BMJ Open

Examining the Safety and Clinical Efficacy of Psilocybin Therapy for Veterans with PTSD: An Open-Label Proof-of-Concept Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068884
Article Type:	Protocol
Date Submitted by the Author:	11-Oct-2022
Complete List of Authors:	Davis, Alan; The Ohio State University College of Social Work, ; Johns Hopkins University, Psychiatry and Behavioral Sciences Levin, Adam; The Ohio State University College of Medicine, Psychiatry Nagib, Paul; The Ohio State University College of Medicine, Psychiatry Armstrong, Stacey; The Ohio State University College of Social Work Lancelotta, Rafael; The Ohio State University College of Social Work
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS, MENTAL HEALTH, CLINICAL PHARMACOLOGY

Examining the Safety and Clinical Efficacy of Psilocybin Therapy for Veterans with PTSD: An Open-Label Proof-of-Concept Trial

Alan K Davis[a,b,c], Adam W Levin[a,b], Paul B Nagib[a,b], Stacey B Armstrong[a], Rafael L. Lancelotta[a]

Affiliations:
[a]Center for Psychedelic Drug Research and Education, College of Social Work, The Ohio State University, Columbus, OH 43210
[b]College of Medicine, The Ohio State University, Columbus, OH 43210
[c]Center for Psychedelic and Consciousness Research, Johns Hopkins University, Baltimore, MD 21224

Corresponding Author: Alan K Davis, Center for Psychedelic Drug Research and Education, College of Social Work, The Ohio State University, Columbus, OH 43210. Email: Davis.5996@osu.edu. Telephone: 614-292-5251

Study Sponsor: Principal investigator/Corresponding author

Acknowledgments: The authors would like to thank Usona Institute for providing the study drug for this trial. We also thank Dr. Emil Coccaro for their work as medical monitor of this study.

Word Count: 4000

KEYWORDS: Posttraumatic Stress Disorder, PTSD, psilocybin, clinical trial, therapy

ABSTRACT

Introduction: Psilocybin-assisted therapy has shown significant promise in treating the cluster of mood and anxiety symptoms that comprise post-traumatic stress disorder (PTSD) but has yet to be tested specifically in this condition. Furthermore, current pharmacologic and psychotherapeutic treatments for PTSD are minimally effective and difficult to tolerate, especially in the United States Military Veteran (USMV) population. This open-label pilot study will examine the safety and efficacy of two psilocybin administration sessions (15MG and 25MG), combined with psychotherapy, among USMV with severe, treatment resistant PTSD. **Methods and Analysis:** We will recruit 15 USMV with severe, treatment resistant PTSD. Participants will receive one low dose (15 mg) and one moderate/high dose (25 mg) of psilocybin in conjunction with preparatory and post-psilocybin therapy sessions. The primary safety outcome will be the type, severity, and frequency of Adverse Events (AEs) and suicidal ideation/behavior, as measured by the Columbia Suicide Severity Rating Scale (CSSR-S). The primary outcome measure for PTSD will be the Clinician Administered PTSD Scale-5 (CAPS-5). The primary endpoint will be one month following the second psilocybin administration session, and the total follow-up time will be 6 months. **Ethics and dissemination:** All participants will be required to provide written informed consent. The trial has been authorized by the Ohio State University Institutional Review Board (Study Number: 2022H0280). Dissemination of results will occur via a peer-reviewed publication and other relevant media. **Registration details:** ClinicalTrials.gov Identifier NCT05554094

ARTICLE SUMMARY:

Strengths and limitations of this study

- This study is the first to provide evidence for the feasibility of psilocybin-assisted therapy to treat PTSD in Veterans, a population regularly impacted by trauma- and stressor-related disorders
- Primary outcomes will be assessed by self-report and structured interviews by clinicians not affiliated with the study
- The study design includes long-term follow-up of participants to assess the durability of the treatment over time
- The single-arm design comes with limitations such as having no comparison group or blinding procedures
- Due to a small sample size, generalization of findings will be limited

INTRODUCTION

In recent years, there has been increasing interest in investigating the use of psilocybin, a classic hallucinogen, as an adjunct to psychotherapy for the treatment of various psychiatric conditions. Recently completed trials have shown positive effects of this treatment among patients with depression and anxiety,[1–3] obsessive compulsive disorder, [4] and substance use disorders [5–7]. Results from these studies demonstrate that psilocybin-assisted therapy is safe and has a minimal adverse event profile, with no documented serious adverse events. Additionally, data revealed robust short and long-term improvements in the constellation of mood, substance use, and anxiety symptoms that represent the core aspects of Posttraumatic Stress Disorder (PTSD) [8].

Consistent with current evidence supporting the notion that psilocybin-assisted therapy may be effective in treating PTSD, a recent open-label trial of psilocybin-assisted group therapy for demoralization in long-term AIDS survivors showed a clinically meaningful change in PTSD symptom severity, as measured by the PTSD Checklist-5 (PCL-5), from baseline to 3-month follow-up with a large effect size [9]. However, this study was not designed specifically to address symptoms of PTSD, nor did it focus on the broader population of people with this diagnosis. Furthermore, no study to date has focused on examining the safety and efficacy of psilocybin-assisted therapy among United States Military Veterans (USMV), a population with a substantial burden of mental health problems compared to the general population. For example, despite inherent resiliencies and specialized training, members of the armed forces are often exposed to a number of military deployments and intense combat incidents, which are associated with a higher risk of PTSD compared to the civilian population [10,11]. Additionally, there has been an alarming increase in the incidence of suicides in Veterans, set in the context of limited effective treatment methods for this unique population [11,12].

Although several pharmacological and psychotherapy interventions have been developed to treat PTSD [13,14], these treatments are difficult to complete, challenging to access, and are lacking in efficacy for many Veterans [15–17]. Furthermore, there is emerging evidence that standard pharmacologic treatments are not as effective in Veterans with PTSD as they are in civilians [15,18], and are consequently no longer recommended as a front-line treatment in this population [19]. Although there is encouraging preliminary data on the safety and efficacy of psilocybin-assisted therapy from a variety of patient populations, more research is needed to establish safety and efficacy of this treatment among USMV with PTSD. Not only could this novel treatment help ameliorate the burden of PTSD in this population, but it could also potentially reduce the risk of suicides among USMV and reduce the devastating impact of this mental health crisis in families and communities across the US.

Therefore, the current study was designed as an open-label pilot study testing the following primary hypotheses in USMV with severe, treatment resistant PTSD: 1) Psilocybin-assisted therapy is safe to administer among Veterans with PTSD 2) Psilocybin-assisted psychotherapy will be associated with decreases in PTSD symptom severity at 1-month after final psilocybin session as measured by the Clinician Administered PTSD Scale-5 (CAPS-5) and the PTSD Checklist for DSM-5 (PCL-5).

METHODS AND ANALYSIS

Objectives

The primary objective of the study is to investigate the safety of psilocybin-assisted therapy among USMV with severe, treatment-resistant PTSD based on the type, severity, and frequency of Adverse Events (AEs) and suicidal ideation/behavior (as measured by the Columbia Suicide Severity Rating Scale (CSSR-S) from baseline to primary endpoint, 1-month post-second psilocybin administration.

The secondary outcomes of the study are as follows:

1. Investigate the effect of psilocybin-assisted therapy on clinician rated PTSD symptom severity through the Clinician Administered PTSD Scale-5 (CAPS-5) measured at baseline and 1-, 3-, and 6-month(s) post-second psilocybin administration

2. Investigate the effect of psilocybin-assisted therapy on participant rated PTSD symptom severity utilizing PTSD Checklist for DSM-5 (PCL-5) measured at baseline and 1-, 3-, and 6-month(s) post-second psilocybin administration

Setting

This study takes place at the Davis Medical Research Center within the Wexner Medical Center at The Ohio State University (OSU) in Columbus, Ohio.

Design

The study was designed to partially replicate the psilocybin-assisted therapy intervention used in a trial for people with major depressive disorder [1] by conducting an open-label pilot study of two psilocybin administration sessions combined with psychotherapy for PTSD among USMV with severe, treatment resistant PTSD (Trial Protocol Version #1). Because this study is a single group open-label pilot safety and feasibility study, there is no randomization procedure or blinding to condition.

Participants and Recruitment

Recruitment

We will consent up to 100 volunteers (some will not pass the in-person screening), to achieve 15 individuals who will be enrolled in the study and subsequently complete both psilocybin sessions and the final follow-up assessment. We will attempt to reflect recent data from the 2019–2020 National Health and Resilience in Veterans Study (NHRVS), which showed that 26.7% of US Veterans with past-month PTSD were female and 34.8% were non-white [20]. Extrapolating from this analysis, we expect to recruit 11 male participants, 4 female participants, 10 white, and 5 non-white participants. Recruitment will consist of electronic dissemination of study flyers, social media ads, provider network communications via in-person meetings/telephone/email, email networking, and word of mouth.

Screening

Initial pre-screening will occur via a secure online questionnaire to determine major inclusion/exclusion criteria are met. Participants who meet all study criteria, and who are not currently taking any psychiatric medications, will be invited to the OSU Department of Psychiatry and Behavioral Health Davis Medical Research Center for in-person screening. Written informed consent will be obtained by study staff during a scheduled meeting after participants have passed the initial online pre-screening.

Inclusion/Exclusion Criteria

Inclusion:

- Participants must be US military Veterans
- Must have DSM-5 diagnosis of PTSD with symptom duration of at least 6 months with a CAPS-5 total severity score of ≥35 at baseline
- Have had at least 3 months of prior SSRI or SNRI treatment in addition to at least 6 months of psychotherapy

- Have at least a high-school level of education or equivalent (e.g., GED).
- No antidepressant medications for approximately 5 half-lives prior to baseline assessment and enrollment
- Be judged by study team clinicians to be at low risk for suicidality
- Be medically stable as determined by screening for medical problems via a personal interview, a medical questionnaire, a physical examination, an electrocardiogram (ECG), and routine medical blood and urinalysis laboratory tests
- Have limited lifetime use of hallucinogens (the following criteria are preferred: no use in the past 5 years; total hallucinogen use less than 10 times)

Exclusion:

- Participants who were assigned female at birth who are pregnant (as indicated by a positive urine pregnancy test assessed at intake and before each drug session) or nursing; people who are of child-bearing potential and sexually active who are not practicing a highly effective means of birth control (i.e., implants, injectables, combined oral contraceptives, progestin containing IUDs, or vasectomized partner).
- Participants who were assigned male at birth with partners of childbearing potential who are sexually active and not practicing a highly effective means of contraception (i.e., condom with spermicidal foam/gel/film/cream/suppository).
- Current medical condition incompatible with psilocybin administration (e.g., coronary artery disease, uncontrolled hypertension)
- Systolic blood pressure (SBP) > 139 mm HG; diastolic blood pressure (DBP) > 89 mm HG; heart rate (HR) > 90 bpm.
- Currently taking on a regular (e.g., daily) basis any medication(s) having a primary centrally-acting serotonergic effect, including MAOIs
- Current or past history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), Bipolar I or II Disorder
- Current or history of (within one year of meeting DSM-5 criteria) a moderate or severe alcohol, tobacco, or other drug use disorder (excluding caffeine)
- Have a first- or second-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I or II Disorder
- Has a psychiatric condition which precludes the establishment of therapeutic rapport
- History of a medically significant suicide attempt
- Current antidepressant use

Enrollment

After enrollment, participants will receive preparation psychotherapy followed by one low dose (15 mg) and one moderate/high dose (25 mg) of psilocybin followed by post-psilocybin therapy sessions. Each psilocybin session will last approximately 8 hours and will be overseen by two trained session facilitators (session facilitators can vary from one participant to another due to scheduling or other treatment considerations). Before the first psilocybin session, participants will meet with one or both session facilitators for a total of approximately 8 hours of contact time (or up to 4 meetings). Two post-psilocybin therapy session visits will follow Psilocybin Sessions 1 and 2. Psilocybin Sessions 1 and 2 will occur at least two weeks apart. Follow-up visits will occur 1 and 2 week(s) and 1, 3, and 6 month(s) after the final psilocybin session, with additional contact hours scheduled as needed. Thus, the intervention and

follow-up require 15 visits over a period of about 8-10 months. A schematic of trial activities is provided in Figure 1. Protocol amendments will be reported to the Food and Drug Administration, IRB, and clinicaltrials.gov.

Preparation

Before the first psilocybin session, participants will meet with both session facilitators for a total of 8 hours before the first psilocybin session day. The main purpose of the preparation meetings is to develop rapport and trust, which helps minimize the risk of fear or anxiety reactions during the psilocybin sessions. This approach has been successful in previous studies conducted by the Principal Investigator, including in a recent psilocybin study of depression [1]. Additional meetings and contact hours will be scheduled if it is judged necessary to establish sufficient rapport and trust prior to psilocybin administration. Consistent with previous psilocybin protocols authored and conducted by the lead investigator and others, the participant's life history and current situation in life will be reviewed, and intentions and expectations for the psilocybin sessions will be discussed [21,22]. Additionally, during these sessions the facilitators will explore the participant's goals, values, and perceived strengths and weaknesses. Lastly, an overview of common and uncommon psilocybin effects will be discussed, and skills for navigating such experiences will be explored and practiced.

Psilocybin Dosing Sessions

Procedures for psilocybin administration and the conduct of the session will be similar to procedures used in previous studies with psilocybin among patients diagnosed with Major Depressive Disorder [1]. Psilocybin is provided by Usona Institute in opaque gelatin capsules and will be administered with approximately 100 ml water. At least one session monitor, under the supervision of the investigators, will be present in the room and available to respond to participants' physical and emotional needs during the full course of psilocybin effects and for at least 8 hours. Typically, both session monitors are present unless one needs to step out of the session room to manage personal needs or to communicate with study team members. A physician on the study team will be immediately available via pager or mobile phone for at least 3 hours, or until the peak effects of psilocybin have subsided -whichever is longer. The physician will also be available for consultation by phone for up to 8 hours post-dosing.

During the psilocybin session, participants will be encouraged to lie on a couch, wear eyeshades, and listen to a program of music through headphones [1]. The participant will be encouraged to focus their attention inward. The eyeshades and music are intended to encourage this inward reflection. Vital signs and measures of the intensity of behaviors, signs, and reported symptoms will be assessed throughout the day by the session monitors. Acute anxiety, agitation or panic will be handled with reassurance. In the unlikely event that these symptoms do not respond to reassurance, or in the unlikely event that the volunteer experiences unexpected psychosis, clinical judgment of a study physician will determine the most appropriate medical treatment.

At the end of the experimental drug session, participants will complete paper or computer-based questionnaires designed to assess acute subjective experiences associated with the psilocybin session. Participants will also be asked to write a narrative description of the experience of the psilocybin session before their next in-person meeting. Study facilitators will complete a safety assessment (C-SSRS) which will be completed at all visits throughout the study.

Participants will be released to the care of a significant other who will pick them up at the end of the day and transport them to their residence or place of lodging. The pick-up person will remain with them over night. At the permission of the participant, the pick-up person will be invited in the session room prior to leaving with the participant wherein they will be instructed about procedures for care during the

evening/night following the psilocybin session. Additionally, at least one session monitor will be on-call via telephone for 24 hours after each psilocybin session.

Follow-up

The follow-up period is 6 months total with debriefing visits occurring immediately (1-3 days) following the psilocybin sessions, 1-week post-psilocybin sessions, and then at various time points following the final psilocybin dosing session. Additional clinician and monitor contact hours will be scheduled if it is judged that the participant would benefit from additional meetings to discuss experiences from their session(s) or prepare for the next session. During the visits immediately following a psilocybin session, participants will be asked to discuss a narrative description of their most recent psilocybin session and psychological support will be provided. The primary goal of these sessions is to offer support for the participant's reflections on the psilocybin session. Study clinicians will support the participant's narrative expression of their experience and use their experience as a foundation for discussion about how to move forward and integrate this experience into their lives.

Fidelity

Those involved in providing the intervention in this trial will complete checklists to ensure consistency across staff in delivery of intervention content.

Participant Retention

Retention activities will include: 1) obtaining various methods of contact (i.e., email, primary phone number, home address, secondary phone number), 2) release of information to contact primary physician or mental health provider, 3) release of information to contact primary supportive friend/partner/spouse. Participants will be engaged in the trial on a weekly basis through the primary endpoint (1-month post psilocybin session 2). During each weekly study contact, participants will receive therapeutic intervention to assess for safety and need for ongoing support as necessary. During safety assessments, any unforeseen challenges with study participation will be addressed. During long-term follow-up time periods (between primary end point at 1-month and follow-up at 3- and 6-months) participants will receive a monthly contact from study personnel reminding them of upcoming visits and encouraging them to schedule a telephone or in-person visit should one be needed prior to the next scheduled study visit.

To aid in study retention, participants will also receive monetary compensation for the time they spend participating in the preparatory, psilocybin, and post-psilocybin therapy session meetings and measurements taken at the OSUMC. Remuneration will consist of $25 per study visit after enrollment, with the exception of psilocybin session visits which will be compensated at the rate of $100/session visit as they will spend more time at the clinic on these days. Total remuneration will be up to $475 per participant.

Outcomes

Data Collection

Primary safety and clinical outcome data is collected by clinician interview (e.g., adverse events, suicidal ideation and behavior, PTSD symptoms via the CAPS-5) and self-report (e.g., PTSD symptoms via the PCL-5). Data will be entered by study staff (into a secure data collection platform; RedCap), using a double data entry method. Data will be stored on secure cloud servers and accessed only by approved study personnel.

Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party. All research activities will be conducted in as private a setting as possible. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a locked room. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Some therapy sessions may occur via telephone or videoconferencing (e.g. if a participant is unable to travel to our study site for an integration session or for a follow-up qualitative interview). Such sessions may be recorded using an encrypted audio/video format (e.g. Zoom). The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived. A Certificate of Confidentiality (CoC) has also been obtained for this study.

Safety outcomes

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to assess severity of suicidal ideation during every study visit (in-person and virtual). It was developed by researchers at Columbia University and is widely used in clinical and research settings (https://cssrs.columbia.edu/) [23]. The C-SSRS is divided into four subscales based on 1) severity of ideation 2) intensity of ideation 3) suicidal behavior, and 4) lethality of attempt. Respondents are categorized as low, medium, and high risk based on where their affirmative answers are in the various subscales as opposed to their total score.

Additionally, the primary clinician/session facilitator for each participant will identify/record adverse events (i.e., the emergence of any untoward physical or psychological events or symptoms) and safety concerns at each study visit. The type, severity, and frequency of adverse events will be collected to identify and characterize any safety concerns that may arise.

Clinical outcomes

PTSD symptom severity will be measured using the CAPS-5 and PCL-5. The CAPS-5 is an extensively validated, widely utilized 30-item structured-interview that assesses PTSD diagnostic status and symptom severity. It is scored on a scale of 0-80 with moderate and severe PTSD ranges rationally derived and defined as 23 to 34 and ≥35 respectively [24]. In addition to assessing the 20 *DSM-5* PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). The CAPS-5 will be administered by independent raters (blinded to all other aspects of study participation) at baseline assessment, at the primary endpoint (1-month), and at 3- and 6-months following psilocybin session 2. Independent raters will be comprised of IRB-approved team members of this protocol and trained in assessment of PTSD using the CAPS-5.

The PCL-5 is one of the most widely used self-report measures of PTSD with scores ranging from 0 to 80 and higher scores indicating greater PTSD symptom severity [25]. The PCL-5 will be self-administered at baseline as well as at additional timepoints (Preparatory Session 4, Therapy Session 1.2, 2.2, and Follow Up 1, 2, and 3) to assess whether there is an immediate post-psilocybin effect on PTSD symptom severity.

Statistical Analysis

No prior investigations of the effects of psilocybin on PTSD symptoms have been published to date. Because this trial has a primary objective of establishing the safety of this treatment approach among this population, and based on effect sizes in prior laboratory studies of psilocybin for other clinical populations [1,2], we believe that a sample size of 15 will provide sufficient power to detect a moderate effect size of pre- and post-psilocybin changes in PTSD symptoms. If the data suggest possible efficacy, these data should be sufficient to conduct a power analysis for a subsequent randomized controlled trial.

All participants enrolled in the trial and who complete both psilocybin sessions will be the evaluable population for analyses. Missing data will be managed through use of imputation. For primary and secondary measures assessed at baseline and follow-up, repeated-measures ANOVAs with post-hoc comparisons will be conducted to test for differences from baseline and the follow-up visits. Planned comparisons from baseline to 1-month post final psilocybin session will be conducted for primary outcome measures. These longitudinal outcome measures will be regressed on measures of acute and persisting psilocybin effects to examine whether such effects predict clinically relevant outcomes.

Primary Hypotheses/Endpoints:

1) Psilocybin-assisted therapy will be safe to administer among USMV with PTSD as indicated by no statistically significant increases in mean ratings of suicidal ideation on the C-SSRS from Baseline through 1-month post psilocybin session 2.
    a. Ratings of suicidal ideation on the C-SSRS will be included from baseline, 1-day post psilocybin session 1, 1-day post psilocybin session 2, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of suicidal ideation from baseline through 1-month post psilocybin session 2.
    b. Data will be presented with F-tests using an alpha (p-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

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

Secondary Hypotheses/Endpoints

1) We will find statistically significant decreases in PTSD symptom severity from baseline to 1-month after the final psilocybin session as measured by the Clinician Administered PTSD Scale-5 (CAPS-5).
    a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit 4, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptoms severity from baseline through 1-month post psilocybin session 2.

b. Data will be presented with F-tests using an alpha (*p*-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

2) We will find statistically significant decreases in PTSD symptom severity from baseline to 1-month after final psilocybin session as measured by the self-report PTSD Checklist for DSM-5 (PCL-5).
   a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit 4, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptom severity from baseline through 1-month post psilocybin session 2.
   b. Data will be presented with F-tests using an alpha (*p*-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

ETHICS AND DISSEMINATION

All participants will be required to provide written informed consent (See Patient Consent Form) Dissemination of results will occur via a peer-reviewed publication and other relevant media.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public have not been involved in the design and conduct of this study, the choice of outcome measures, or recruitment. There are no plans to include patients/public in dissemination efforts. Research questions were informed by the professional experiences working with Veterans with PTSD.

Author contributions: AKD: principal investigator, project coordination, trial monitoring, manuscript writing. SBA: study coordinator, measurement selection, protocol development, manuscript writing. AWL: protocol development, manuscript writing, measurement selection, medical protocol development. RLL: contributed to protocol development, contributed to measure selection, analytical strategy, designed music playlist, led playlist validation process, made comments on the manuscript. PBN: protocol writing and development, medical protocol development, led music playlist validation process, manuscript review and editing, visualization, provided feedback during playlist development.

Competing interest statement: AKD and RLL are board members of Source Research Foundation. This organization was not involved in the design/execution of this study or the interpretation or communication of findings.

Funding: This work was funded by the Center for Psychedelic Drug Research and Education (Award number: NA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data Statement: Data will be made available upon request by the corresponding author after the primary outcomes of the paper have been published.

Ethics Approval: The trial has been authorized by the OSU Institutional Review Board (Study Number: 2022H0280).

REFERENCES

1. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021 May 1;78(5):481–9.

2. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol Oxf Engl. 2016 Dec;30(12):1181–97.

3. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, et al. Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. Arch Gen Psychiatry. 2011 Jan 3;68(1):71–8.

4. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder. J Clin Psychiatry. 2006 Nov 15;67(11):0–0.

5. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. J Psychopharmacol (Oxf). 2015 Mar 1;29(3):289–99.

6. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot Study of the 5-HT2AR Agonist Psilocybin in the Treatment of Tobacco Addiction. J Psychopharmacol Oxf Engl. 2014 Nov;28(11):983–92.

7. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017 Jan;43(1):55–60.

8. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci. 2015 Jun;17(2):141–50.

9. Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine [Internet]. 2020 Oct 1 [cited 2021 Jul 29];27. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30282-0/abstract

10. Hanwella R, de Silva V. Mental health of Special Forces personnel deployed in battle. Soc Psychiatry Psychiatr Epidemiol. 2012 Aug 1;47(8):1343–51.

11. Hing M, Cabrera J, Barstow C, Forsten R. Special operations forces and incidence of post-traumatic stress disorder symptoms. J Spec Oper Med. 2012 Jan 1;12(3):23–35.

12. Rocklein Kemplin K, Paun O, Godbee DC, Brandon JW. Resilience and suicide in special operations forces: state of the science via integrative review. J Spec Oper Med. 2019;19(2):57–66.

13. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: Premises, principles, and priorities. Brain Res. 2009 Oct 1;1293:24–39.

14. Watkins LE, Sprang KR, Rothbaum BO. Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions. Front Behav Neurosci [Internet]. 2018 [cited 2021 Jul 21];0. Available from: https://www.frontiersin.org/articles/10.3389/fnbeh.2018.00258/full

15. Hertzberg MA, Feldman ME, Beckham JC, Kudler HS, Davidson JRT. Lack of Efficacy for Fluoxetine in PTSD: A Placebo Controlled Trial in Combat Veterans. Ann Clin Psychiatry. 2000 Jun 1;12(2):101–5.

16. Krystal JH, Davis LL, Neylan TC, A Raskind M, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017 Oct 1;82(7):e51–9.

17. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. JAMA. 2015 Aug 4;314(5):489.

18. van der Kolk BA. The body keeps the score: Brain, mind, and body in the healing of trauma. New York, NY, US: Viking; 2014. xvi, 443 p. (The body keeps the score: Brain, mind, and body in the healing of trauma).

19. VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. 2017;200.

20. Wisco BE, Nomamiukor FO, Marx BP, Krystal JH, Southwick SM, Pietrzak RH. Posttraumatic Stress Disorder in US Military Veterans: Results From the 2019–2020 National Health and Resilience in Veterans Study. J Clin Psychiatry. 2022 Feb 22;83(2):39779.

21. Davis AK, Averill LA, Sepeda ND, Barsuglia JP, Amoroso T. Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. Chronic Stress. 2020 Jan 1;4:2470547020939564.

22. Johnson MW, Richards WA, Griffiths RR. Human Hallucinogen Research: Guidelines for Safety. J Psychopharmacol Oxf Engl. 2008 Aug;22(6):603–20.

23. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011 Dec;168(12):1266–77.

24. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and Initial Psychometric Evaluation in Military Veterans. Psychol Assess. 2018 Mar;30(3):383–95.

25. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (PCL-5) in veterans. Psychol Assess. 2016 Nov;28(11):1379–91.

Figure 1: Trial Schematic

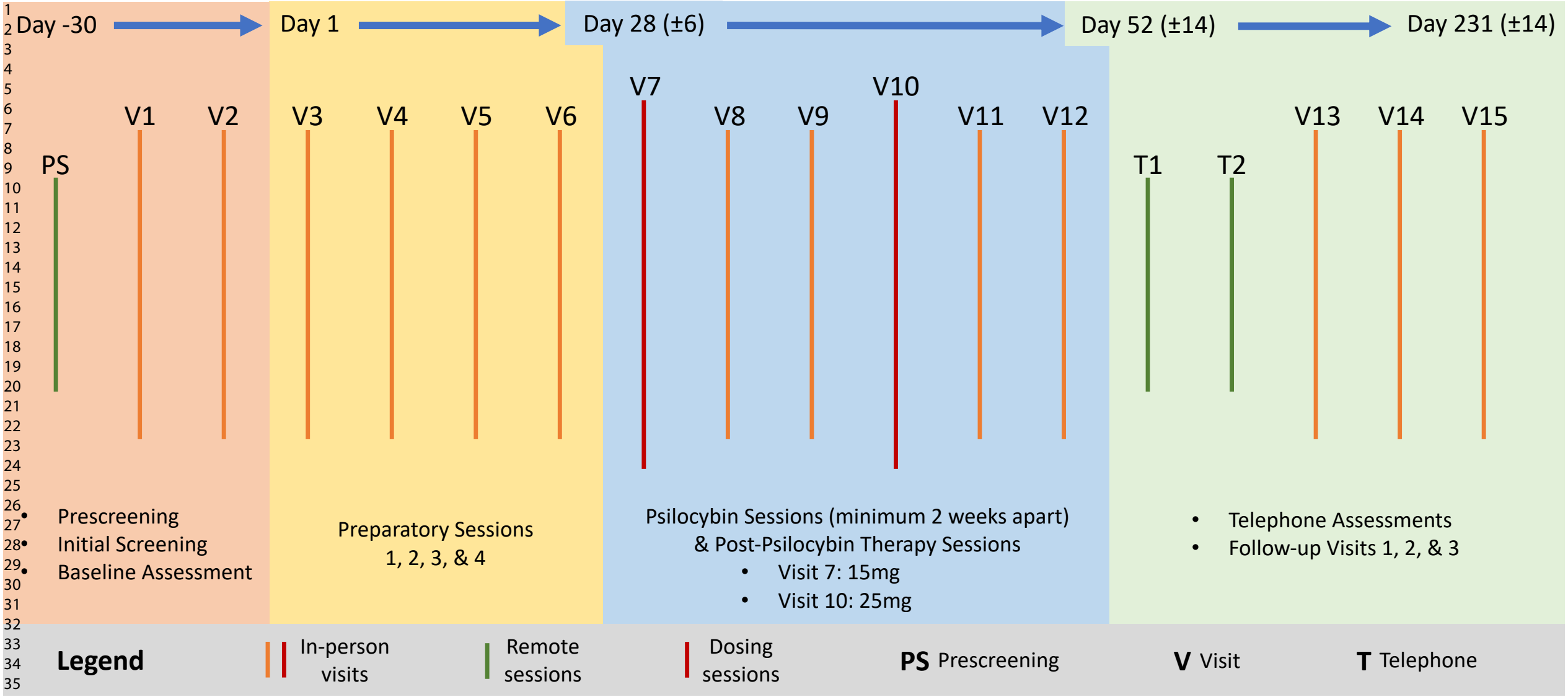

Figure 1. Trial Schematic.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1, 4
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	3-4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	n/a

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details	7-8

		of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7-8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2 (IRB approved)
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, Appendix 1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7-8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

A Study Protocol of an Open-Label Proof-of-Concept Trial Examining the Safety and Clinical Efficacy of Psilocybin-assisted Therapy for Veterans with PTSD

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068884.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2023
Complete List of Authors:	Davis, Alan; The Ohio State University College of Social Work, ; Johns Hopkins University, Psychiatry and Behavioral Sciences Levin, Adam; The Ohio State University College of Medicine, Psychiatry Nagib, Paul; The Ohio State University College of Medicine, Psychiatry Armstrong, Stacey; The Ohio State University College of Social Work Lancelotta, Rafael; The Ohio State University College of Social Work
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Mental health
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS, MENTAL HEALTH, CLINICAL PHARMACOLOGY

A Study Protocol of an Open-Label Proof-of-Concept Trial Examining the Safety and Clinical Efficacy of Psilocybin-assisted Therapy for Veterans with PTSD

Alan K Davis[a,b,c], Adam W Levin[a,b], Paul B Nagib[a,b], Stacey B Armstrong[a], Rafaelle L. Lancelotta[a]

Affiliations:
[a]Center for Psychedelic Drug Research and Education, College of Social Work, The Ohio State University, Columbus, OH 43210
[b]College of Medicine, The Ohio State University, Columbus, OH 43210
[c]Center for Psychedelic and Consciousness Research, Johns Hopkins University, Baltimore, MD 21224

Corresponding Author: Alan K Davis, Center for Psychedelic Drug Research and Education, College of Social Work, The Ohio State University, Columbus, OH 43210. Email: Davis.5996@osu.edu. Telephone: 614-292-5251

Study Sponsor: Principal investigator/Corresponding author

Acknowledgments: The authors would like to thank Usona Institute for providing the study drug for this trial. We also thank Dr. Emil Coccaro for their work as medical monitor of this study, and Deanna Golden-Kreutz, Holly Bookless, and the nursing staff at the Clinical Research Center at Ohio State University for their support during the trial. We also thank the following Ohio State University administrators, faculty, and staff who have been instrumental in establishing the infrastructure for this study: Tom Gregoire, Bridget Friesthler, David Jenkins, Peter Mohler, Courtney Mankowski, Julia Behnfeldt, Hallie Barr, Kaitlyn Vitek, Ellen Patricia, Susan Garfinkel, Dana McTigue, Brooke McDaniel, Richard Gumina, Kent Kiffner, Erin Scott, Elysabeth Bonar-Bouton, and Grace Adams.

Word Count: 4677

KEYWORDS: Posttraumatic Stress Disorder, PTSD, psilocybin, clinical trial, therapy

ABSTRACT

Introduction: Psilocybin-assisted therapy has shown significant promise in treating the cluster of mood and anxiety symptoms that comprise post-traumatic stress disorder (PTSD) but has yet to be tested specifically in this condition. Furthermore, current pharmacologic and psychotherapeutic treatments for PTSD are difficult to tolerate and limited in efficacy, especially in the United States Military Veteran (USMV) population. This open-label pilot study will examine the safety and efficacy of two psilocybin administration sessions (15mg and 25mg), combined with psychotherapy, among USMVs with severe, treatment resistant PTSD. **Methods and Analysis:** We will recruit 15 USMVs with severe, treatment resistant PTSD. Participants will receive one low dose (15 mg) and one moderate/high dose (25 mg) of psilocybin in conjunction with preparatory and post-psilocybin therapy sessions. The primary safety outcome will be the type, severity, and frequency of Adverse Events (AEs) and suicidal ideation/behavior, as measured by the Columbia Suicide Severity Rating Scale (CSSR-S). The primary outcome measure for PTSD will be the Clinician Administered PTSD Scale-5 (CAPS-5). The primary endpoint will be one month following the second psilocybin administration session, and the total follow-up time will be 6 months. **Ethics and dissemination:** All participants will be required to provide written informed consent. The trial has been authorized by the Ohio State University Institutional Review Board (Study Number: 2022H0280). Dissemination of results will occur via a peer-reviewed publication and other relevant media. **Registration details:** ClinicalTrials.gov Identifier NCT05554094

ARTICLE SUMMARY:

Strengths and limitations of this study

- A strength of the study design includes long-term follow-up of participants to assess the durability of the treatment over time.
- Another strength is that primary outcomes will be assessed by self-report and structured interviews by clinicians not affiliated with the study.
- A third strength is that the study includes clinician ratings after the preparatory psychotherapy and prior to the first psilocybin dosing to account for change that may be due solely to therapy.
- The single-arm design comes with limitations, such as having no comparison group or blinding procedures.
- Due to a small sample size, generalization of findings will be limited.

INTRODUCTION

In recent years, there has been increasing interest in investigating the use of psilocybin, a classic hallucinogen, as an adjunct to psychotherapy for the treatment of various psychiatric conditions. Recently completed trials have shown positive effects of this treatment among patients with depression and anxiety,[1–3] obsessive compulsive disorder, [4] and substance use disorders [5–7]. Results from these studies demonstrate that psilocybin-assisted therapy (PAT) is safe and has a minimal adverse event profile, with no documented serious adverse events when provided in a context that includes substantial psychological support. Additionally, data revealed robust short and long-term improvements in the constellation of mood, substance use, and anxiety symptoms that represent the core aspects of Posttraumatic Stress Disorder (PTSD) [8].

Current evidence supports the notion that PAT may be effective in treating PTSD, in part due to the high rates of co-morbidity with depression and anxiety, and the overlap in symptomology in these conditions [9]. Consistent with this hypothesis, a recent open-label trial of group PAT for demoralization in long-term AIDS survivors showed a clinically meaningful change in PTSD symptom severity, as measured by the PTSD Checklist-5 (PCL-5), from baseline to 3-month follow-up with a large effect size [10]. However, this study was not designed specifically to address symptoms of PTSD, nor did it focus on the broader population of people with this diagnosis. Furthermore, no study to date has focused on examining the safety and efficacy of PAT among United States Military Veterans (USMV), a population with a substantial burden of mental health problems compared to the general population. For example, despite inherent resiliencies and specialized training, members of the armed forces are often exposed to several military deployments and intense combat incidents, which are associated with a higher risk of PTSD compared to the civilian population [11,12]. Additionally, there has been an alarming increase in the incidence of suicides among Veterans, set in the context of limited effective treatment methods for this unique population [12,13]. Although the association between PTSD and suicide risk is complex and sometimes related to other factors, such as psychiatric comorbidity and demographic, social, and psychological characteristics [14,15], the need to reduce the risk associated with suicidality in this population remains critical. Moreover, evidence suggests a general association between psychedelic administration and reduced suicidality in the general population and in PAT trials [16–18], suggesting this approach could be helpful regardless of the etiology of suicidality.

Although several pharmacological and psychotherapy interventions have been developed to treat PTSD [19,20], these treatments are difficult to complete, challenging to access, and are lacking in efficacy for many Veterans [21–23]. Furthermore, there is emerging evidence that standard pharmacologic treatments are not as effective in Veterans with PTSD as they are in civilians [21,24], and are consequently no longer recommended as a front-line treatment in this population [25]. Although there is encouraging preliminary data on the safety and efficacy of PAT from a variety of patient populations, more research is needed to establish safety and efficacy of this treatment among USMV with PTSD. Not only could this novel treatment help ameliorate the burden of PTSD in this population, but it could also potentially reduce the risk of suicides among USMV and reduce the devastating impact of this mental health crisis in families and communities across the US.

Therefore, the current study was designed as an open-label pilot study testing the following primary hypotheses in USMVs with severe, treatment resistant PTSD: 1) PAT is safe to administer among Veterans with PTSD 2) PAT will be associated with decreases in PTSD symptom severity at 1-month after final psilocybin session as measured by the Clinician Administered PTSD Scale-5 (CAPS-5) and the PTSD Checklist for DSM-5 (PCL-5).

METHODS AND ANALYSIS

Objectives

The primary objective of the study is to investigate the safety of PAT among USMVs with severe, treatment-resistant PTSD based on the type, severity, and frequency of Adverse Events (AEs) and suicidal ideation/behavior (as measured by the Columbia Suicide Severity Rating Scale (CSSR-S) from baseline to primary endpoint, 1-month post-second psilocybin administration.

The secondary objectives of the study are as follows:

1. Investigate the effect of PAT on clinician rated PTSD symptom severity through the Clinician Administered PTSD Scale-5 (CAPS-5) measured at baseline and 1-, 3-, and 6-month(s) post-second psilocybin administration

2. Investigate the effect of PAT on participant rated PTSD symptom severity utilizing PTSD Checklist for DSM-5 (PCL-5) measured at baseline and 1-, 3-, and 6-month(s) post-second psilocybin administration

Setting

This study takes place in the Clinical Research Center at the Davis Medical Research Center within the Wexner Medical Center at The Ohio State University (OSU) in Columbus, Ohio.

Design

The study was designed to partially replicate the PAT intervention used in a trial for people with major depressive disorder [1] by conducting an open-label pilot study of two psilocybin administration sessions combined with psychotherapy for PTSD among USMV with severe, treatment resistant PTSD (Trial Protocol Version #1). Because this study is a single group open-label pilot safety and feasibility study, there is no randomization procedure or blinding to condition.

Participants and Recruitment

Recruitment

We will consent up to 100 volunteers (some will not pass the in-person screening), to achieve 15 individuals who will be enrolled in the study and subsequently complete both psilocybin sessions and the final follow-up assessment. We will attempt to reflect recent data from the 2019–2020 National Health and Resilience in Veterans Study (NHRVS), which showed that 26.7% of US Veterans with past-month PTSD were female and 34.8% were non-white [26]. Extrapolating from this analysis, we expect to recruit 11 male participants, 4 female participants, 10 white, and 5 non-white participants. Recruitment will consist of electronic dissemination of study flyers, social media ads, provider network communications via in-person meetings/telephone/email, email networking, and word of mouth.

Screening

Potential participants will be invited to pre-screen for the study via word of mouth, clinician referrals, listserv postings, social media advertising, and email distribution. Initial pre-screening will occur via a secure online questionnaire to determine if major inclusion/exclusion criteria are met. Participants who meet all study criteria, and who are not currently taking any psychiatric medications, will be invited to the OSU Department of Psychiatry and Behavioral Health Davis Medical Research Center for an in-person screening. If a potential participant is currently taking psychiatric medications, they must taper off their medications under the direction and monitoring of their prescribing physician before they can be invited

to an in-person screening. Written informed consent will be obtained by study staff during a scheduled meeting after participants have passed the initial online pre-screening.

Inclusion/Exclusion Criteria

Inclusion:

- Participants must be US military Veterans
- Must have DSM-5 diagnosis of PTSD with symptom duration of at least 6 months with a CAPS-5 total severity score of ≥35 at baseline
- Have had at least 3 months of prior SSRI or SNRI treatment in addition to at least 6 months of any psychotherapy
- Have at least a high-school level of education or equivalent (e.g., GED).
- No antidepressant medications for approximately 5 half-lives prior to baseline assessment and enrollment
- Be judged by study team clinicians to be at low risk for suicidality
- Be medically stable as determined by screening for medical problems via a personal interview, a medical questionnaire, a physical examination, an electrocardiogram (ECG), and routine medical blood and urinalysis laboratory tests
- Have limited lifetime use of hallucinogens (the following criteria are preferred: no use in the past 5 years; total hallucinogen use less than 10 times)

Exclusion:

- Participants who were assigned female at birth who are pregnant (as indicated by a positive urine pregnancy test assessed at intake and before each drug session) or nursing; people who are of child-bearing potential and sexually active who are not practicing a highly effective means of birth control (i.e., implants, injectables, combined oral contraceptives, progestin containing IUDs, or vasectomized partner).
- Participants who were assigned male at birth with partners of childbearing potential who are sexually active and not practicing a highly effective means of contraception (i.e., condom with spermicidal foam/gel/film/cream/suppository).
- Current medical condition incompatible with psilocybin administration (e.g., coronary artery disease, uncontrolled hypertension)
- Systolic blood pressure (SBP) > 139 mm HG; diastolic blood pressure (DBP) > 89 mm HG; heart rate (HR) > 90 bpm.
- Currently taking, on a regular (e.g., daily) basis, any medication(s) having a primary centrally acting serotonergic effect, including MAOIs
- Current or past history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), Bipolar I or II Disorder
- Current or history of (within one year of meeting DSM-5 criteria) a moderate or severe alcohol, tobacco, or other drug use disorder (excluding caffeine)
- Have a first- or second-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition) or Bipolar I or II Disorder
- Has a psychiatric condition that precludes the establishment of therapeutic rapport
- History of a medically significant suicide attempt

- Current antidepressant use

Enrollment

After enrollment, participants will receive preparation psychotherapy followed by one low dose (15 mg) and one moderate/high dose (25 mg) of psilocybin, followed by post-psilocybin therapy sessions. Each psilocybin session will last approximately 8 hours and will be overseen by two trained session facilitators (session facilitators can vary due to scheduling or other treatment considerations). Before the first psilocybin session, participants will meet with one or both session facilitators for approximately 8 hours of contact time (or up to 4 meetings). Two post-psilocybin therapy session visits will follow Psilocybin Sessions 1 and 2. Psilocybin Sessions 1 and 2 will occur at least two weeks apart. Follow-up visits will occur 1 and 2 week(s) and 1, 3, and 6 month(s) after the final psilocybin session, with additional contact hours scheduled as needed. Thus, the intervention and follow-up require 15 visits over a period of about 8-10 months. A schematic of trial activities is provided in Figure 1. Protocol amendments will be reported to the Food and Drug Administration, IRB, and clinicaltrials.gov.

Preparation

Before the first psilocybin session, participants will meet with both session facilitators for approximately 8 hours before the first psilocybin session day. The main purpose of the preparation meetings is to develop rapport and trust, which helps minimize the risk of fear or anxiety reactions during the psilocybin sessions. This approach has been successful in previous studies conducted by the Principal Investigator, including in a recent psilocybin study of depression [1]. Additional meetings and contact hours will be scheduled if it is judged necessary to establish sufficient rapport and trust prior to psilocybin administration. Consistent with previous psilocybin protocols authored and conducted by the lead investigator and others, the participant's life history and current situation in life will be reviewed, and intentions and expectations for the psilocybin sessions will be discussed [27,28]. Additionally, during these sessions, the facilitators will explore the participant's trauma history and experience of PTSD symptoms, as well as their goals, values, and perceived strengths and weaknesses. Lastly, an overview of common and uncommon psilocybin effects will be discussed, and skills for navigating such experiences will be explored and practiced.

Psilocybin Dosing Sessions

Procedures for psilocybin administration and the conduct of the session will be similar to procedures used in previous studies with psilocybin among patients diagnosed with Major Depressive Disorder [1]. Psilocybin is provided by Usona Institute in opaque gelatin capsules and will be administered with approximately 100 ml water. At least one session monitor, under the supervision of the investigators, will be present in the room and available to respond to participants' physical and emotional needs during the full course of psilocybin effects and for at least 8 hours. Typically, both session monitors are present unless one needs to step out of the session room to manage personal needs or to communicate with study team members. A physician on the study team will be immediately available via pager or mobile phone for at least 3 hours, or until the peak effects of psilocybin have subsided -whichever is longer. The physician will also be available for consultation by phone for up to 8 hours post-dosing.

During the psilocybin session, participants will be encouraged to lie on a couch, wear eyeshades, and listen to a program of music through headphones [1]. The music playlist for this trial was designed by the research team specifically for this study and a detailed description of the methods used to develop this playlist will be available in a forthcoming manuscript. During the session, the participant will be encouraged to focus their attention inward. The eyeshades and music are intended to encourage this inward reflection. Vital signs and measures of the intensity of behaviors, signs, and reported

symptoms will be assessed throughout the day by the session monitors will be monitored at 30, 60, 90, 120, 180, 240, 300, and 360 minutes after capsule administration. Acute anxiety, agitation, or panic will be handled with reassurance. In the unlikely event that these symptoms do not respond to reassurance, or in the unlikely event that the volunteer experiences unexpected psychosis, the clinical judgment of a study physician will determine the most appropriate medical treatment.

At the end of the experimental drug session, participants will complete paper or computer-based questionnaires (e.g., mystical experience [29,30], psychological insight [31], challenging experience [32]) designed to assess acute subjective experiences associated with the psilocybin session. Participants will also be asked to write a narrative description of the experience of the psilocybin session before their next in-person meeting. Study facilitators will complete a safety assessment (C-SSRS) which will be completed at all visits throughout the study.

Participants will be released to the care of a significant other, who will pick them up at the end of the day and transport them to their residence or place of lodging. The pick-up person will remain with them overnight. At the permission of the participant, the pick-up person will be invited to the session room prior to leaving with the participant, wherein they will be instructed about procedures for care during the evening/night following the psilocybin session. Additionally, at least one session monitor will be on-call via telephone for 24 hours after each psilocybin session.

Follow-up

The follow-up period is 6 months in total, with debriefing visits occurring immediately (1-3 days) following the psilocybin sessions, 1-week post-psilocybin sessions, and then at various time points following the final psilocybin dosing session. The follow-up sessions will include a discussion of the narrative description of the psilocybin session(s), an exploration of the participant's experience of PTSD symptoms, as well as the ongoing integration of their therapy experience into their day-to-day lives. Additional clinician and monitor contact hours will be scheduled if it is judged that the participant would benefit from additional meetings to discuss experiences from their session(s) or prepare for the next session. During the visits immediately following a psilocybin session, participants will be asked to discuss a narrative description of their most recent psilocybin session and psychological support will be provided. The primary goal of these sessions is to offer support for the participant's reflections on the psilocybin session. Study clinicians will support the participant's narrative expression of their experience and use their experience as a foundation for discussion about how to move forward and integrate this experience into their lives.

Psilocybin Session Facilitators

Each dyad of psilocybin session facilitators for this study includes at least one independently licensed clinician (e.g., clinical psychologist, psychiatrist, social worker, counselor) with clinical training in PAT and in the treatment of trauma and PTSD. The secondary facilitator could be another licensed clinician or a license-eligible person under the supervision of the primary facilitator. Training in PAT is provided to all facilitators via a 2-day workshop led by the principal investigator, as well as direct clinical supervision and training in the therapeutic approach during the study. To qualify as a primary facilitator, each facilitator who is eligible for this role will first serve as a secondary facilitator under the supervision of the principal investigator (serving as primary facilitator) or another approved primary facilitator for at least two participants before determining whether they can serve as a primary facilitator. The principal investigator will continue to monitor the facilitators in this study via regular meetings for the duration of the study.

Fidelity

Those involved in providing the intervention in this trial will complete checklists to ensure consistency across staff in the delivery of intervention content.

Participant Retention

Retention activities will include: 1) obtaining various methods of contact (i.e., email, primary phone number, home address, secondary phone number), 2) release of information to contact a primary physician or mental health provider, 3) release of information to contact a primary supportive friend/partner/spouse. Participants will be engaged in the trial on a weekly basis through the primary endpoint (1-month post psilocybin session 2). During each weekly study contact, participants will receive therapeutic intervention to assess for safety and need for ongoing support as necessary. During safety assessments, any unforeseen challenges with study participation will be addressed. During long-term follow-up time periods (between primary endpoint at 1-month and follow-up at 3- and 6-months), participants will receive a monthly contact from study personnel reminding them of upcoming visits and encouraging them to schedule a telephone or in-person visit should one be needed prior to the next scheduled study visit.

To aid in study retention, participants will also receive monetary compensation for the time they spend participating in the preparatory, psilocybin, and post-psilocybin therapy session meetings and measurements taken at the OSUMC. Remuneration will consist of $25 per study visit after enrollment, except for psilocybin session visits which will be compensated at the rate of $100/session visit as they will spend more time at the clinic on these days. Total remuneration will be up to $475 per participant.

Outcomes

Data Collection

Primary safety and clinical outcome data are collected by clinician interview (e.g., adverse events, suicidal ideation and behavior, PTSD symptoms via the CAPS-5) and self-report (e.g., PTSD symptoms via the PCL-5). Data will be entered by study staff (into a secure data collection platform; RedCap), using a double data entry method. Data will be stored on secure cloud servers and accessed only by approved study personnel. There was no requirement for a data monitoring committee for this trial and thus none will be used for this trial.

Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party. All research activities will be conducted in as private a setting as possible. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a locked room. This will not include the participant's contact or identifying

information. Rather, individual participants and their research data will be identified by a unique study identification number. Some therapy sessions may occur via telephone or videoconferencing (e.g., if a participant is unable to travel to our study site for an integration session or for a follow-up qualitative interview). Such sessions may be recorded using an encrypted audio/video format (e.g., Zoom). The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived. A Certificate of Confidentiality (CoC) has also been obtained for this study.

Safety outcomes

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to assess the severity of suicidal ideation during every study visit (in-person and virtual; https://cssrs.columbia.edu/) [33]. The C-SSRS is divided into four subscales based on 1) severity of ideation, 2) intensity of ideation, 3) suicidal behavior, and 4) lethality of attempt. Respondents are categorized as low, medium, and high risk based on where their affirmative answers are in the various subscales as opposed to their total score.

Additionally, the primary clinician/session facilitator for each participant will identify/record adverse events (i.e., the emergence of any untoward physical or psychological events or symptoms) and safety concerns at each study visit using a non-standardized form developed for use in prior studies [1]. The type, severity, and frequency of adverse events will be collected to identify and characterize any safety concerns that may arise.

Clinical outcomes

PTSD symptom severity will be measured using the CAPS-5 and PCL-5. The CAPS-5 is an extensively validated, widely utilized 30-item structured interview that assesses PTSD diagnostic status and symptom severity. It is scored on a scale of 0-80 with moderate and severe PTSD ranges rationally derived and defined as 23 to 34 and ≥35, respectively [34]. In addition to assessing the 20 *DSM-5* PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). The CAPS-5 will be administered by independent raters (blinded to all other aspects of study participation) at baseline assessment, at the primary endpoint (1-month), and at 3- and 6-months following psilocybin session 2. Independent raters will be comprised of IRB-approved team members of this protocol and trained in the assessment of PTSD using the CAPS-5.

The PCL-5 is one of the most widely used self-report measures of PTSD, with scores ranging from 0 to 80, with higher scores indicating greater PTSD symptom severity [35]. The PCL-5 will be self-administered at baseline as well as at additional time points (Preparatory Session 4, Therapy Session 1.2, 2.2, and Follow Up 1, 2, and 3) to assess whether there is an immediate post-psilocybin effect on PTSD symptom severity. Other clinical outcomes (e.g., depression and anxiety symptoms, psychological flexibility, personality) will be assessed in supplemental analyses separately from primary and secondary outcomes.

Statistical Analysis

No prior investigations of the effects of psilocybin on PTSD symptoms have been published to date. Because this trial has a primary objective of establishing the safety of this treatment approach among this population, and based on effect sizes in prior laboratory studies of psilocybin for other clinical populations [1,2], we believe that a sample size of 15 will provide sufficient power to detect a moderate effect size of pre- and post-psilocybin changes in PTSD symptoms. If the data suggest possible efficacy, these data should be sufficient to conduct a power analysis for a subsequent randomized controlled trial.

All participants enrolled in the trial and who complete both psilocybin sessions will be the evaluable population for analyses. Missing data will be managed through the use of imputation. For primary and secondary measures assessed at baseline and follow-up, repeated-measures ANOVAs with post-hoc comparisons will be conducted to test for differences between baseline and follow-up visits. Planned comparisons from baseline to 1-month post final psilocybin session will be conducted for primary outcome measures. These longitudinal outcome measures will be regressed on measures of acute and persisting psilocybin effects to examine whether such effects predict clinically relevant outcomes.

Primary Hypotheses/Endpoints:

1) PAT will be safe to administer among USMV with PTSD as indicated by no statistically significant increases in mean ratings of suicidal ideation on the C-SSRS from Baseline through 1-month post psilocybin session 2.
    a. Ratings of suicidal ideation on the C-SSRS will be included from baseline, 1-day post psilocybin session 1, 1-day post psilocybin session 2, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of suicidal ideation from baseline through 1-month post psilocybin session 2.
    b. Data will be presented with F-tests using an alpha (*p*-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

2) PAT will be safe to administer among USMV with PTSD as indicated by no serious adverse event reporting related to the administration of psilocybin.
    a. A descriptive analysis of adverse event reporting logs will be conducted to determine if any serious adverse events have been reported related to psilocybin administration.

Secondary Hypotheses/Endpoints

1) We will find statistically significant decreases in PTSD symptom severity from baseline to 1-month after the final psilocybin session as measured by the Clinician Administered PTSD Scale-5 (CAPS-5).
    a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit 4, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptoms severity from baseline through 1-month post psilocybin session 2.
    b. Data will be presented with F-tests using an alpha (*p*-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

2) We will find statistically significant decreases in PTSD symptom severity from baseline to 1-month after the final psilocybin session as measured by the self-report PTSD Checklist for DSM-5 (PCL-5).
    a. Mean ratings of PTSD symptoms severity will be included from baseline, preparation visit 4, and 1-month post psilocybin session 2. A repeated-measures ANOVA will be conducted with post-hoc mean pairwise comparisons to test for differences in ratings of PTSD symptom severity from baseline through 1-month post psilocybin session 2.
    b. Data will be presented with F-tests using an alpha (*p*-value) cutoff of .05 for statistical significance. Partial eta squared effect sizes will be reported with 90% confidence intervals.

ETHICS AND DISSEMINATION

This study was granted an IND from the Food and Drug Administration (IND#162567). The study also is registered with the Drug Enforcement Administration. All participants will be required to provide written informed consent (See Patient Consent Form). The trial has been authorized by the Ohio State University Institutional Review Board (Study Number: 2022H0280). Dissemination of results will occur via a peer-reviewed publication and other relevant media.

PATIENT AND PUBLIC INVOLVEMENT

Neither patients nor the public has been involved in the design and conduct of this study, the choice of outcome measures, or recruitment. There are no plans to include patients/public in dissemination efforts. Research questions were informed by the professional experiences working with Veterans with PTSD.

Author contributions: AKD: principal investigator, project coordination, trial monitoring, manuscript writing. SBA: study coordinator, measurement selection, protocol development, manuscript writing. AWL: protocol development, manuscript writing, measurement selection, medical protocol development. RLL: contributed to protocol development, contributed to measure selection, analytical strategy, designed music playlist, led playlist validation process, made comments on the manuscript. PBN: protocol writing and development, medical protocol development, led music playlist validation process, manuscript review and editing, visualization, provided feedback during playlist development.

Competing interest statement: AKD and RLL are board members of Source Research Foundation. This organization was not involved in the design/execution of this study or the interpretation or communication of findings. AKD is a Lead Trainer at Fluence.

Funding: This work was funded by the Center for Psychedelic Drug Research and Education (Award number: NA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data Statement: Data will be made available upon request by the corresponding author after the primary outcomes of the paper have been published.

REFERENCES

1. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021 May 1;78(5):481–9.

2. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol Oxf Engl. 2016 Dec;30(12):1181–97.

3. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, et al. Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. Arch Gen Psychiatry. 2011 Jan 3;68(1):71–8.

4. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder. J Clin Psychiatry. 2006 Nov 15;67(11):0–0.

5. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. J Psychopharmacol (Oxf). 2015 Mar 1;29(3):289–99.

6. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot Study of the 5-HT2AR Agonist Psilocybin in the Treatment of Tobacco Addiction. J Psychopharmacol Oxf Engl. 2014 Nov;28(11):983–92.

7. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017 Jan;43(1):55–60.

8. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci. 2015 Jun;17(2):141–50.

9. Bird CIV, Modlin NL, Rucker JJH. Psilocybin and MDMA for the treatment of trauma-related psychopathology. Int Rev Psychiatry. 2021 Apr 3;33(3):229–49.

10. Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine [Internet]. 2020 Oct 1 [cited 2021 Jul 29];27. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30282-0/abstract

11. Hanwella R, de Silva V. Mental health of Special Forces personnel deployed in battle. Soc Psychiatry Psychiatr Epidemiol. 2012 Aug 1;47(8):1343–51.

12. Hing M, Cabrera J, Barstow C, Forsten R. Special operations forces and incidence of post-traumatic stress disorder symptoms. J Spec Oper Med. 2012 Jan 1;12(3):23–35.

13. Rocklein Kemplin K, Paun O, Godbee DC, Brandon JW. Resilience and suicide in special operations forces: state of the science via integrative review. J Spec Oper Med. 2019;19(2):57–66.

14. Stanley IH, Chu C, Gildea SM, Hwang IH, King AJ, Kennedy CJ, et al. Predicting suicide attempts among U.S. Army soldiers after leaving active duty using information available before leaving active duty: results from the Study to Assess Risk and Resilience in Servicemembers-Longitudinal Study (STARRS-LS). Mol Psychiatry. 2022 Mar;27(3):1631–9.

15. Holliday R, Borges LM, Stearns-Yoder KA, Hoffberg AS, Brenner LA, Monteith LL. Posttraumatic Stress Disorder, Suicidal Ideation, and Suicidal Self-Directed Violence Among U.S. Military Personnel and Veterans: A Systematic Review of the Literature From 2010 to 2018. Front Psychol [Internet]. 2020 [cited 2023 Jan 29];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.01998

16. Jones GM, Nock MK. Race and ethnicity moderate the associations between lifetime psychedelic use (MDMA and psilocybin) and psychological distress and suicidality. Sci Rep. 2022 Oct 10;12(1):16976.

17. Jones GM, Nock MK. MDMA/ecstasy use and psilocybin use are associated with lowered odds of psychological distress and suicidal thoughts in a sample of US adults. J Psychopharmacol (Oxf). 2022 Jan 1;36(1):46–56.

18. Ross S, Agin-Liebes G, Lo S, Zeifman RJ, Ghazal L, Benville J, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy

for Psychiatric and Existential Distress in Life-Threatening Cancer. ACS Pharmacol Transl Sci. 2021 Apr 9;4(2):553–62.

19. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: Premises, principles, and priorities. Brain Res. 2009 Oct 1;1293:24–39.

20. Watkins LE, Sprang KR, Rothbaum BO. Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions. Front Behav Neurosci [Internet]. 2018 [cited 2021 Jul 21];0. Available from: https://www.frontiersin.org/articles/10.3389/fnbeh.2018.00258/full

21. Hertzberg MA, Feldman ME, Beckham JC, Kudler HS, Davidson JRT. Lack of Efficacy for Fluoxetine in PTSD: A Placebo Controlled Trial in Combat Veterans. Ann Clin Psychiatry. 2000 Jun 1;12(2):101–5.

22. Krystal JH, Davis LL, Neylan TC, A Raskind M, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017 Oct 1;82(7):e51–9.

23. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. JAMA. 2015 Aug 4;314(5):489.

24. van der Kolk BA. The body keeps the score: Brain, mind, and body in the healing of trauma. New York, NY, US: Viking; 2014. xvi, 443 p. (The body keeps the score: Brain, mind, and body in the healing of trauma).

25. VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. 2017;200.

26. Wisco BE, Nomamiukor FO, Marx BP, Krystal JH, Southwick SM, Pietrzak RH. Posttraumatic Stress Disorder in US Military Veterans: Results From the 2019–2020 National Health and Resilience in Veterans Study. J Clin Psychiatry. 2022 Feb 22;83(2):39779.

27. Davis AK, Averill LA, Sepeda ND, Barsuglia JP, Amoroso T. Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. Chronic Stress. 2020 Jan 1;4:2470547020939564.

28. Johnson MW, Richards WA, Griffiths RR. Human Hallucinogen Research: Guidelines for Safety. J Psychopharmacol Oxf Engl. 2008 Aug;22(6):603–20.

29. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol (Oxf). 2015 Nov 1;29(11):1182–90.

30. MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol (Oxf). 2011 Nov 1;25(11):1453–61.

31. Davis AK, Barrett FS, So S, Gukasyan N, Swift TC, Griffiths RR. Development of the Psychological Insight Questionnaire among a sample of people who have consumed psilocybin or LSD. J Psychopharmacol (Oxf). 2021 Apr 1;35(4):437–46.

32. Barrett FS, Bradstreet MP, Leoutsakos JMS, Johnson MW, Griffiths RR. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. J Psychopharmacol Oxf Engl. 2016 Dec;30(12):1279–95.

33. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011 Dec;168(12):1266–77.

34. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and Initial Psychometric Evaluation in Military Veterans. Psychol Assess. 2018 Mar;30(3):383–95.

35. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (PCL-5) in veterans. Psychol Assess. 2016 Nov;28(11):1379–91.

Figure 1: Trial Schematic

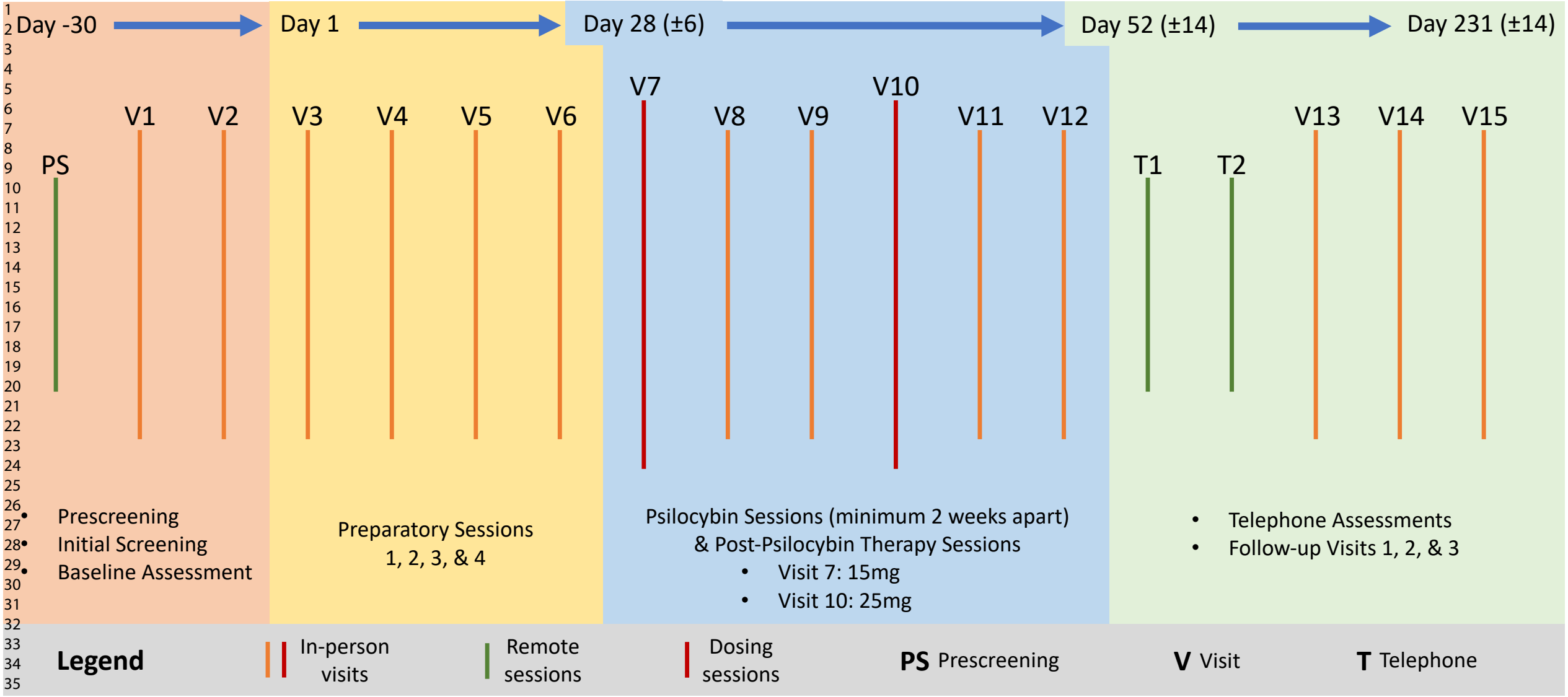

Figure 1. Trial Schematic.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1, 4
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	3-4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for	n/a

		stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details	7-8

		of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7-8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2 (IRB approved)
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, Appendix 1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7-8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7-8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a