessions 1-3 will be preparatory sessions for the psilocybin experience. As time allows in these first three sessions, psychoeducation about depression, the theoretical rational for CBT, and behavioral activation will be presented to the participant, and the participant will be asked to begin behavioral activation activities (i.e., scheduling pleasant events during periods of low mood).
- The first drug session (10mg psilocybin) will be held following the third therapy session. As time permits towards the end of the drug experience (e.g., 5-6 hours after ingestion) and if the subject is agreeable to it, the subject will be engaged in the preliminary cognitive skills of CBT (e.g., thought monitoring and cognitive restructuring).
- Therapy session 4 will involve discussion of the psilocybin experience integration of the experience with their pre-stated intentions for therapy.
- Therapy sessions 5-7 will include a full presentation of cognitive skills, culminating with cognitive restructuring, as well as additional discussion towards behavioral activation.
- The second psilocybin session (25mg psilocybin) will take place after therapy session 7. If the subject is agreeable to it towards the end of the drug experience, they will be engaged in cognitive skills of CBT.
- Therapy session 8 will again involve integration of the drug experience.
- Therapy sessions 9-12 will include further cognitive and behavioral work specific to CBT and forming a relapse prevention plan (i.e., identifying risk and protective factors, early mood symptoms, and coping strategies).

The two drug administrations will be conducted with one individual participant at a time, each done in a single day. The first drug session (10mg dose) will be conducted over a 6-hour period and the second, high dose session (25mg) will be conducted over an 8-hour period. The first drug administration will be conducted following the third CBT session; the second will be conducted following the sixth session. Participants will be instructed to eat a light, low-fat breakfast on the day of the drug session and to arrive at the study site at 8am.

When the participant arrives at the UCLA Semel Institute for the drug session, prior to the psilocybin's administration, the participant will conduct a urine screen to test for the presence of and illicit drugs and, if the participant is biologically female, to confirm that she is not pregnant. Prior to the psilocybin's administration, participants will also be assessed for recent alcohol use through a breathalyzer test. Participants must have negative toxicology and pregnancy (if applicable) screens as well as no detectable amount of alcohol as measured by the breathalyzer test (i.e., 0.00% BAC) in order to proceed with the drug session. Participants who test positive for any illicit drugs, pregnancy, or alcohol will at any of the study screenings will not be allowed to proceed with the drug session and will be removed from the study. Participants will then be re-oriented to the plan for the day, including that they will be taking psilocybin and remaining in the therapy room for the duration of the drug experience (with the exception of bathroom breaks, as needed). The participant will then be given the psilocybin (10mg [administered in two 5mg capsules] for the first administration; 25mg [administered in one capsule] for the second administration) with a glass of water to begin the drug session. The results of the drug and pregnancy screens, administration of study drug(s), and safety measurements throughout the psilocybin session (see below) will all be catalogued on the study's case report form, which is shown in Appendix I (pg. 25).

Following administration of the drug, the participant will lie down with an eyeshade over their eyes and given a pre-determined playlist of classical music to listen to through headphones (see music playlist in Appendix II, pgs. 26-28). Two therapists, termed drug monitors (i.e., the participant's assigned CBT clinician as well as a second clinician, ideally one male and one female) will remain present with the participant for the entirety of the 6–8-hour drug session. The monitors will check in with the participant every hour to (1) measure their blood pressure, with acceptable ranges not to exceed 140 systolic and 90 diastolic, and to (2) verbally check in on the participant's subjective well-being to ensure that the participant is not experiencing significant distress or in need of support (e.g., "Would you like to describe where you find yourself?").

Overall, participants will be encouraged to spend the drug session immersed in the drug's effects (as opposed to making conversation with the study clinicians), so that they can experience the drug's full effects and plan to discuss the experience in great detail in the therapy sessions. However, drug session monitors will be prepared to provide emotional support and, if necessary, physical support (e.g., holding the participant's hand) if the patient is distressed. Participants will be provided with a notepad to keep track of thought, emotions, and other experiences during the drug session should they choose to do so. Session monitors will also have notepad to write down experiences reported by the participants After the drugs' effects have mostly subsided (i.e., at least 5 hours following the drug's administration), the participant will be asked to complete questionnaires, write notes about their experience, and complete a semi-structured interview with the study monitors.

After the effects of the psilocybin have resolved (at least 6 hours following administration), the participant will be released into the care of an identified support person. In order for the participant to be released following a psilocybin session, he/she must be oriented to person, place, time, and situation; have successfully completed the post-drug session clinical interview and questionnaires; not be experiencing acute distress (e.g., suicidal ideation) that requires

psychiatric attention; and have blood pressure and heart rate measurements within normal ranges.

Participants will be instructed not to drive an automobile or engage in any other potentially dangerous activity for the remainder of the day. The study staff will also orient the identified support person to whom the participant is being released to be available to provide emotional support, if necessary, but also to provide space if the participant would rather be alone. Each participant will be given one of the study clinician's direct pager/cellphone number to call if he/she needs support prior to their next CBT session. Within a couple of days following the drug session, participants will conduct their next weekly session of CBT, where the study clinician will inquire about any persisting or adverse effects of the psilocybin.

PARTICIPANTS:
Participants will be adults (ages 21-60) who meet current criteria for major depressive disorder.

STUDY INCLUSION AND EXCLUSION CRITERIA:

All participants must meet the following inclusion criteria to be eligible for the study:

- Ages 21-60,
- Able to swallow capsules,
- Patients with a current major depressive episode or a history of major depressive episodes based on the DSM-5 criteria (American Psychiatric Association, 2013),
- Active current depressive symptoms (i.e., scores >16 on the Hamilton-Depression Rating Scale covering the prior 2 weeks; Hamilton, 1986),
- Have an identified support person who can pick up the individual from UCLA Semel Institute and drive individual home following psilocybin sessions,
- For women of child-bearing potential – using one form of highly effective contraception (e.g., oral contraceptive pill) and willingness to continue contraceptive use for duration of study. Must be willing to take on-site pregnancy tests.
- Agree to refrain from any psychoactive drug (including alcohol) within 24 hours of each drug session and during the drug sessions. Participants will be allowed to consume their usual amount of caffeine prior to and after the drug sessions.
- Agree to not take any PRN medications on the mornings of the drug sessions
- Patient has been medically cleared for the study by a physician
- Participants must remain on anti-hypertensive medications if prescribed previously to manage hypertension

Participants will not be enrolled in the study if the meet any of the following exclusion criteria:

- A personal or family history (first or second-degree) of psychosis or bipolar disorder
- Resting blood pressure above 140 systolic, 90 diastolic or heart rate > 90 beats per minute (averaged across four separate measurements)
- Meeting criteria for a DSM-5 cluster B personality disorder (narcissistic, histrionic, borderline, antisocial personality disorder),
- Active suicidality (i.e., HAM-D item 3 score of 3 or greater) or other psychiatric disturbance requiring acute treatment

- Current use of antidepressants or other serotonergic-affecting substances (e.g., St. John's Wort and 5-hydroxytryptophan), lithium, or efavirenz [regardless of whether the drug(s) is/are prescribed for MDD or other conditions]
- Current use of opioids (e.g., codeine, fentanyl, hydrocodone, meperidine, tramadol)
- Currently receiving cognitive behavioral therapy,
- Any of the following cardiovascular conditions: uncontrolled hypertension, coronary artery disease, congenital long QT syndrome, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction, tachycardia, artificial heart valve, a clinically significant screening ECG abnormality, or any other significant cardiovascular condition
- QTc interval measurement of > 450 ms in males or > 460 ms in females as measured by the baseline ECG
- A history of stroke or Transient Ischemic Attack (TIA)
- Epilepsy or history of seizures
- Insulin-dependent diabetes
- Meeting criteria for a DSM-5 substance abuse or dependence within prior 6 months (including for nicotine and cannabis)
- Positive urine drug screen for illicit substances (not including cannabis)
- Use of other psychedelics or ketamine within prior 12 months
- Adverse prior reaction to a 5-HT2A receptor agonist psychedelic agent
- Pregnant, trying to get pregnant, or nursing

SCREENING AND TESTING PROCEDURES:

Each participant will undergo a physical screening by a qualified health practitioner at UCLA's Clinical and Translational Research Center (CTRC). The physical screening will include a general physical exam (i.e., recording participant's blood pressure, pulse, height, and weight, and conducting non-invasive check of heart, lungs, ear/nose/throat, and reflexes). Since psilocybin can increase pulse and blood pressure (Griffiths et al., 2006; Johnson et al., 2008), patients with resting blood pressure above 140 systolic, 90 diastolic or heart rate > 90 beats per minute (averaged across four separate measurements within the screening process) will be excluded. The physical screening will also include an electrocardiogram (ECG) and a 30-cc blood draw for a complete blood count (CBC), a metabolic panel, a thyroid-stimulating hormone (TSH) test, liver functioning tests, and a C-reactive protein (CRP) blood test. Finally, the physical screening will include a urine drug screen to determine any current drug use and a urine pregnancy screen to rule out pregnancy in females.

In addition to the physical screen at the UCLA Clinical Trial Research Center (CTRC), the participant will undergo a medical interview with a study assessor. The study assessor will inquire about and record the participant's current medical conditions and medication use. Medications taken by the participants (both prescribed and over the counter) will be recorded, including SSRIs or any other serotonergic-acting drug (e.g., St. John's Wort). Chronic and/or recent use of antidepressants (e.g., serotonin reuptake inhibitors) and other substances that affect serotonergic functioning can attenuate the effects of hallucinogens (Bonson, 2012; Strassman, 1992), and thus pose a scientific confound. For eligible participants with prior exposure to a drug with serotonergic activity, the serotonergic-acting drug will need to have been discontinued for at least five half-lives of active major metabolites prior to psilocybin exposure. Participants will not be able to proceed past the study screening if/while they are currently on serotonergic

agents, lithium, or efavirenz (regardless of whether the drug(s) is/are prescribed for a depressive disorder or another condition). Additionally, participants will be excluded if they are taking agents that may interact with psilocybin metabolism/effects (e.g., antipsychotics, other dopamine antagonists) or agents that may increase the risk of psychotic symptoms (e.g., dopamine agonists, stimulants). The study team will not work with subjects to taper them off medications. Subjects will be excluded if they, prior to screening, have not already discontinued any medications excluded for this study.

The results of the physical screening (including the blood panels, urine toxicology, and ECG) will be reviewed by a study physician. To be eligible, participants must have a clear ECG screening (no clinically significant abnormalities and QTc measurement > 450 milliseconds in males or > 460 milliseconds in females). Participants will also be excluded if they report or are found to have any cardiovascular conditions, including uncontrolled hypertension, coronary artery disease, congenital long QT syndrome, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction, tachycardia, artificial heart valve, a clinically significant screening ECG abnormality, or any other significant cardiovascular condition. A personal history of stroke, Transient Ischemic Attack (TIA), hepatic impairment, epilepsy, and insulin-dependent diabetes will also be exclusionary. Individuals who have any medical conditions or take medications that are exclusionary for this study will be withdrawn from the study. In addition to a negative pregnancy test, women of child-bearing potential will need to be on at a form of highly effective contraception (e.g., oral contraceptive pill) for at least one month prior to study entry and for the duration of the study.

For individuals with whom the study physician requires more clarification regarding their medical condition(s) or medications, a release of information (ROI) will be obtained to consult with the participant's primary care physician. For participants with which the study physician cannot gather a clear medical history or in which there is ambiguity around whether they meet criteria for any of the above-mentioned conditions will be excluded from the study. Participants who do not clear the medical screening will be withdrawn from the study.

In addition to a physical screening, each participant will undergo a psychiatric evaluation with a study psychologist. The Structured Clinical Interview for DSM-5 (SCID-5; First & Williams, 2016) and a Family History Screening instrument (Weissman et al., 2000) will be used to determine participants' personal and family mental health history. Individuals with a personal or family history with psychosis will be withdrawn from the study, as there is a risk that psilocybin can induce psychosis, particularly in patients with a predisposition for these conditions (Strassman, 1984). Additionally, individuals with elevated personality symptomatology have a higher likelihood for negative hallucinogenic experiences (Dittrich, 1994; Hasler et al., 2004). Thus, individuals with a Cluster B Personality Disorder (narcissistic, histrionic, borderline, and antisocial personality disorder) will be withdrawn during the screening process. Study clinicians will rate each participant on their depressive symptom severity using the Hamilton Depression Rating Scale (Hamilton, 1986).

Participants will be also assessed for their current engagement in psychotherapy. Participants who are receiving psychotherapy (other than cognitive behavioral therapy; CBT) at the study entrance may participate in this study if the frequency of the therapy has been stable for the past

two months and is expected to remain stable during participation in the study. Because this is a study of CBT, participants who are currently receiving CBT will not be eligible for this study.

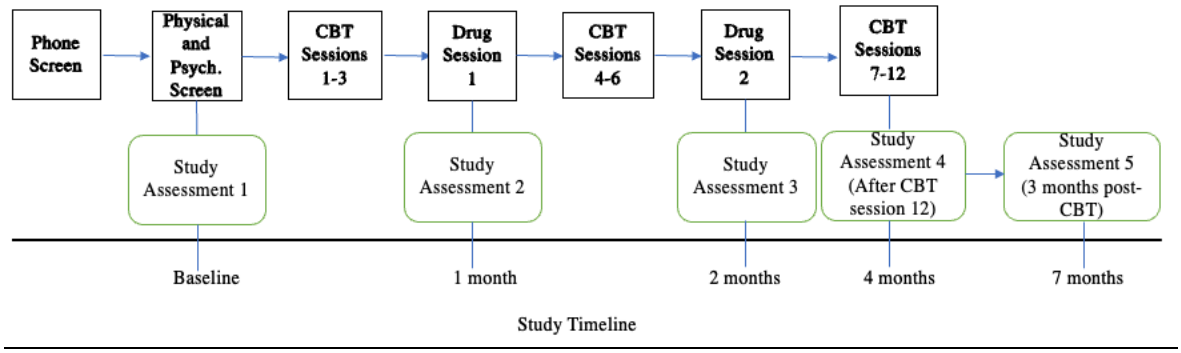
The study will screen for participants' age, requiring participants to be 21-60. Compared to previous trials with psilocybin, including psilocybin trials with patients with depression, this study has a narrower acceptable age range. The typical age range is early adulthood (18 or 21) to 75-80 years (e.g., Carhart-Harris et al., 2021; Davis et al., 2021). Since cardiac conditions are a concern with psilocybin use, we decided to lower the upper age limit to minimize potential cardiac complications. However, the current psilocybin literature does not indicate any differences in drug's psychological effect based on age. Considering this study is a pilot with the broader goal of testing the acceptability of CBT as an adjunct to psilocybin as well as protocolizing psychotherapy as an adjunct to psilocybin, we are interested in sampling from a broad age and depressive population.

PRIMARY OUTCOME MEASURES AND STATISTICAL ANALYSIS PLAN:
The study's primary assessments will be held prior to starting the CBT (i.e., baseline), within two weeks following the CBT's completion, and three months following the treatment's completion. Secondary measurements will also be collected immediately following each drug session. The study will terminate following the three-month follow-up assessment. A schematic of the study design is presented in Figure 1 below.

To determine feasibility, we will track the number of participants engaged at each phase of screening (i.e., phone screen, physical screen, and psychological screen), the number consented and enrolled, and the number who completed the 4-month treatment. Acceptability was measured by participants at the post-treatment assessment using the Client Satisfaction Questionnaire 8 (CSQ-8; Larsen et al., 1979). Participants' and clinicians' quantitative and qualitative feedback will be collected, using an internally-created questionnaire containing 5-point scales of helpfulness. Depressive symptom severity over the previous 1-2 weeks will be assessed using the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1986). Psychosocial functioning over the two weeks prior to the assessment will be rated by a study assessor assessed using the 100-point Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 2000).

Feasibility metrics will be tabulated by calculating percentages of participants enrolled and retained through the treatment divided by the total number of participants consented and screened. Acceptability metrics will be calculated based on the participant-rated CSQ-8. We will calculate the mean and standard deviation. We will examine within-subjects changes in depressive symptoms (HAM-D) and functioning (GAF) using repeated measures analyses of variance (ANOVA) in IBM's SPSS version 30.0. Time will the independent fixed factor variable, based on the interval assessments of the study (baseline, post-treatment, follow-up).

Figure 1. Study Design Schematic for Eligible Participants



STUDY DRUGS:

The psilocybin will be produced according to GMP regulations by Psilo Scientific Ltd. (a wholly-owned subsidiary of Filament Health Corp.; 4475 Wayburne Dr., Burnaby, B.C., Canada) under their Schedule I license. Stability and purity are verified with a Certificate of Analysis. A letter of authorization from Psilo Scientific Ltd. to reference their Drug Master Files (DMF #035999 (DS) and #036004 (DP)) has been submitted to the FDA for IND for the study. Psilocybin (Schedule I) will be stored in Dr. Weintraub's Schedule I highly secured storage facility in the UCLA Semel Institute under Dr. Weintraub's DEA license.

Operating Procedures

The operating procedures for receiving, storing, dispensing, and transporting the drug are outlined here. See the full details of the Drug Management Protocol in Appendix III (pg. 29-31) as well as the security provisions for drug storage in Appendix IV (pg. 32). In summary, the psilocybin will be received by Dr. Weintraub (along with an authorized personnel on Dr. Weintraub's DEA Schedule I license as witness) – shipped to Dr. Weintraub's laboratory at UCLA Semel Institute from Psilo Scientific Ltd. Immediately upon receipt, the psilocybin will be checked to ensure correct product and quantities received. The drug and quantities will be recorded into inventory in the study's drug log, signed by authorized personnel and locked in Dr. Weintraub's DEA approved storage location (see attached UCLA Controlled Substances Program Usage Log in Appendix V; pgs. 33-34).

The study drugs will be prescribed by a study physician with appropriate DEA authorization. Prior to a psilocybin drug session, the appropriate dose of psilocybin will be prepared. The drug will be placed in a plastic Ziplock bag and labeled with the drug's name and dose. The study drug log will be updated by a DEA authorized study personnel to indicate the drugs dispensed. The study drug will be transported by a DEA authorized personnel from Dr. Weintraub's DEA-approved storage location on the A floor of the UCLA Semel Institute to the drug session room (also on the A-floor of the UCLA Semel Institute) in a zippered medication bag. The subject will be given the study drug to self-administer and will be observed taking the study drug as prescribed by the study physician.

LABORATORY FACILITY:

All experimental sessions will be conducted in a therapy room in the UCLA Semel Institute. This study will utilize a family therapy room (~225 sq. ft.) for all the study procedures (i.e., screening, preparatory meetings, drug, and therapy sessions), which has all of the criteria to meet the setting condition. This room has comfortable furniture, including a couch for the participant to lie on, pleasant wall art, and sufficient space for the participant and drug session monitors to comfortably spend the 6–8-hour drug session. The therapy room is also adjacent to a private bathroom, which will be accessible by the patient throughout the drug session.

Protection of Human Subjects

SOURCES OF RESEARCH MATERIAL:

Volunteers will be informed that data will be obtained specifically for research purposes. Only the research team, authorized UCLA personnel, and regulatory agencies such as the Food and Drug Administration (FDA) will have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify participants by name.

1. POTENTIAL RISKS:

-Possible psilocybin effects and side effects

Psilocybin is a hallucinogenic drug with effects similar to other hallucinogens such as LSD and mescaline. Psilocybin is not thought to be physically harmful. However, psilocybin has not been put through the standard range of animal and human tests that are used to assess the toxicity of therapeutic drugs. This means there is no scientific data to prove either toxicity or safety. There is a chance, which we believe to be small, of physical toxicity not yet found in historical religious use, contemporary illicit use, or in the past 40 years of experimental and clinical use of this drug.

The main effects of psilocybin are psychological. A high dose of psilocybin, which participants would receive in this study, can bring about a very broad range of profound changes in perception and consciousness during the hours of drug action. About one-third of people in our previous study reported moderate to strong feelings of fear or anxiety after receiving psilocybin. Changes in normal perception can include visual or hearing changes (pseudo-hallucinations), and unusual smells, tastes, or other bodily sensations. Participants may experience anxiety, panic, or paranoia (suspiciousness) during the period of drug action. Participants may behave in ways such as intense crying, laughing, or panic that participants might later find embarrassing. Participants may experience powerful emotions, both pleasant and unpleasant. Participants' sense of time may be altered, such that time seems to pass more quickly or slowly than usual. Participants may have a sense that the participant's body and mind have separated. The effects of psilocybin usually last about 5-7 hours.

As with other experiences of a strongly positive or negative nature, participants may have dreams and/or lasting memories of psilocybin session experiences. After the psilocybin session, there may be short-term to permanent changes in personality, attitude, or creativity.

During the period of drug action, psilocybin may also cause dizziness, nausea, vomiting, incontinence, increased pulse and blood pressure, dilated pupils, increased reflexes, tremors, and muscle twitching. A few people in an earlier study had blood pressure increases during

psilocybin sessions. Taking any drug also involves a possibility of allergic reactions such as itching, rash, or hives. Some people have reported headache starting about 7 hours after taking psilocybin and sometimes lasting into the following day. Some participants have reported leg pain lasting 1-2 days after the session.

In addition, there are risks, which appear to be uncommon, of adverse effects that last for hours to days after the psilocybin session. These include mood disorders (such as depression), psychotic disorder, and anxiety disorder. There are rare reports where hallucinogen exposure appears to cause, speed up, or precipitate the onset of significant or lasting psychiatric illnesses such as psychoses and occasional or lasting visual perceptual disorders ("flashbacks", visual disturbances). There are no large well-controlled studies of psilocybin to prove or disprove that such long-term effects occur. However, we believe the chance of such lasting effects is very small.

The risks of adverse effects due to psilocybin will be minimized through the volunteer selection and screening procedures, the hours of preparation participants will have with a trained and experienced guide before the psilocybin session, and the supportive environment and care that will be given during the psilocybin session.

Participants will be carefully monitored throughout the session, and medical care will be given if and as needed. This medical care could involve increased medical monitoring and giving of medically appropriate drugs. Sublingual (under the tongue) clonidine may be given to lower participants blood pressure. Possible side effects of clonidine treatment are headache, low blood pressure, skin flushing, dizziness and weakness as well as other signs of low blood flow to the brain. Other possible effects are nausea, vomiting, restlessness, paleness, sweating, collapsing, rash, skin irritation, a feeling of skin tingling or creeping, nasal inflammation, swelling in the body, loss of strength, and abdominal pain. Medical care may also include transport to the Emergency Department. If medical intervention is required, a doctor will do a physical examination.

Prior to discharge from the psilocybin session, each participant will be given one of the study clinician's direct pager/cellphone number to call if he/she needs support that evening or prior to their next CBT session. Within a couple of days following the drug session, participants will conduct their next weekly session of CBT. The study clinician will inquire about any persisting or adverse effects from the psilocybin in this CBT session.

-Drug and medication restrictions

Participants must agree not to take other drugs while taking part in this study unless approved by the study team. Participants must not use illicit drugs and you must report to us the use of any prescribed, over-the- counter, or herbal medications. Subjects who test positive for illicit drugs or alcohol at any of the study screenings will be removed from the study. Psilocybin may interact with antidepressant medications and other serotonergic agents. Therefore, participants cannot proceed past the study screening if they are currently on serotonergic agents. If participants need to start taking a restricted during the study, they will not be administered psilocybin but will otherwise remain in the study. Restricted drugs which may interact with psilocybin include:

- **Selective serotonin reuptake inhibitors** (SSRIs), such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro), and fluvoxamine,
- **Serotonin and norepinephrine reuptake inhibitors** (SNRIs), such as venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta), and levomilnacipran (Fetzima),
- **Atypical antidepressants**, such as bupropion (Wellbutrin), mirtazapine (Remeron), trazodone (Oleptro), vortioxetine (Brintellix), vilazodone (Viibryd), and milnacipran (Savella),
- **Tricyclic antidepressants**, such as clomipramine, amitriptyline, imipramine (Tofranil), nortriptyline (Pamelor), desipramine (Norpramin), doxepin, trimipramine (Surmontil), and protriptyline (Vivactil),
- **Monoamine oxidase inhibitors** (MAOIs), such as Selegiline (Emsam), tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan),
- **Tetracyclic antidepressants**, such as maprotiline,
- **Serotonin modulators**, such as nefazone (Serzone),
- **Agents that may be associated with serotonin syndrome**, such as lithium, efavirenz (Sustiva), St. John's Wort, and 5-hydroxytryptophan, opioids, buspirone, carbamazepine
- **Agents that may interact with psilocybin metabolism/effects**, such as serotonin antagonists (e.g., cyclobenzaprine, ondansetron), antipsychotics, dopamine antagonists, nicotine, modulators of uridine diphosphate (UDP) or glucuronosyltransferase
- **Agents that may increase the risk of psychotic symptoms**, such as carbidopa-levodopa, dopamine agonists, stimulants, anticholinergics, N-methyl-D-aspartate (NMDAR) antagonists

If participants must take a nonprescription medication, participants will be asked to stop using it for 24 hours before a psilocybin session. Pain relievers containing only aspirin, ibuprofen, or acetaminophen are acceptable for normal use without special permission. Participants must also agree to leave urine samples upon request or to take a breathalyzer test to allow the study team to monitor participants' compliance with the drug and alcohol restrictions.

-Cognitive behavioral therapy (CBT)

There are no significant risks of CBT; however, CBT does involve asking patients to engage in activities that can be aversive and/or opposite of their typical thoughts and behaviors. As such, participants may experience discomfort as a result to engaging in CBT skills such as cognitive restructuring, behavioral activation, relaxation exercises.

-Depressive symptoms

Cognitive-behavioral therapy and psilocybin have been shown to have a beneficial effect of depressive symptoms. Nonetheless, it is possible that depressive symptoms will worsen during the study. An increase in depressive symptoms could be due to the study interventions (including psilocybin), not continuing in standard clinical care, or the natural course of depression. Depressive symptoms which could worsen include, but are not limited to: suicidal thoughts, low mood, feeling hopeless or guilty, fatigue, lack of pleasure, poor concentration, and change in sleep or appetite.

-Alcohol restrictions

The effects of psilocybin may interact with alcohol. This means that if participants consume alcohol while the drug is in their system, they could experience magnified or unpredictable effects of the drug, which could impair their ability to do everyday tasks such as driving an automobile. Such undesirable effects are possible for at least 24 hours following a visit to the research unit. Therefore, participants will be asked to not consume alcohol for a period of at least 24 hours before and 24 hours following the psilocybin session.

-Activity restrictions

For safety reasons, participants will not be allowed to drive themselves home after a day-long psilocybin session. It is possible that effects of psilocybin may persist after the time participants are scheduled to leave the research unit. We recommend participants stay with a trusted friend or relative overnight and that they refrain from operating dangerous machinery or a motor vehicle for at least 24 hours after psilocybin administration. Participants may also be asked by the study team to restrict other activities or to stay at the research unit until psilocybin effects lessen.

-Psychological risks

Some of the questions the therapist and researchers ask participants may be upsetting, or participants may feel uncomfortable answering them. Participants may get tired or bored when we are asking questions or are completing questionnaires. If participants do not wish to answer a question, you can skip it and go to the next question.

-Confidentiality

Although we will do our best to keep your participation in this study confidential, taking part in this study may entail the unlikely risk of loss of confidentiality of sensitive information.

-Unknown risks

There may be side effects and discomforts of this study that are not yet known.

2. ADEQUACY OF PROTECTION AGAINST RISKS:

Recruitment and Informed Consent:

Flyers will be available at appropriate locations (e.g., approved UCLA bulletin boards and UCLA Semel outpatient clinic waiting rooms). Information about the study will be sent to relevant groups and may be posted on their group social media pages. Examples of these include the Bipolar and Depression Support Alliance (DBSA) and local chapters of the National Alliance on Mental Illness (NAMI). Study flyers will also be sent to local mental health providers and local school counselors and mental health personnel.

Interested individuals will contact a research associate, who will provide information about the study. Potential participants will be given opportunities to ask questions about the study. A brief screening will be conducted with the interested individual. If the potential participant appears eligible agrees to an initial evaluation, a first appointment will be scheduled for consenting and eligibility assessment. At this meeting, the study team will explain the study procedures and ask for written consent from the participant. The participant will then undergo the study assessment process - medical screenings, diagnostic interview, and complete initial self-report measures.

Protection Against Risk:

Training of Study Monitors in Psychedelic Assisted Therapy (PAT): Marc Weintraub, PhD, and Megan Ichinose, PhD, (licensed clinical psychologists) will be trained in PAT by Charles Grob, MD and Jessica Jeffrey, MD, MPH, MBA. Dr. Grob has led and consulted on previous research trials using psilocybin and has significant experience leading PAT sessions. Dr. Jeffrey is certified in PAT following intensive training from the Integrative Psychiatry Institute (IPI) and the Multidisciplinary Association for Psychedelic Studies (MAPS). Dr. Jeffrey had extensive 200-hour training in Psychedelic-Assisted Psychotherapy (PAT) from the IPI between 2021-2022. As part of this training, she led multiple PAT sessions using ketamine and she has continued to provide PAT with ketamine to patients in her private practice since completing her training. Dr. Jeffrey also completed the 100-hour MAPS PAT training program for MDMA-assisted therapy in 2022.

The trainings for this study are modeled after the trainings conducted for Dr. Grob's previous psilocybin trial. The trainings will first involve structured didactics in the methods of PAT, management of difficult experiences patients may have, and crises that may arise. Following the didactics, Drs. Grob and Jeffrey will facilitate role-plays to practice common psilocybin-induced scenarios and PAT practices. The PAT training plan for will be conducted as follows:

Dr. Grob will be the lead therapist/monitor for the first session with Dr. Jeffrey as the co-therapist and Drs. Weintraub and Ichinose observing. Dr. Grob will be the co-therapist/monitor for an additional session with Dr. Jeffrey as the lead therapist and Drs. Weintraub and Ichinose observing. Then, if/when Dr. Grob deems Dr. Jeffrey is ready, Dr. Jeffrey can lead sessions and serve as a trainer for the other study clinicians. Drs. Jeffrey or Grob will lead two sessions each with Drs. Weintraub and Ichinose as co-leaders. Then, Drs. Weintraub and Ichinose will each lead two sessions with Dr. Jeffrey or Dr. Grob co-leading. Then, if/when Drs. Jeffrey/Grob deem Drs. Weintraub and Ichinose are ready, they may also lead psilocybin sessions. Drs. Weintraub and Ichinose will continue to undergo direct supervision from either trainer until both trainers agree to their competence to co-lead sessions without their direct supervision. As the primary study psychiatrist, Dr. Jeffrey will be available for immediate consultation throughout each drug session that she is not directly monitoring/leading. Dr. Grob will provide on-going monthly advisement for the study personnel on matters pertaining to PAT throughout the duration of the study. Any future clinicians for the study will undergo the same aforementioned training.

The primary drug monitors for this study will include Drs. Jeffrey, Weintraub, and Ichinose. Dr. Jeffrey is a board-certified psychiatrist who will serve as the lead psychiatrist. Dr. Jeffrey serves as the Medical Director and Lead Psychiatrist of UCLA's Behavioral Health Access, Associate Director of the Division of Population Behavioral Health, and the Associate Medical Director of the UCLA Ambulatory Services. These positions all involve extensive work with adult populations with a range of psychiatric conditions. Dr. Weintraub is a licensed clinical psychologist. Dr. Weintraub has significant expertise in evidence-based treatments (including CBT) for mood and psychotic disorders. His doctoral training was almost exclusively with adults with mood and psychotic disorders. During his postdoctoral fellowship at the UCLA Semel Institute, he continued working with adult mood populations through multiple research trials, including an adult mood registry study as well as a longitudinal study of adult mood disturbances. Additionally, Dr. Weintraub's clinical work consists of adult and adolescent

patients with mood disorders. Dr. Ichinose is a licensed clinical psychologist. She has extensive training from her graduate and postdoctoral training in the psychosocial treatment of mood, psychotic, and anxiety disorders. Both in her work at UCLA and her private practice, she specializes in cognitive-behavioral therapy for these disorders. Additionally, Drs. Weintraub and Ichinose have taken a Psychedelic Assisted Psychotherapy (PAT) course that was being delivered at a Los Angeles-based counseling center (Maple Counseling). The course is a 7-part course that includes the fundamentals of PAT as well as safety and ethical considerations when delivering PAT.

Prior to Drug Sessions: All participants are fully informed of the side effects that they might experience. Multiple entrance criteria and study protocols have been put in place to ensure safety of participants, including a detailed medical history screening and blood pressure readings at four times on at least two days prior to the drug administration. Participants with resting blood pressure exceeding 140 systolic and 90 diastolic (mmHg) averaged across their four readings will be withdrawn from the study. Further, to avoid risk of a serotonin syndrome reaction (Callaway & Grob, 1998), we will exclude participants who are currently taking any medications that affect serotonergic functioning, including serotonin reuptake inhibitors as well as over the counter supplements such as St. John's Wort. For eligible participants with prior exposure to a drug with serotonergic activity, the serotonergic-acting drug will need to have been discontinued for at least five half-lives of active major metabolites prior to psilocybin exposure.

We will thoroughly assess for psychiatric contraindications by gathering personal and family psychiatric history of psychotic, bipolar, and personality disorders. Additionally, any participants whose psychiatric symptoms require acute treatment (e.g., severe suicidal ideation) will be excluded. Suicidal ideation and behavior will be assessed via clinician-based assessment on the Hamilton-Depression Inventory and the Columbia Suicide Severity Rating Scale at each study assessment as well as the Depressive Disorders Module of the Structured Clinical Interview for DSM-5 Disorders at the baseline screening assessment. Additionally, participants will self-report on suicidal ideation on the Patient Health Questionnaire and Quick Inventory of Depressive Symptomatology at each study assessment.

Following a thorough screening of participants' physical and psychiatric status, further safety precautions will be in place throughout the course of the study. Prior to the first drug administration, each participant will undergo approximately 3-4 hours of preparation for the drug. These preparatory sessions will overlap with the beginning of the psychosocial treatment (CBT). In these sessions, the therapist will begin to develop rapport with the participant, discuss meaningful aspects of the participant's life, and discuss the range of experiences to be expected from the drug. The therapist and the patient will also discuss the patient's intentions for the drug session, which will include seeking a better understanding of the causes and consequences of their mood difficulties as well as exploring ways to improve their depression.

Additionally, participants will be prepared with strategies to overcome difficult experiences during the drug session. Relative to other classes of drugs, the subjective effects of psilocybin are more variable and more difficult to describe. Therefore, sufficient time to fully discuss the potential effects of the drug, provide recommendations for how to respond to various experiences, and to answer the participants' questions and concerns will help ensure that the

participant is psychologically prepared for the drug experience. In cases where a participant experiences distress from the drug experience, he/she will be told to "mentally surrender to the experience" and trust that their usual state of consciousness will return when the drug effects resolve. Additionally, participants will be encouraged to mentally approach and "dive in" to their experience, as this helps to alleviate both physical and emotional discomfort (McCabe, 1977).

*Set and Setting: "*Set and setting" have become well-recognized conditions that should be met prior to the administration of a hallucinogen to decrease the likelihood of adverse psychological reactions to the drug (Malitz et al., 1960; Rinkel et al., 1960). Set refers to the patient's psychological state (i.e., mindset). The screening and preparatory meetings help to ensure that the participant will be in good psychological health and in a positive mindset for the drug experience. Further precautions to meet the condition of mindset will include having a pleasant interpersonal atmosphere created by the study staff and to have staff with the expertise to appropriately monitor the sessions. Our study investigators are all trained as clinical researchers with significant experience with patients with mood disorders as well as the conduct of clinical trials.

The setting refers to the environment, with an aesthetically pleasing, private, and comfortable environment decreasing the probability of acute psychological distress (Johnson et al., 2008). This study will utilize a family therapy room (~225 sq. ft.) for all the study procedures (i.e., screening, preparatory meetings, drug and therapy sessions), which has all of the criteria to meet the setting condition. This room has comfortable furniture, including a couch for the participant to lie on, pleasant wall art, and sufficient space for the participant and drug session monitors to comfortably spend the 6 – 8-hour drug session. The therapy room is also adjacent to a private bathroom, which will be accessible by the patient throughout the drug session.

For the psilocybin sessions, participants must agree to remain at the UCLA Semel Institute until the research team says they are ready to leave. At the end of the sessions, they must be driven home by a trusted support person who has been identified to the study staff. The study staff will release the participant to this identified person at the end of the psilocybin session. However, if the UCLA staff believes it is necessary for safety reasons, the participant will stay overnight. If the participant stays overnight, the UCLA staff will interview the participant before they return home.

<u>Exclusion criteria:</u>
The following exclusionary criteria are designed to minimize the risks to participants:

- Currently receiving cognitive behavioral therapy,
- A personal or family history (first or second-degree) of psychosis or bipolar disorder
- Resting blood pressure above 140 systolic, 90 diastolic or heart rate > 90 beats per minute (averaged across four separate measurements)
- Meeting criteria for a DSM-5 cluster B personality disorder (narcissistic, histrionic, borderline, antisocial personality disorder),
- Active suicidality (i.e., HAM-D item 3 score of 3 or greater) or other psychiatric disturbance requiring acute treatment

- Current use of antidepressants or other serotonergic-affecting substances (e.g., St. John's Wort and 5-hydroxytryptophan), lithium, or efavirenz [regardless of whether the drug(s) is/are prescribed for MDD or other conditions]
- Current use of opioids (e.g., codeine, fentanyl, hydrocodone, meperidine, tramadol)
- Any of the following cardiovascular conditions: uncontrolled hypertension, coronary artery disease, congenital long QT syndrome, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction, tachycardia, artificial heart valve, a clinically significant screening ECG abnormality, or any other significant cardiovascular condition
- QTc interval measurement of > 450 ms in males or > 460 ms in females as measured by the baseline ECG
- A history of stroke or Transient Ischemic Attack (TIA)
- Epilepsy or history of seizures
- Insulin-dependent diabetes
- Meeting criteria for a DSM-5 substance abuse or dependence within prior 6 months (including for nicotine and cannabis)
- Positive urine drug screen for illicit substances (excluding cannabis)
- Use of other psychedelics or ketamine within prior 12 months
- Adverse prior reaction to a psychedelic agent
- Pregnant, trying to get pregnant, or nursing

Participant Education:

- All participants will be informed of the possible side effects and risks previously mentioned through the informed consent form and discussions with study psychologists and research staff.

Consent Procedures:

- Participants will provide informed consent to screening and all study procedures prior to study entrance.

Participant Monitoring and Removal from the Study:

- The research team will continually assess the participant's health throughout the study and will remove participants from the study if physical or mental deterioration is observed.
- Immediate removal from the study will result if significant adverse reaction to psilocybin or assessment procedure is noted.
- Upon removal of a participant from the study, he or she will be provided with the appropriate follow-up treatment by the study physician.

3. SAFETY MEASURES:

Two drug session monitors will be present for the entire drug session. One of the monitors will be the participant's assigned clinician for the psychotherapy. A second monitor will be present to help with the drug session and ensure that the participant will never be alone if the primary monitor needs to step out (e.g., to use the restroom). Both session monitors will be psychologists and/or psychiatrists. These clinicians will receive didactic training in psychedelic-assisted therapy (PAT; see above). They will also have extensive experience with both mood and psychotic disorders and be experienced in managing acute distress in patients through various

stress-reduction techniques, including leading relaxation exercises and providing reassurance to participants as needed. Before drug administration, hourly for the first four hours, and before discharge from the drug session blood pressure will be measured. Participant's experience of headaches and adverse visual-perceptual effects will be elicited at the end-of-drug session. Additionally, at each participant-contact (i.e., each CBT session and study assessment), a study therapist/assessor will inquire about any persisting headaches and/or visual-perceptual effects. Participants will be asked about any somatic symptoms and sensory experiences (i.e., visual, auditory, tactile, olfactory, gustatory) that have continued since the psilocybin's effects have subsided. Participants with persisting headache and/or persisting visual-perceptual effects that meet DSM-5 criteria for hallucinogen persisting perception disorder will be further assessed by a study psychiatrist to determine whether pharmacological treatment is indicated. Participants will also be asked about any alcohol use in the 24 hours following the psilocybin session.

A study psychiatrist will be onsite and available within 15 minutes for the entire duration of each drug session for an emergency and to administer rescue medication(s) as necessary.

Heart rate and blood pressure will be recorded at study's baseline screening assessment (averaged across 4 separate measurements). Heart rate and blood pressure will be re-recorded on the morning of the psilocybin drug session and monitored at hourly intervals following drug administration from 60 to 360 minutes. Heart rate and blood pressure will be taken prior to participant's discharge from the psilocybin drug session as well. Each participant's vital sign measurements and administration will be logged on the study case report form (see attached in Appendix I; pg. 25). In case of a medical emergency, the follow procedures will be followed:

Psychological Distress: For cases in which acute psychological distress is insufficiently addressed with the clinician's reassurance/support, the study physician will be notified for consideration of treatment with a benzodiazepine anxiolytic (10mg oral dose of diazepam) will be given. This is based on recommendations from both historical and more recent trials with psilocybin (Grinspoon & Bakalar, 1979; Johnson et al., 2008). Participants who are experiencing acute psychological distress in addition to elevated blood pressure will first be given the 10mg of diazepam. If the participant's blood pressure remains elevated one hour following the administration of diazepam, he/she will be given 0.1mg sublingual clonidine (see below).

Acute hypertension: Blood pressure found to be elevated (i.e., systolic BP >160 or Diastolic BP >100) will be monitored at an increased frequency of every 15 minutes until resolved. If blood pressure remains greater than 160/100 for four consecutive 15-minute intervals or reaches 220/120 (without signs of end-organ dysfunction or distress), the research physician will be notified for consideration of administering anti-hypertensive medication (0.1mg sublingual clonidine). Blood pressure will be monitored every 5 minutes until resolved. Another administration of 0.1mg clonidine will be provided an hour later if the participant's blood pressure continues to be elevated above 160 systolic and 100 diastolic. If signs of end-organ dysfunction or distress and blood pressure is greater than 180 Systolic or 110 Diastolic, the research team will call 911.

Tachycardia: If the participant's heart rate is over 120 beats per minute, the study monitors will recheck vital signs every 5 minutes until resolved and instruct patient to take slow, deep abdominal breaths. If heart rate measurement goes over 150, the study monitors will notify

the on-call research physician for consideration of administering diazepam (10mg) or sublingual clonidine (0.1mg). If signs of end-organ dysfunction or distress, the study team will call 911.

Unmanageable psychosis: Antipsychotic medication (1mg risperidone) will be available if an adverse reaction escalates to unmanageable psychosis. Antipsychotic rescue medication will be used as a last resort, as the experience of the drug is abrupt, unpleasant, intense, and may result in subsequent psychological problems (McCabe, 1977). A psychiatric emergency response team will be called for participants who continue to experience unmanageable acute psychosis at the end of the psilocybin drug session.

Allergic reaction: An antihistamine (25mg diphenhydramine) will be available in case there is any allergic reaction to the psilocybin that produces pain, itching, or swelling. If the participant begins to have trouble breathing, the study team will call 911.

In a circumstance that requires evacuation from the building (e.g., fire alarm goes off), the patient will be walked by the session monitors to UCLA's arboretum until it is safe to return to the therapy room.

Prior to discharge from each psilocybin session, participants will be given one of the study clinician's direct pager/cellphone number to call if he/she needs support or experiences any adverse events. Participants will be instructed to call 911 or go to the nearest emergency room in case of any adverse events or persisting experiences that are require immediate medical attention. Within a couple of days following the drug session, participants will conduct their next weekly session of CBT. At each remaining CBT session and at each remaining study assessment (i.e., post-treatment and 3-month follow-up) study clinician will inquire about any persisting or adverse effects from the psilocybin (e.g., flashbacks or recurrent psychotic experiences). Thus, study participants will be monitored for persisting and adverse events up to 6 months following the study's first psilocybin session and 5 months following the second psilocybin drug session. In the case of any participant experiencing persisting or adverse events during the study, the symptom(s)/event(s) will be documented, presented to, and discussed with the study team, and reported to the IRB and FDA. The participant will also be scheduled to be seen by the study physician or else taken/referred to the nearest emergency room in the case of an emergency. When discharged from the study, participants will be instructed to contact their primary care doctor or mental health provider in the event of any mental health concerns.

<u>Participant Monitoring and Removal from the Study:</u>
Noncompliance. Participants will be withdrawn from the protocol if they are noncompliant with the study procedures (for example, missing 2 or more consecutive CBT without calling ahead; refuse to participate in follow-up interviews).

Failing the medical or psychological screening. Participants will be withdrawn from the study if any of the following are evidenced during the medical screen or psychological screen, or if any of the following are elucidated during study:

- A personal or family history (first or second-degree) of psychosis or bipolar disorder
- Resting blood pressure above 140 systolic, 90 diastolic or heart rate > 90 beats per minute (averaged across four separate measurements)

- Meeting criteria for a DSM-5 cluster B personality disorder (narcissistic, histrionic, borderline, antisocial personality disorder),
- Active suicidality (i.e., HAM-D item 3 score of 3 or greater) or other psychiatric disturbance requiring acute treatment
- Current use of antidepressants, other serotonergic-affecting substances (e.g., St. John's Wort and 5-hydroxytryptophan), lithium, or efavirenz [regardless of whether the drug(s) is/are prescribed for MDD or other conditions]
- Current use of opioids (e.g., codeine, fentanyl, hydrocodone, meperidine, tramadol)
- Currently receiving cognitive behavioral therapy,
- Any of the following cardiovascular conditions: uncontrolled hypertension, coronary artery disease, congenital long QT syndrome, cardiac hypertrophy, cardiac ischemia, congestive heart failure, myocardial infarction, tachycardia, artificial heart valve, a clinically significant screening ECG abnormality, or any other significant cardiovascular condition
- QTc interval measurement of > 450 ms in males or > 460 ms in females as measured by the baseline ECG
- A history of stroke or Transient Ischemic Attack (TIA)
- Epilepsy or history of seizures
- Insulin-dependent diabetes
- Meeting criteria for a DSM-5 substance abuse or dependence within prior 6 months (including for nicotine and cannabis)
- Positive urine drug screen for illicit substances (excluding cannabis)
- Use of other psychedelics or ketamine within prior 12 months
- Adverse prior reaction to a psychedelic agent
- Pregnant, trying to get pregnant, or nursing

Any participant who is withdrawn from the study for any of the above exclusionary criteria will be referred to treatment elsewhere. For participants who have begun CBT, they will be retained in the study protocol (but not allowed to participate in forthcoming psilocybin sessions) for as long as possible, or until the CBT has ended.

Adverse drug reaction. Participants will be withdrawn from the study if they have an overwhelmingly distressing response to the first, low dose drug session. An overwhelmingly distressing response is considered one that requires hospitalization due to acute unmanageable psychosis, psychological distress, or a hypertensive crisis (i.e., blood pressure at or exceeding 180 systolic and 120 diastolic mmHg); use of rescue medication due to acute psychosis, psychological distress/anxiety, or elevated blood pressure (i.e., blood pressure exceeding 160 systolic and 100 diastolic mmHg); or otherwise is determined by study staff that the participant cannot be kept safe on a higher dose of the drug. Additionally, participants will be withdrawn from the study if they have an allergic reaction (e.g., swelling, itching) caused by the psilocybin or any persisting headaches or visual-perceptual effects that are distressing or interfering and lasting longer than two days after the first psilocybin administration. The participant will be referred to treatment elsewhere but will be retained in the study protocol for as long as possible or until the CBT has ended. Any participant with an adverse drug reaction to the second psilocybin administration will be offered continued support via the study's outlined CBT protocol.

These circumstances that may require administrative withdrawal will be spelled out in the consent

forms. Despite being withdrawn from study interventions, we will attempt to retain these participants for study assessments with their consent.

Participant worsening or non-response

Each participant will be seen weekly by their study therapist for two months following their first psilocybin session and one month following their second psilocybin session. Participants will continue to engage in biweekly therapy for the next month. Participants will then undergo a study assessment within two weeks of their treatment termination and another three months following treatment termination. At each of these visits, subjects' depressive symptoms (including suicidality) and functioning will be monitored.

If study staff sees evidence of worsening in a participant's depressive symptoms or functioning or if a participant expresses concern of worsening of symptoms or functioning, the clinician and participant will discuss alternative options for treatment, including psychiatric (pharmacotherapy) treatment, intensive outpatient programs, or hospitalization (if appropriate). Any participant who is deemed by study staff or self-identified as needing more intensive treatment will be provided the appropriate referrals and will be disallowed from continuing in the psilocybin portion of the study protocol. The participant will be retained in the study protocol for as long as possible through continued delivery of the CBT protocol and study assessments.

Participants who are found to be non-responsive to the psilocybin and CBT treatments (i.e., showing no change in depressive symptoms as witnessed by the study staff and/or reported to feel no improvement by the participant) by the end of the CBT protocol will be provided with referrals for a medication consultation or other more intensive treatment options.

Suicide Protocol

We will learn of onsets of suicidal ideation or suicidal attempts because we will have regular contact with participants for at least the first 4 months of the study protocol. Following the initial study screening that will assess and exclude participants with significant suicidality (see exclusion criteria), information about suicide will be obtained by the clinicians during treatment and drug sessions and by the independent evaluator during research assessments. When a participant expresses suicidal thoughts, the assigned clinician will conduct a thorough lethality and safety assessment using the Columbia Suicide Severity Rating Scale. If the participant expresses suicidal intent or is determined to be unsafe, the assigned clinician will attempt to provide crisis counseling as a first intervention. If the participant's suicidality continues to pose a safety threat, the assigned clinician will work with the PIs and/or study psychiatrist to arrange hospitalization. Participants will be instructed to call 911 or go to their closest Emergency Room in an emergency that takes place outside of a study encounter.

If the suicide risk is deemed low, the assigned clinician will intervene to prevent deterioration. Prevention includes additional individual sessions with the participant. The prevention sessions would include (a) conducting chain analyses to assess the precipitants and consequences of suicidal thoughts or actions, (b) developing a suicide prevention contract (i.e., identifying triggers for suicidal thoughts; clarifying the steps by which parents can get in touch with the psychiatrist or therapist and what to do if they are unavailable), (c) enhancing social support, if possible; and (d) problem-solving to eliminate triggers of the proband's suicidal thoughts and prevent their worsening.

4. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There is emerging evidence that a single administration of psilocybin produces antidepressant effects in individuals with treatment-resistant depression (i.e., individuals not responding to > 2 trials of antidepressants; Carhart-Harris et al., 2016). Psilocybin increases trait-levels of openness, and it engenders feelings of connectedness and a greater sense of meaning and purpose (Griffiths et al., 2011; MacLean et al., 2011). In the general population, these perceptual and cognitive changes are strongly felt and endure for months following one administration (Griffiths et al., 2006). Psilocybin may be a catalyst for the cognitive and behavioral changes that are sought in psychotherapy. In combination with CBT, it is possible that these effects are magnified.

The risks of psilocybin are minimal, especially with the strict eligibility criteria and screening that will take place for this study. There are no significant risks of CBT. Both treatments are known to have antidepressant effects for individuals with major depressive disorder. Their combination has the potential of magnifying their individual antidepressant effects in the short-term by creating greater reductions in depressive symptoms and in the long-term by leading to more sustained recovery of symptoms. Additionally, the potential benefit for society at-large is significant. Developing an evidence-based psychosocial treatment protocol to adjoin psilocybin treatment can help to improve the safety and efficacy of the drug treatment if/when psilocybin is delivered as a therapeutic agent to the public.

5. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

There are currently no manualized treatment protocols to guide clinicians in the psychosocial treatment that adjoins psilocybin. Developing an evidence-based psychosocial treatment protocol to adjoin psilocybin treatment can help to improve the safety and efficacy of the drug treatment if/when psilocybin is delivered as a therapeutic agent to the public. Additionally, the potential efficacy of psilocybin-assisted CBT for depression could provide benefit to many affected individuals and their family members who are averse to or otherwise unhelped by current medication approaches.

Appendices.

Appendix I. Case Report Form

PSI

Cancel

Subject ID:_____ Date:_____ Monitors:_____ Session:_1 - 10mg_____

Ideal Time	Actual Time	Activity	BP	HR	Rescue drug administered	Study Questionnaires	Persisting effects	Oriented X4
8:00		U-tox & pregnancy screen						
8:30		Review study procedures						
9:00		**Administer Psilocybin**						
9:30		Time Point 1						
10:00		**Time Point 2**						
10:30		Time Point 3						
11:00		**Time Point 4**						
11:30		Time Point 5						
12:00		**Time Point 6**						
12:30		Time Point 7						
1:00		**Time Point 8**						
1:30		Time Point 9						
2:00		**Study Questionnaires**						
3:00		**Discharge**						

*Bolded activities require BP and HR measurement

Important Event Reporting

BASELINE QUESTIONS

Last food: _____

Last caffeine: _____ **or *Not Regular User***

Normal? Y / N

Last nicotine: _____ **or *Not Regular User***

Normal? Y / N

Last alcohol: _____ **or *Not Regular User***

(Must be > 1 day)

Last cannabis: _____ **or *Not Regular User***

(Must be > 30 days)

Last PRN: _____ **or Not in Last Month**

(Must be > 6 hours)

Unusual physical symptom or stress: Y / N

(Must be N)

Anti-hypertensive medication taken: Y / N / NA

(Must be taken as prescribed within past 24 hours, if prescribed)

Pregnancy Test: Positive / Negative

(Must be negative)

Drug Test: Positive / Negative

(Must be negative)

Identified support person for pick up:

Appendix II. Music Playlist

PLAYLIST, MAJOR DEPRESSIVE DISORDER STUDY

Arrival and Ingestion*

MINUTES	SECONDS	
3	32	Antonio Vivaldi, Andante, Concerto RV 532 in G Major for 2 guitars, strings & continuo, Guitar Concertos, Los Romeros, Academy of St. Martin-in-the-Fields, Philips 412-624-2.
3	55	Antonio Vivaldi, Largo, Concerto RV93 in D Major for guitar, strings & continuo, Ibid.
2	22	Antonio Vivaldi, Largo, Concerto RV 356 in A Minor for guitar, Ibid.
3	26	Paul Horn "Mumtaz Mahal", Inside the Taj Mahal, Kuckuck, LC2099.
5	42	Paul Horn "Shah Jahan", Inside the Taj Mahal, Ibid.
2	22	Ron Korb, "Flute Traveller (Alto Flute), Oasis Productions Limited, SOCAN NHCD 205.
6	46	JS Bach: Suite No. 3 (Bach) Brazilian Guitar Quartet, Delos B00004YR6P
10	57	Russill Paul "By the Stream" (PM Yoga Chants), Gaiam, The Relaxation Company, CD 3142.
2	32	"Om Namah Shivaya" (CD from "Yoga of Sound"), Novato CA: New World Library, 2004.
6	18	Edward Elgar, "Nimrod", Enigma Variation #9, Leonard Bernstein, The Artist's Album, DGG 457 691-2.
6	17	Morten Lauridsen "O Magnum Mysterium", A Robert Shaw Christmas: Angels on High, Telarc20 CD-80461.
5	32	"Alleluia, Behold the Bridegroom", Sacred Treasures III: Choral Masterworks from Russia and Beyond, St. Petersburg Chamber Choir, Hearts of Space, 025041111423.

59 minutes, 41 seconds

26	49	Henryk Gorecki, "Lento--Sostenuto Tranquillo ma Cantabile" (Symphony #3, Movement #1), London Sinfonietta, David Zinman, Dawn Upshaw, Elektra Nonesuch 9 79282-2.
10	41	Johannes Brahms, "Selig sind, die da Leid tragen" (Ein Deutches Requiem), San Francisco Symphony & Chorus, Herbert Blomstedt, London 443 771-2.
14	39	Johannes Brahms, "Denn alles Fleish es ist wie Gras" (Ein Deutsches Requiem), Ibid.

		Johannes Brahms, "Adagio, Non Troppo" (Symphony No. 2, Op. 73), New York Philharmonic, Leonard Bernstein, Sony SMK 61829.
10	16	
5	42	Johannes Brahms, "Wie lieblich sind Deine Wohnungen" (Ein Deutsches Requiem), Op. cit.
10	26	J.S. Bach, "Kyrie" (Mass in B Minor), Robert Shaw, Atlanta Symphony & Chamber Chorus, Telarc CDE-80233.
4	28	J.S. Bach, Completion of "Kyrie" (Omiting "Christe Eleison" duet)

1 hour, 23 minutes, 01 second

10	2	Samuel Barber, "Adagio for Strings" New York Philharmonic, Leonard Bernstein, Sony, SMK 63088
6	50	J.S. Bach, "Largo" (Concerto for 2 Violins in D Minor), Hillary Hahn & Margaret Batjer, Bach-Concertos, Los Angeles Chamber Orchestra, Deutsche Grammophon, 474 6392
6	2	Antonio Vivaldi, "Et in terra pax" (Gloria in D Major), Atlanta Symphony, Robert Shaw, Telarc CD-80194
5	57	J.S. Bach, "Komm suesser Tod" (Bach/Stokowski), Full Dimensional Sound, EMI CDM 7243 5 66385 2 5
5	15	W.A. Mozart, "Laudate Dominum", Vesperae solennes de confessore, Kiri Te Kanawa, London Symphony, Sir Colin Davis, Philips 412 873-2
12	4	Max Bruch, "Kol Nidrei", Op. 47, Jacqueline Du Pre & Daniel Barenboim , Brahms Cello Sonatas, EMI

46 minutes, 10 seconds

8	18	Johannes Brahms, "Adagio", Concerto for Violin & Orchestra in D Major, Opus 77, Chicago Symphony, Fritz Reiner, Jascha Heifetz, HMG 09026-61742-2.
9	47	Henryk Gorecki, "Lento e Largo--Tranquillissimo", Symphony No. 3, Op. 36,(Movement #2), Op. cit.
6	33	Sir Edward Elgar, "Larghetto" (Serenade for String Orchestra in E Minor, Op. 20), Halle, Mark Elder, CD HLL 7501.
3	49	Gabriel Faure, "In Paradisum", Requiem, Op.48, Choir of St. John's College, Cambridge, George Guest, London 436-486-2.
7	14	W.A. Mozart, "Adagio", Clarinet Concerto KV622, Jean-Francois Paillard, Jacques Lancelot, Erato 2292-45978-2
6	19	Arvo Part, "Cantus in Memory of Benjamin Britten", from "Sanctuary", Bournemouth Sinfonietta, Richard Studt, Virgin Classics, CSC 7243 5 45314 2 2
6	55	Arvo Part, "Nunc Dimittis", Sabat Mater, Black Box, BBM1071
27	38	El-hadre 2, the Mystik Dance, Klaus Weise, CD-263 (latter half)

8	37	Ludwig van Beethoven, "Adagio un poco moto", Piano Concerto #5 ("Emperor"), Leon Fleisher, George Szell, Cleveland Orchestra, Sony "Essential Classics", SBK 46549.
17	37	Russill Paul, "Om Namah Shivaya", Shakti Yoga, The Yoga of Sound, The Relaxation Company, CD 3133
4	3	WA Mozart, "Ave Verum Corpus" (KKV618, London Symphony, Colin Davis, Phillips: 412 873-2.
10	31	Gustav Mahler, "Adagietto" (Symphony #5), Lorin Maazel, Vienna Philharmonic, Sony 696998985025,

1 hour, 57 minutes, 21 seconds

7	47	Alan Hovhaness, "Andante con moto", Symphony #2, "Mysterious Mountain," Seattle Symphony, Gerard Schwarz, Telarc 089408060427.
5	42	Joseph Canteloube, "Bailero" , Songs of the Auvergne, Orchestre de l"opera National de Lyon, Kent Nagano, Dawn Upshaw, Erato 0630-17577-2.
2	10	Richard Strauss, "Moderato", Death and Transfiguration, Andre Previn, Wiener Philharmoniker, Telarc. CD-80167
6	2	Richard Strauss, "Tranquillo", Death and Transfiguration, Ibid.
23	31	Russill Paul, "Evening Shadows Fall", Nada Yoga, The Yoga of Sound, Gaiam, The Relaxation Company, CD 3133.
14	51	J.S. Bach, "Passacaglia & Fugue in C Minor", Bach/Stokowski, Full Dimensional Sound, EMI: CDM 7243 5 66385 2 5.
8	15	Arvo Part, "Spiegel im Spiegel for violin and piano", Sabat Mater, Black Box, BBM1071

1 hour, 8 minutes, 18 sconds

3	3	Enya, "Storms in Africa II", Watermark, Reprise 9 26774-2.
5	38	Guem, "Transe", Musique de Transe, Le Chant Du Monde LDX 2741008
4	1	Adiemus, "Adiemus", Pure Moods, Virgin, 724384218621.
4	22	Gipsy Kings, "Caminando Por la Calle", Mosaique, Nonesuch, 075596089227.
4	27	Mercedes Sosa, "Gracias a La Vida", Gracias a la Vida, Polygram International, 042283231429.
2	21	Louis Armstrong, "What a Wonderful World", What a Wonderful World, Double Play (Intercontinental 600), 607707405826.
60	9	"Ocean Waves", Echos of Nature: The Natural Sounds of the Wilderness, Delta, 018111591621.

1 hour 24 minutes, 01 seconds

Total Duration: 7 hours, 40 minutes, 54 seconds

Appendix III. Drug Management Protocol

INVESTIGATIONAL DRUG MANAGEMENT PROTOCOL:

The following outlines procedures for study drug management under the direction of the Principal Investigators, Drs. Marc Weintraub, David Miklowitz.

Study Title: Psilocybin-assisted cognitive behavioral therapy for major depressive disorder.
IRB#: 21-002134
IND#: 160212

A. Ordering and Receipt:

1. Dr. Marc Weintraub, holder of the Schedule I drug research license, will place the order for psilocybin from Psilo Scientific Ltd. (Vancouver, B.C., Canada).
2. A record of the request for investigational drugs from the manufacturers will be kept in the study's file as reference
3. Study drugs will be sent to Semel RM A8-259, 650 Charles E Young Drive South, Los Angeles CA 90095. The shipment will be received by Dr. Weintraub along with an approved individual listed on the license as a witness.
4. When the study drug is received, the product will be checked to verify accuracy of the shipment as compared to what was requested for:
    a. Integrity of the study drug for any breakage or inappropriate temperature
    b. The drug, strength, dosage and quantity
5. Any irregularities observed will be reported to the manufacturer
6. The drug shipment receipts will be recorded into the appropriate drug accountability record form documenting the following (Drug Master Log)
    a. Date of receipt (date, month, year)
    b. Study drug supplier
    c. Dosage form and amount received.
    d. Drug lot number
    e. Recorder's initial and date or recording.
7. Inventory will be confirmed by an additional approved individual listed on the license who will also sign and date the drug accountability form.
8. Psilocybin will immediately be stored in the Dr. Weintraub's DEA-approved Schedule I study drug facility under conditions consistent with those recommended by the manufacturer.

B. Storage

1. Psilocybin will be stored under conditions consistent with those recommended by the manufacturer, in a secure location only accessible to the Principal Investigators and authorized designees. A delegation of authority list will identify individuals authorized to have access to the study drugs.
2. Psilocybin will not be stored with other non-study drug products. The storage container (drug safe) will be labeled with "investigational and study drug" and the IRB study number.
3. The security management for Schedule 1 drug storage will follow the protocol approved by the DEA.
4. Investigational and study drug agents will be clearly labeled with:
    a. Name of the drug
    b. IRB protocol number
    c. Name of the Principal Investigator
    d. "Investigational and study drug use only" designation
    e. Drug doses: 10 mg psilocybin or 25 mg psilocybin (per capsule)

C. Accountability

1. A complete and accurate system for psilocybin will be maintained
2. The inventory record will document each transaction from receipt and storage to dispensing or disposal of the drug.
3. For each transaction, the following information will be recorded:
   a. The date (day/month/year)
   b. Destination of drug transfers or returns
   c. Participant's study ID number, session number, and date of dispensing
   d. Dose dispensed
   e. Initials of the person completing the inventory record
   f. A copy of the signed informed consent form for the protocol and prescription will be included in the participant's study record. The maintenance of this information is the direct responsibility of the investigator.
   g. The protocol and basic information concerning the pharmacology, dosage, preparation, administration, adverse effects of the study drugs will be readily available in a protocol-specific central laboratory binder that is maintained on site and readily available for review. This laboratory binder will include the name and method of contact for the investigator and study physician responsible for handling any problems or emergencies that occur. The provision of this information is the direct responsibility of the investigator.
4. Inventory logs
   a. The Usage Inventory Log will show: Batch information (purchase order, date of receipt, individuals who received drug), Drug information (substance and dosages). Underneath the header information previously listed will be the following dispensing information: Individual doses dispensed to participants, Date of dispensing, remaining balance, study psychiatrist dispensing substance, and participant number, session number and date
      i. This is a single-blinded study, researchers will be aware of the psilocybin dispensed to participants.
5. Any discrepancies in accountability that cannot be rectified (i.e., missing drug) will immediately be reported to the DEA.
6. At the end of the study, unused doses will be destroyed or sent to a reverse distributor with a Schedule I license for destruction.

D. Dispensing

<u>General dispensing and administration procedures:</u>

1. Once a participant is enrolled in the study, a study physician designated by Dr. Weintraub's DEA license, will prepare an investigational drug prescription for psilocybin. The prescription will include the following:
   a. Date and protocol number
   b. The full name (first and last name) of the participant, date of birth, known allergies
   c. The subject's study ID and session number (1-4)
   d. The identity of the study drug and strength (10mg or 25 mg psilocybin), route of administration, (oral), and "no refills."

   Dr. Marc Weintraub (Schedule I license holder) will be a co-signer on prescriptions.
2. Two copies of the prescription will be made for keeping in the participant's study file and the original prescription will be filed, chronologically in the study drug room after dispensing with drug inventory logs in the Schedule I storage location labeled with the IRB #, IND #, and study drug.

3. The study drug will be transported by authorized personnel on Dr. Weintraub's DEA license from the storage location in the UCLA Semel Intitute to the drug session room (also within the UCLA Semel Institute) in a zippered medication bag. This location will be added to Dr. Weintraub's Schedule I registration.
4. The subject will be observed taking the study drug(s) as prescribed by the study physician.
5. The investigator will verify that the dose was administered on the study session checklist with initials, time of administration, and date and on the log verifying that a dose was dispensed.

Appendix IV. Security Provisions for Drug Storage

Building Level Security: CHS- Center for Health Sciences, SEMEL Institute
650 Charles E Young Drive S, Los Angeles, CA 90095

Building access is restricted by swipe access at the building entrance 7:00 PM- 6:00 AM. Our General Laboratory resides on the A floor in the 8-wing (i.e., south corridor) of the UCLA Semel Institute.

Laboratory Level Security
Business hours are 8am - 7pm and doors to the General Laboratory are maintained locked outside of business hours. A waiting room (room A8-216) at the entrance of the general laboratory is staffed by a UCLA Health administrator during business hours who monitors the entrance to the general laboratory. The waiting room also has security camera that records all activity at the entrance of the laboratory 24/7. The security camera is monitored by UCLA CHS security.

Storage Room Security
The drug storage room (A8-259) is located towards the very back of the laboratory space and is maintained locked at all times. Within the drug storage room, the controlled substances will be locked in a Hollon burglar safe (ID/Serial#: B2015E). The burglar safe is made with steel construction, 4 solid steel active locking bolts, a drill resistant hard plate and a UL listed Type 1 Securam Audit Trail digital lock. The safe is anchored to the floor with 4 bolts. The dimensions of the safe are 20” H x 15” W x 15” D

Appendix V. Controlled Substances Program Usage Log

UCLA Environment, Health & Safety

Controlled Substances Program Usage Log

Complete the following usage log in its entirety for each container. Controlled substance usage must be tracked on a per dose (use) basis. The log balance must match physical balance of original container contents at all times. Record total quantity of the substance to the nearest metric unit weight or the total number of units finished form.

Principal Investigator: _____

Purchase Order	Date Received	Initial Volume Received	Container ID:

Drug Information			
Lot		Expiration Date	

CS Transported by (print name and initial):	Witness (print name and initial):	Date

Date (M/D/YY)	Amount Dispensed	Remaining Balance	Person Dispensing Substance (Print Name)	Reason for Use, Protocol, Animal Species n/ In Vitro, and Dilution Container ID (if applicable)

FINAL DISPOSITION	
☐ CS remaining balance zero Container deface and disposed	☐ Remaining unused CS item relinquished Contact EH&S CS Program for disposal of remaining CS. Submit request via E-mail to:controlledsubstances@ehs.ucla.edu

Disposed by: _____ Date: _____ Submit copy of log sheet to controlledsubstances@ehs.ucla.edu Keep original log sheet in the controlled substance binder secured in EH&S approved location.	FOR EH&S USE ONLY: CS transferred to EH&S for disposal. Date: _____ EH&S Initials:_____ Disposal # _____
**Retain log sheet until: _____ Retain for 3 years from the date of transfer to EH&S for disposal or date of complete use.	

Product: _____ Schedule: _____ Container ID: _____

Date (M/D/YY)	Amount Dispensed	Remaining Balance	Person Dispensing Substance (Print Name)	Reason for Use, Protocol, Animal Species n/ In Vitro, and Dilution Container ID (if applicable)
	---		-----	Enter Date and Remaining Balance from the first page.

PAGE _____ of _____