DF/HCC Protocol #: 21-202

TITLE: **Pilot study of Psilocybin-Assisted Therapy for demoralization in patients receiving Hospice care – PATH study**

Coordinating Center: Dana-Farber Cancer Institute

Study site: Care Dimensions hospice

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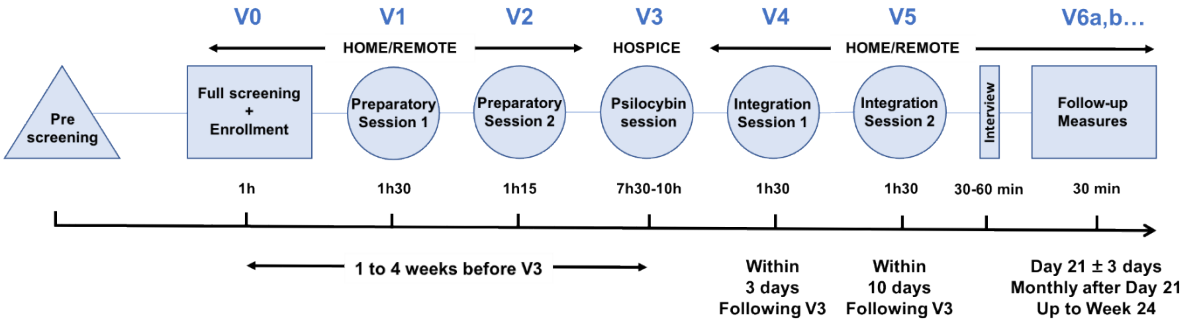
NCI-Supplied Agent(s): *None*
Other Agent(s): psilocybin, Usona Institute
IND #: 154113
IND Sponsor: Yvan Beaussant, MD, MSc

Protocol Type / Version 26 / Version Date: April 18, 2023

Summary of changes April 18, 2023

1. **Section 5.1.1 *Pre-Screening* pg. 15 to include option for the Hospice Interdisciplinary Team to provide the Study Information flyer by *email or paper* to potentially eligible and interested study participants.**
2. **Protocol scheduled allowable window of time for psilocybin administration updated from "9am +/- 15 minutes" to "as soon as possible – typically between 9 and 9:30am" in section 5.1.2 *Visit V3: psilocybin session* pg. 17.**
3. **Protocol scheduled window of allowable time for patient and caregiver post-intervention qualitative interviews updated from "after V5 +/- 3 days" to "after V5" in section 5.1.4 *Post-Intervention Assessments – Qualitative Assessment* pg. 19 and *Semi-Structured Interview Guides – patient and caregiver* pg. 23.**
4. **Scheduled duration after which recorded content will be destroyed "10 years" removed from section 5.1.6 *Recorded Content* pg. 24.**
5. **Anticipation of incomplete intervention assessments for participants throughout intervention given their terminal condition indicated in section 11. *Study Calendar*, footnote (8).**
6. **Protocol scheduled window of allowable time for V1 updated to "</=3 weeks prior to Day 0" instead of "2 weeks" in section 11. *Study Calendar – V1.***
7. **Protocol scheduled window of allowable time for V2 updated to "</= 7 days prior to Day 0" instead of "3 days" in section 11. *Study Calendar – V2.***
8. **Protocol scheduled window of allowable time for V5 updated to "Up to day 14" instead of "Day 10" in section 11. *Study Calendar – V5.***
9. **Protocol scheduled window of allowable time for Follow Up visits updated from "Week 3 +/- 3 days" to "Week 3 +/- 14 days" (post-dosing) in section 11. *Study Calendar – F/U*.**
10. **Protocol Version and Version Date updated accordingly.**

SCHEMA


V0
V1
V2
V3
V4
V5
V6a,b…
HOME/REMOTE
HOSPICE
HOME/REMOTE
Pre screening
Full screening + Enrollment
Preparatory Session 1
Preparatory Session 2
Psilocybin session
Integration Session 1
Integration Session 2
Interview
Follow-up Measures
1h
1h30
1h15
7h30-10h
1h30
1h30
30-60 min
30 min
1 to 4 weeks before V3
Within 3 days Following V3
Within 10 days Following V3
Day 21 ± 3 days
Monthly after Day 21
Up to Week 24

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1. OBJECTIVES

The overall objective of this study is to develop, and pilot test a novel regimen of psilocybin-assisted psychotherapy for demoralization in patients receiving hospice care.

1.1 Study Design

Open label, single center, concurrent mixed-methods phase 2 pilot trial of a single dose of psilocybin for demoralization in patients receiving hospice care.

1.2 Primary Objectives

To assess, using quantitative and qualitative measures, the feasibility of delivering a single dose of psilocybin 25 mg under supportive psychotherapeutic conditions to patients with moderate-to-severe demoralization (Demoralization Scale-II ≥ 8) who receive hospice care at home.

Hypothesis:
Treatment and week 1 assessments will be successfully completed in at least 60% of recruited subjects, and ≥ 80% of subjects who completed Week 1 assessment will evaluate favorably acceptability.

1.3 Secondary Objectives

To explore the safety of psilocybin-assisted therapy in this population and its preliminary efficacy on demoralization and other patient-reported and family caregiver-reported outcomes.

Hypotheses:
No serious adverse-event related to the intervention will occur and week 1 outcomes assessment will show improvement in demoralization.

2. BACKGROUND

2.1 Study Disease(s)

Terminal illness related to cancer and non-cancer diagnoses.

2.2 IND Agent

The IND agent, psilocybin, is manufactured by Usona Institute, a 501(c)(3) non-profit medical research organization that obtained Breakthrough therapy status from the Federal Drug Administration (FDA) for its Current Good Manufacturing Practice (cGMP) psilocybin in the treatment of Major Depressive Disorders (IND 129532).

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a natural product produced by numerous species of Psilocybe mushrooms, which is

manufactured for clinical use to control potency and purity. It is a tryptamine derivative, and in humans the phosphate group is rapidly enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which in this setting is the 5-HT2A receptor.[1,2] Oral psilocybin has about a 50% bioavailability and psilocin is detectable in plasma within 20 minutes of administration of the parent compound.[3,4] The half-life of psilocin in blood is 2-3 hours. Onset of noticeable psychoactive effects occurs within one hour, peaks at about two hours after a dose, and loss occurs typically around six hours after the dose. Based on this time course, in the clinical trial setting, protocols mandate observation until approximately 8 hours after dosing.

Psilocybin reliably induces profound changes in sensory perception, emotion, thought, and sense of self, characterized by marked alterations in all mental functions, including perception, mood, volition, cognition and self-experience.[5,6] These profound changes are often referred to as mystical-type experiences. Measures of mystical-type experience occurring during psilocybin treatment have been repeatedly observed to predict later effects on behavior and emotions, including reductions in depressive and anxious symptoms.[7–9]

Non-clinical in vivo and in vitro studies, found via literature searches, demonstrate that similar to humans, when psilocybin is administered orally to rats it is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract. Maximum plasma levels are achieved after approximately 90 minutes.[10] When administered systemically (i.e., bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with in vitro studies indicating the kidneys as being among the most active metabolic organs.[11] Across species tested, the highest levels of psilocin were found in the neocortex, hippocampus, and thalamus.[12]

Recent clinical studies utilizing pharmaceutical-grade oral psilocybin under controlled conditions have been performed upon healthy participants and various subpopulations in order to gauge safety events and preliminary clinical efficacy. Though the safety reporting criteria and the level of data verification varied greatly between studies, including many participant-reported outcomes, these data have been utilized to elucidate the expected adverse event (AE) profile of psilocybin. The clinical studies summarized in the investigator brochure present similar safety profiles, with both psychological and physical adverse events reported. The most common adverse psychological events included transient anxiety, negative emotional states and paranoid/delusional thinking during dosing sessions, and the most common physical effects were increased blood pressure (BP) and heart rate, mild nausea, and mild headache.

Preliminary efficacy of psilocybin in these studies showed a substantial and sustained decrease in symptomatic response in indications including obsessive compulsive disorder (OCD), substance use disorder, depression, anxiety, and psychological and existential distress in patients with serious illness (e.g. cancer). Overall, psilocybin has been well-tolerated at the doses examined in the clinic. Due to the psychoactive nature of the compound, it should only be administered in a controlled setting and per the accompanying clinical protocol.

Psilocybin is currently under phase 2b of drug development in patients with depression and treatment-resistant depression (NCT03866174 and NCT03775200 respectively), and if the outcomes are positive, then it seems plausible that psilocybin will become a licensed medicine for a range of indications in psychiatry and serious illness care when used in an approved treatment model.[13] In the past few years, many renowned academic medical centers in the United States have (re)started investigating the clinical applications of psilocybin, among which John Hopkins University School of Medicine, New York University, Harbor-UCLA, and more recently Yale, Mass General Hospital and Berkley.

2.3 Rationale

More than 1.4 million Americans receive hospice care each year, of whom 30% have a principal diagnosis of cancer. For most of these patients and families, emotions such as fear, anger or sadness are common and normal. However, 38 to 50% of patients experience clinically relevant anxiety and/or depression that significantly impacts their and their caregivers quality of life (QOL).[14,15] High quality hospice care ought to seek, as a fundamental goal, to address this psychological distress. Yet, symptoms such as depression are often underrecognized and undertreated in this population.[16] This may be due to clinicians or patients not recognizing depressive symptoms in the context of serious illness,[17–19] to the lack of effective treatment,[20–22] or both. In addition, existential suffering, commonly experienced at the end of life and manifested through demoralization syndrome, exacerbates anxiety and depression.[23–26] Improving the management of these symptoms would benefit healthcare outcomes of millions of patients and family caregivers, and society at large.

Psilocybin-assisted therapy presents a novel potential therapeutic modality for hospice patients, as preliminary evidence suggests its safety and efficacy to treat psychosocial distress in people with serious illness.[8,9,27–30] Psilocybin is a serotoninergic psychedelic derived from a class of fungi. Based on therapeutic models developed in the 1960s, this drug-facilitated psychotherapy combines an inner-directed psychotherapy to the consciousness-expanding properties of psilocybin, by agonism of the serotonin receptor 5HT2A, to facilitate the processing and resolution of psychological and existential issues.[1,31–34] In patients with cancer, recent double-blind, randomized controlled trials of psilocybin-assisted therapy showed pronounced and prolonged reductions in depression and anxiety, as well as sustained benefits in existential distress, spiritual well-being and quality of life.[8,9,27]

Grob et al.'s study included 12 patients and demonstrated the safety and feasibility of administering psilocybin-assisted therapy within cross-over randomized controlled trials in this setting.[27] Using similar designs in larger sample sizes, Griffith et al.'s and Ross et al.'s studies further documented safety and feasibility, and demonstrated rapid, robust and sustained improvements of depression and existential distress in cancer patients. In particular, Griffith et al.'s study found sustained remission of depression symptoms at 6 months in 70% of patients (n=51)[8] and Ross et al.'s study found enduring antidepressant and anxiolytic effect following psilocybin administration in 80 and 60% of patients respectively (n=29).[9] In the latter study, 3.2 and 4.5 years follow-up showed continued reductions in depression or anxiety, sustained benefits in existential distress and quality of life, and improved attitudes towards death anxiety in most

patients.[28] Following these results, the FDA approved two large multicenter confirmatory trials in non-cancer patients with MDD and treatment resistant depression (TRD) respectively.[35,36]

Another study conducted by Anderson et al. and recently published in EClinicalMedicine provides useful background for our study.[37] This open-label study assessed the safety and feasibility of psilocybin-assisted group therapy for demoralization in 18 older long-term AIDS survivor (OLTAS) men, a population of patients with serious illness with particularly complex medical and psychiatric needs. Findings demonstrated a clinically meaningful change in demoralization from baseline to 3-month follow-up. Zero serious adverse reactions and two unexpected adverse reactions to psilocybin were detected, and seven participants experienced self-limited, severe expected adverse reactions (see adverse events table in section 7.1).

Psychedelic-assisted therapies raise both excitement and concern among key stakeholders in serious illness care.[38,39] Our group conducted in-depth interviews of experts involved in serious illness care and/or psychedelic research that highlighted the need to conduct rigorous psilocybin trials in the context of interdisciplinary psychosocial and palliative care.[39] Rapid evolution in the legal and regulatory status of psychedelics has heightened the urgency of obtaining scientific evidence to inform future standards of care for psychedelic-assisted therapies.[13,40,41] This is particularly true for patients with cancer receiving hospice care, who may derive substantial benefit and yet may have particular vulnerabilities.

To date, no study has assessed the safety and efficacy of psilocybin-assisted therapy to address psychosocial, existential, or spiritual distress in patients with a terminal illness receiving hospice care. Defining relevant eligibility criteria and treatment regimen is critical for patient safety. Conducting rigorous randomized controlled studies in this population presents unique challenges, warranting feasibility studies that carefully prepare larger confirmatory trials. To bridge this gap, our Department has partnered with Care Dimensions, a non-profit leader in hospice care and the largest hospice organization in Massachusetts. Our group is uniquely equipped and positioned to deliver, assess and refine this novel intervention. This study, by pilot-testing a new model of psilocybin-assisted therapy in patients receiving hospice care, will facilitate the success of future randomized multi-center trials necessary to confirm the intervention's efficacy in this patient population and shape the therapeutic model. Given the unmet need in this large population of patients and family caregivers, the potential to positively impact healthcare outcomes in the field is high.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients enrolled in hospice care at home

3.1.2 Age ≥ 21 years.

3.1.3 Any terminal illness with respect of exclusion criteria

3.1.4 Palliative Performance Scale (PPS) ≥ 40 % (see Appendix A)

3.1.5 Moderate-to-severe demoralization as measured by Demoralization Scale-II ≥ 8 (see Appendix A)

3.1.6 Significant other or other caregiver present at home the night of study drug administration

3.1.7 No driving for 24 hours following study drug administration.

3.1.8 English proficiency

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.1.10 Psilocybin is very likely to have no genotoxic effects. One study that directly focused on the mutagenic potential of psilocybin did not found this type of toxicity.[42] However, due to the lack of clinical and non-clinical studies on the effects of psilocybin on the developing human fetus, women and men of child-bearing potential and who are sexually active must agree to use an acceptable contraceptive method (hormonal or barrier method of birth control; abstinence) throughout their participation in the study. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of psilocybin administration.

3.1.11 Patients with first-degree relatives with schizophrenia or bipolar disorder may be eligible depending on their age and personal and family psychiatric history. The decision will be made by the principal investigator and study psychiatrist based on risk assessment.

3.2 Exclusion Criteria

3.2.1 Current General Inpatient (GIP) hospice status

3.2.2 Patients currently receiving chemotherapy

3.2.3 Condition impairing oral intake or digestive absorption

3.2.4 Presence of a delirium diagnosed by the CAM (see Appendix A)

3.2.5 Significant suicide risk as defined by suicidal ideation with intend and a plan as endorsed on item 5 on the C-SSRS within the past month or at V0 (see Appendix A)

3.2.6 Current or past history of schizophrenia, psychotic disorder, bipolar disorder, delusional disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder, as assessed by medical history

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to psilocybin

3.2.8 Other personal circumstances and behavior that would limit compliance with study requirements, or judged by the study psychiatrist and/or principal investigator to be incompatible with establishment of rapport or safe exposure to psilocybin

3.2.9 Potential for adverse drug-drug interactions. Concomitant medications with significant potential to interact with study medications will be exclusionary if they cannot be tapered. These include the following:

- Serotoninergic antidepressants
- Centrally-acting serotonergic agents (e.g. MAO inhibitors)
- Antipsychotics (e.g. first and second generation)
- Mood stabilizers (e.g. lithium, valproic acid)
- Aldehyde dehydrogenase inhibitors (e.g. disulfiram)
- Significant inhibitors of UGT 1A0 or UGT 1A10

Any psychiatric medication will be tapered if possible in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the psilocybin Session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug and active metabolites' half-life). See section 9 of the protocol for concomitant medications and tapering instructions.

3.2.10 End stage liver disease or cirrhosis as primary hospice diagnosis

3.2.11 Patients who have elevated AST and ALT five times above the normal laboratory limit on their last available bloodwork and patients with symptoms suggestive of liver failure including confusion, asterixis or jaundice.

3.2.12 Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal condition or any other unstable condition that, in the opinion of the principal investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study. This may include but is not limited to clinical symptoms or recent history of significant tachyarrhythmias; severe angina or myocardial ischemia; poorly controlled congestive heart failure; poorly controlled hypertension; poorly controlled hypo- or hyperthyroidism; uncontrolled diabetes; severe renal or liver disfunction; acute respiratory failure; sepsis; history of cerebral aneurysms; glaucoma; increased intracranial pressure and any intracranial mass.

3.2.13 Women who are pregnant, nursing, or planning a pregnancy.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Caregivers' Inclusion/Exclusion criteria

Inclusion Criteria	Exclusion Criteria
Individual identified as a support person by a patient enrolled in the PATH study	Unable to participate
18 years of age and older	Deemed inappropriate for the study by the patient's clinician
English proficiency	Unable to respond in or read English
Ability to understand and the willingness to sign a written informed consent document	Unable to obtain informed consent due to cognitive or emotional status

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the

subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Study Coordinator. All sites should email the Sponsor (yvan_beaussant@dfci.harvard.edu) to confirm and plan intervention. The required forms can be found in Appendices.
Following registration, participants should begin intervention within 7 days. Issues that would cause intervention delays should be discussed with the Principal Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and e-mailed (yvan_beaussant@dfci.harvard.edu and isabel_kristan@dfci.harvard.edu) to the Study Coordinator:

- Signed participant consent form
- HIPAA authorization form
- Eligibility check-list
- Copy of demoralization scale, PPS score, C-SSRS, CAM scores

The participating site will then call (857-272-5830) or e-mail (yvan_beaussant@dfci.harvard.edu) the Study Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration.

4.5 Initiation of Therapy

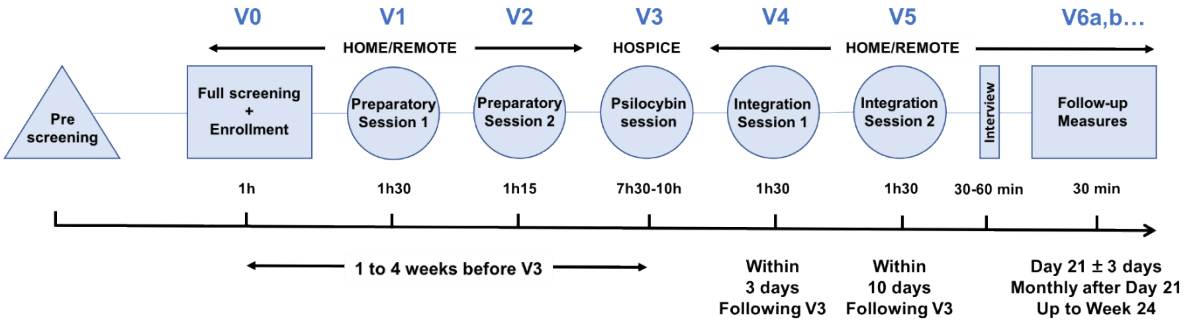
Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Care Dimension's pharmacy must confirm registration is complete prior to dispensing study drug. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

5. TREATMENT PLAN

5.1. Treatment Regimen

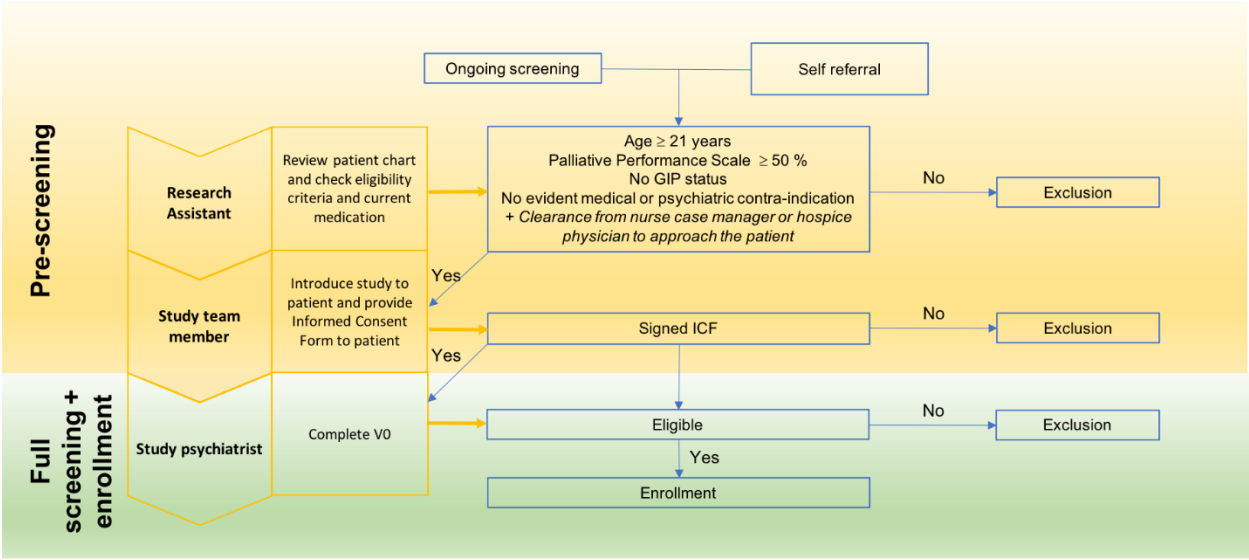
The treatment regimen consists of a single administration of psilocybin 25 mg orally combined with a supportive psychotherapy including 2 preparation sessions and 2 integration sessions.

The study schema is the following:



5.1.1 Enrollment and study entry

Consent process flowchart



Pre-screening (remote)

The study population will include 15 adult patients, 21 years or older, who receive hospice care at home from Care Dimensions hospice in Massachusetts. The study team will screen potential participants by reviewing new admissions and reviewing the current census on a reoccurring basis. For potentially eligible patients, the study team will contact a referent hospice clinician (nurse case manager or physician) to discuss the patient case and confirm the possibility to further the consent process. A member of the interdisciplinary team will provide an information flyer (paper or electronic via email) to the potentially eligible patients. Patients can reach out to

the study team via the contact indicated on the flyer or a member of the study team will reach out to them to assess further interest in participation. Interested patients will be scheduled to meet with the study psychiatrist and given the opportunity to review the inform consent form either on paper (ICF) or electronically (eICF). Additionally, for reference the following link to the Heffter Research Institute website will be given to potential participants: https://www.heffter.org/future-research. This website provides information about psilocybin-assisted therapy research in patients with cancer and features video accounts from previous participants in similar studies.

Visit V0: full screening + enrollment (patient's home or remote)

Patients who signed the inform consent form (ICF) or the electronic ICF (eICF) will have a first visit (V0) with the study psychiatrist and the investigator, taking place either at their home or remotely, to confirm their eligibility, and complete screening assessments including: the Demoralization Scale-II (DS-II); the Columbia-Suicide Severity Rating Scale (C-SSRS); the Confusion Assessment Method (CAM) and medical and psychiatric history. Physical examination and vital signs will be obtained from the clinical team and/or patient chart and reviewed by the study psychiatrist and the investigator. The lead physician will review last available bloodwork and exclude patients who have elevated AST and ALT five times above the normal laboratory limit. The lead physician as part of the medical evaluation will observe for clinical signs of liver disease, including confusion, asterixis or jaundice. Patients with these symptoms suggestive of liver failure will be excluded from the study. Only patients who meet all eligibility criteria will be enrolled in the study. Caregivers of enrolled patients will be offered to consent for the caregiver survey (CarGOQoL), the HADS, and the post-intervention qualitative interview. The study staff will follow the registering processes described in Section 4.0.

The duration of V0 will be 30-60 min.

5.1.2 Treatment regimen

Visit V1: baseline assessment + preparation session #1 (patient's home or remote)

V1 includes baseline assessment and a first preparation session with the study therapists (see section below for details about the therapy dyads).

Baseline assessment consists in patient-reported questionnaires that patients will complete on paper either on their own prior to V1 or with the help of a study staff member. Baseline assessment includes the following measurements (see details in section 5.1.5): the Functional Assessment of Chronic Illness therapy – Palliative Care (FACIT-Pal); the PROMIS pain interference scale (if pain presented); the Hospital Anxiety and Depression Scale (HADS A and D); the PROMIS social isolation scale; the Life Attitude Profile – revised, Death acceptance subscale (LAP-R, DA); the FACIT-spirituality; the Schedule of Attitudes Toward Hastened Death (SAHD). Consenting caregivers will complete the CarGOQoL and HADS at V1. In addition, the study psychiatrist will complete the C-SSRS and the CAM.

Following baseline assessments, the lead therapist (LT) and the co-therapist (CT) will conduct the first preparation session. The main objectives of the preparation sessions are to educate

patients and families on psilocybin-assisted therapy, to build rapport between them and the study therapists, and to identify intentions for the psilocybin session as well as personal themes and struggles that might impact the psilocybin experience.

V1 and V2 will be conducted within about a week to a month prior to the psilocybin session.

The duration of V1 will be up to 90 min (30 min assessment + 60 min preparation).

Visit V2: preparatory session #2 (patient's home or remote)

The second preparatory session (V2) will take place at home or remotely. Patients and therapists will conduct V2 assessments as indicated on the schedule of assessment (see 5.1.6) and continue to set expectations for treatment, discuss set and setting and build the therapeutic alliance.

The duration of V2 will be up to 75 min (15 min assessment + 60 min preparation).

Visit V3: psilocybin session (hospice facility) – day 0

The psilocybin session will take place in an individual room at the Care Dimensions Hospice House and will last 8 h (30 min assessment + 7h30 hour psychotherapeutic support).

Participants will arrive at 8 am and complete the following assessments at V3, prior to receiving the medication: DS-II and HADS A and D. In addition, the lead therapist will complete the C-SSRS and the CAM.

The participant will take the study drug capsule (psilocybin 25 mg) under the therapy team supervision as soon as possible – typically between 9 and 9:30 am. No dose modifications will be necessary.

Blood pressure and heart rate will be measured at the following time-points after psilocybin administration: 30, 60, 120, 180, 240, 300, and 360 min.

During the psilocybin session, facilitators' role will be to monitor, assist and support patients while they are experiencing the effect of the medicine. The monitoring will focus on vital signs and distress level. The assistance and support, whether it's physical or emotional will follow patients' needs in a non-directive way. At the onset of the study agent effect, therapists will invite participants to lie down on the bed, put on eyeshades and put on headphones that will play a pre-selected play-list throughout the session. Therapists will encourage participants to focus inward and stay open to and present with whatever their inner experience is.

Psilocybin effect on perception and consciousness lasts 4 to 6 hours in most individuals. When the participant appears to have returned to his/her baseline psychological and physiological state, and he or she expresses a readiness to begin the discharge process, they will complete the Mystical Experience Questionnaire (MEQ-30) and the Challenging Experience Questionnaire (CEQ), and the Lead Therapist and co-investigator will determine if participant is safe and ready to be discharged home. Patients who are unable to be discharged home for medical or psychiatric

reasons will have the possibility to stay overnight at the hospice house for medical supervision. If for any reason the patient cannot stay at the hospice house and their situation requires medical supervision, arrangements would be made by the study team to admit them to a hospital.

Visit V4: Integration session #1 (patient's home or remote) – Day 1 (up to day 3)

The integration session 1 will occur the day after the psilocybin session (allowable window 3 days) and start with medical and psychological assessment as indicated on the schedule of assessments.

The objective of the integration sessions is to help patients consolidate insights gained from the psilocybin experience. Patient will have the opportunity to discuss their experience with the goal of maximizing the therapeutic benefit.

The duration of V4 will be 75 min (15 min assessment + 60 min preparation).

Visit V5: Integration session #2 (patient's home or remote) – Day 7 (up to day 14)

The integration session 2 will occur within 14 days after the psilocybin session. After V5, patient clinical follow-up will be continued as part of usual care by the hospice team.

The duration of V5 will be 75 min (15 min assessment + 60 min preparation).

Summary of treatment regimen

<table>
<tr><th colspan="5">Regimen Description</th></tr>
<tr><th>Agent</th><th>Premedications; Precautions</th><th>Dose</th><th>Route</th><th>Schedule</th></tr>
<tr><td>Psilocybin</td><td>None</td><td>25 mg</td><td>PO in under 5 mins</td><td>Visit 3</td></tr>
<tr><th>Psychotherapy</th><th>Focus</th><th>Length</th><th>Therapists</th><th>Schedule</th></tr>
<tr><td>Preparation 1</td><td rowspan="2">Psychoeducation, intention setting and relaxation technics</td><td>60 min</td><td rowspan="6">Lead therapist and co-therapist</td><td>Visits 1</td></tr>
<tr><td>Preparation 2</td><td>60 min</td><td>Visits 2</td></tr>
<tr><td>Psilocybin session</td><td>Inner-directed psychotherapeutic support</td><td>7h30</td><td>Visits 3</td></tr>
<tr><td>Integration 1</td><td rowspan="2">Debriefing, journaling and goals setting</td><td>60 min</td><td>Visits 4</td></tr>
<tr><td>Integration 2</td><td>60 min</td><td>Visits 5</td></tr>
</table>

Unscheduled Visits

Additional visits or phone calls may be scheduled to perform procedures other than those listed above. This may be done for patient's safety and will be based on the judgment of the study staff.

5.1.3 Therapists dyads

Therapy teams will be composed of a Lead Therapist and a Co-Therapist. The dyads will be present at all therapy sessions, namely V1, V2, V3, V4 and V5.

The LT will be an actively licensed, Master's-level or doctoral-level MD/PhD/PsyD-level psychotherapist. The CT will hold a minimum of a bachelor's degree and be trained in mental health or spiritual care. Preference will be given to those with experience working in the hospice field and/or prior experience working in clinical research trials, especially with psilocybin.

5.1.4 Post-intervention assessments

Visits V6a,b…: Post-intervention outcome measures

Post-intervention period will consist of outcome measures at V4, V5, V6a and subsequent monthly visits (see detailed outcomes in section 5.1). We will conduct these visits at home or remotely depending on the patient and family situation. We anticipate that given their terminal condition, participants might not be able to complete post-intervention measures or may only be able to complete part of them. To reduce administrative burden, we will not report those missing questionnaires as protocol violations.

Qualitative assessment

All sessions between the therapists and the participant during the intervention period will be audio and video recorded for fidelity rating, qualitative analysis and education purposes.

In addition, after the intervention, we will conduct audio-recorded semi-structured interviews with patients and caregivers to qualitatively assess feasibility and outcomes. Patient interviews will be conducted as soon as possible after the first or second integration session (V4 or V5) in order to optimize acceptability data collection in a context – hospice - defined by the potential for rapid clinical deterioration. Caregivers' post-dosing interviews will be conducted within the same timeframe but may be conducted later if needed.

Semi-structured interviews with a selected sample of hospice staff providers involved in enrolled participants' care will also be conducted. The main objective of these interviews is to explore hospice staff's perspectives on the feasibility and acceptability of the PATH study intervention. We will recruit a convenient sample of 5-7 clinicians who were actively involved in the care of study participants and represent a diversity of perspectives and roles (e.g. physicians, nurses, social workers, chaplains and team leaders). Recruitment of hospice staff will happen at 3 different times over the study enrollment period, each time after 4 or 5 patients have completed the study intervention. The recruitment email will include information needed for informed verbal consent. We request a waiver of documented informed consent for hospice staff.

Participating hospice staff will receive $50 gift cards to acknowledge their time and contribution.

The interviews with hospice staff will be conducted in-person or remotely (over the phone or a DFCI Zoom account), last **about 40 min** and be audio-recorded. Audio recording will start only after participant's information and verbal consent, according to the interview script attached. Recording will be transcribed verbatim using a HIPAA compliant service. All recordings and transcripts will be stored in secure, restricted-access locations. Recordings and transcripts will be tied to a unique study ID number, and the only documents linking the study ID to identifiable information are in restricted access files stored securely in restricted access folders. Potential patient's health information will be de-identified, and all audio recordings will be destroyed when analyses are complete.

5.1.5 Instruments measuring study outcomes:

Demographic questionnaire (V0)
Variables of interest will be obtained via self-report and include: age, ethnicity, race, marital status, education, and occupational status.

Medical Record Review (V0, V5, V6a,b…)
A member of the study team will record clinical data, including diagnosis, disease stage, and treatments. Comorbidities or current medical history will also be extracted from medical records.

Demoralization Scale-II (Baseline [V1], V5, V6a,b…)
The DS-II measures of the experience of disheartenment and helplessness and is well validated in terminally ill patients.[43] It's a 3-point response, self-report scale comprising 16 items and 2 subscales (meaning and purpose, and distress and coping ability). The presence of baseline moderate-to-severe demoralization, as measure by a DS-II score ≥ 8, is necessary for inclusion in this study. For V5 assessment, we will ask subjects how they felt over the past week instead of over the past two weeks as originally framed in the instrument.
Estimated time for administration: 3 minutes

Hospital Anxiety and Depression Scale (Baseline [V1], V5, V6a,b…)
HADS was developed for use in medically ill patients and validated in palliative care populations.[44,45] It is a self-report questionnaire consisting of 14 items, and subjects rate how they felt during the previous week on a 4-point Likert scale. The HADS consists of an anxiety and depression subscale (0–21 points each), and total scores can range from 0 to 42. Higher scores indicate more severe depression and anxiety. Participating subject's caregivers also will complete the HADS at V1, V5 and V6a,b…
Estimated time for administration: 5 minutes

Functional Assessment of Chronic Illness Therapy - Palliative Care 14 (Baseline [V1], V5, V6a,b…)
FACIT-Pal 14 measures quality of life in palliative care patients. It has good internal consistency and there is evidence of construct validity.[46] FACIT-Pal 14 consists in 14 items, and subjects rate how they felt during the previous week on a 5-point Likert scale.

Estimated time for administration: 3 minutes

PROMIS® Pain Interference Scale – 8 items (Baseline [V1], V5, V6a,b…)
The PROMIS is a National Institutes of Health (NIH) Roadmap initiative that aims at providing precise, reliable, valid, and standardized questionnaires measuring patient-reported outcomes across the domains of physical, mental, and social health.[51]
The PIS measures the self-reported consequences of pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities.[52] We will use 8 validated items pertaining to social and emotional consequences of pain during the previous week, that subjects will rate on a 5-point Likert scale. The PIS will only be collected from a patient if the patient indicates pain at a given assessment period.
Estimated time for administration: 2 minutes

Life Attitude Profile – revised, Death acceptance subscale (Baseline [V1],V6a)
LAP-R Death Acceptance is a validated, self-rated 9-item, 7-point Likert scale assessing acceptance and anxiety about death.[53]
Estimated time for administration: 2 minutes

Social Isolation Scale-6a (Baseline [V1], V5, V6a,b…)
The PROMIS® SIS-6a assesses perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others. We will use the short form of the instrument consisting in a 6-item, 5-point Likert scale.[54]
Estimated time for administration: 2 minutes

Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 (Baseline [V1], V5, V6a,b…)
The FACIT-sp-12 scale is a measure of spiritual well-being validated for use in cancer and widely used in palliative care research.[47,48] The FACIT-sp-12 has subscales that measure faith, meaning and peace, which are broadly consistent with conceptual models of spiritual well-being.[55]
Estimated time for administration: 2 minutes

Mystical Experience Questionnaire (V3 [end of session] or V4)
The MEQ-30[56] is a self-report questionnaire that evaluates discrete mystical experiences induced by serotoninergic psychedelics and is sensitive to detecting psilocybin-induced mystical experiences.[7] In addition to a MEQ total score, the questionnaire generates four empirically derived factors: mystical; positive mood; transcendence of time and space; and ineffability.
Estimated time for administration: 10 minutes

Challenging Experience Questionnaire (V3 [end of session] or V4)
The CEQ is a validated instrument with 26 items rated on a 5-item Likert scale, characterizing psychologically difficult aspects of experiences occasioned by psilocybin, according to seven factors: grief, fear, death, insanity, isolation, physical distress, and paranoia.[57]
Estimated time for administration: 5 minutes

Schedule of Attitudes toward Hastened Death (Baseline [V1], V6a)
The SAHD is a reliable and valid measure of desire for death among terminally ill patients. It includes 20 items that subjects rate as true or false.[58,59]
Estimated time for administration: 5 minutes

Columbia-Suicide Severity Rating Scale (Baseline V0, [V1], V2, V3, V4, V5)
The C-SSRS will be used to assess suicide potential or tendency as a study entry criterion and monitored throughout the study.
The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period.[60] The measurement of suicidal ideation is based on five "yes" or "no" questions with accompanying descriptions arranged in order of increasing severity. If the patient answers "yes" to either questions 1 or 2, the intensity of ideation is assessed in five additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior.
If any item(s) on the C-SSRS are answered "yes", the primary investigator or physician investigator must review the patient's responses in order to (a) at screening and Baseline determine the patient's study eligibility and potential need for referral to a mental health professional, and (b) during the study evaluate the patient's need for appropriate medical management such as a referral to a mental health professional.
A significant suicide risk is defined by suicidal ideation with intend and a plan as endorsed on item 5 on the C-SSRS within the past month at V0 or since previous visit later during the study. This must be reported as an AE or SAE as appropriate and followed up accordingly.
Additionally, if a patient responds "yes" to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for reporting this as an AE or SAE and the need for any appropriate referral.
The C-SSRS will be collected at every visit.
Estimated time for administration: 3 minutes

Confusion Assessment Method (Baseline V0, [V1], V2, V3, V4, V5)
The CAM will be used to assess delirium as a study entry criterion and monitored throughout the study.
The CAM instrument is a clinician-rated diagnosis tool assessing the presence, severity, and fluctuation of 9 delirium features: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and altered sleep-wake cycle. The CAM diagnostic algorithm is based on four cardinal features of delirium: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. A diagnosis of delirium according to the CAM requires the presence of features 1, 2, and either 3 or 4. The CAM demonstrated sensitivities from 94–100%, specificities from 90–95%, positive predictive accuracy of 91– 94%, negative predictive accuracy of 90–100%, interrater reliability ranging from .81–1.00; and convergent agreement with other mental status tests including the Mini-Mental State Examination (MMSE).[61,62]
The CAM will be collected at every visit.

Estimated time for administration: 5 minutes

Reactions to Research Participation Questionnaire Revised (V5)
The RRPQR assess patient's experience and acceptability related to participation in clinical research according to 5 factors: participation, personal benefit, emotional reactions, perceived drawbacks and global evaluation. It is a validated, 23-item and 5-poinit Likert scale.[63]
Estimated time for administration: 5 minutes

CareGiver Oncology Quality of Life questionnaire (Baseline [V1], V5, V6a,b…)
The CarGOQoL is a well-designed and well-validated 29-item, multidimensional, self-administered questionnaire assessing QoL of cancer caregivers.
Estimated time for administration: 10 minutes

Semi-structured Interview guides – patient (after V5) and caregiver (after V5)
The semi-structured interview guides – patient and caregivers will explore acceptability and subjective experiences from the patient's and the caregiver's perspective, respectively. They will explore the acceptability of the intervention through seven component constructs: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-efficacy (see theoretical framework of acceptability in section 12.1). To explore patient's experience, we will focus on expectations before the treatment, subjective experience during the psilocybin effect and effects post-treatment.
Estimated time for administration: 30-60 minutes

Semi-structured Interview guides – hospice staff (convenient sample after each 5 patients completing study intervention)
The semi-structured interview guide – hospice staff explores the study intervention's feasibility and acceptability from the hospice staff's perspective.
Estimated time for administration: 40 minutes

5.1.6 Recorded Content

All therapy sessions will be recorded for research and training purposes. Audio/video recording means may include Digital A/V recording devices and Zoom local recording for in-person and remote visits, respectively. The recordings are necessary for developing the experimental treatment and assessing adherence to the Treatment Manual. Any requests for use of video outside of research and training requests will result in participants (or their health care proxy if the participant is no longer able to consent) receiving information on the request. They will have control over any presentation of this material beyond viewing by researchers or regulatory agencies.

The sponsor-investigator uses encrypted, secure technology to transfer and store recordings (e.g. DFCI's secured DropBox), but there is always a risk of a security breach. The sponsor-investigator is committed to taking preventative measures to avoid such an event. Only investigators/delegated study members will have access to this data. Recorded content will be erased from the recording device's memory disk once transferred. No recording will be stored on the cloud. In the case of a security breach, the participant and/or their families will be notified,

and all efforts will be made to minimize the dissemination of recorded content. Recorded contents will be destroyed by the Sponsor-Investigator after sufficient storage.

5.2. Pre-Treatment Criteria

5.2.1. Cycle 1, Day 1

- Vital signs in the normal range
- Palliative Prognosis Score ≥ 50 %
- No significant suicide risk
- No delirium
- No contra-indicated medication

5.2.2. Subsequent Cycles

None

5.3. Agent Administration

Administration – A capsule of psilocybin is administered orally with a full glass of water. Capsules should not be opened or chewed.

Dosing – This is a single dose study. Capsules contain 25 mg of pharmaceutical grade psilocybin, corresponding to the recommended dose in previous studies of healthy volunteers[64,65] and cancer patients[8,9,27].

Observation period – The participant will have adequate counselling and preparation ahead of dosing, and after ingesting the dose will be attended by two therapists, for the subsequent 8 hours. The setting will minimize distraction and interruption, and the patient will be attended following the dose by the therapists trained in providing reassurance and a safe environment until the effects of the single dose have dissipated. Upon discharge from the study setting, the patient will be delivered to the care of a responsible individual who can observe the patient for the remainder of 24 hours after the dose was administered.

Protocol specific procedures –Blood pressure and heart rate will be measured at the following time-points after psilocybin administration (V3): 30, 60, 120, 180, 240, 300, and 360 min (±*10 minutes)*. Although there have been no reports of their use in well reported clinical trials with oral psilocybin, medications should be available for the treatment of causal symptomatic hypertension, agitation, or severe psychosis. Typically, these supplies are two dosage units of labetalol, nitroglycerin, lorazepam and/or diazepam, and risperidone or similar orally-disintegrating antipsychotic.

Oral Agents – Participants will be advised to avoid consuming high fat meals for one hour before and after study drug consumption. Examples of foods to avoid include those high in butter, cream, oil, cheese, whole milk, mayonnaise, salad dressing, jam, syrup, honey, nuts, as well as

soft drinks, juices, sweets or desserts, pastas, breads, crackers, chips and meats. No other protocol specific procedures are necessary.

Caregiver Precautions – Study participants should not drive or operate heavy machinery for 24 hours post study drug consumption.

5.4. General Concomitant Medication and Supportive Care Guidelines

Psilocybin is contraindicated in participants who are on monoamine oxidase inhibitors or who have a known sensitivity to the drug or its metabolites. It is contraindicated in medications that are known uridine diphosphate glucuronosyltransferase enzyme modulators. It is contraindicated in patients with schizophrenia or bipolar disease, or in those with first degree relatives with these disorders. The concurrent use of selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) medications is assumed to be contraindicated due to the potential to increase the risk of serotonin syndrome and/or to attenuate the binding of psilocin to the HT2A receptor.

Prior to enrollment participants will be screened per the clinical protocol for contraindicated psychologic conditions or interacting medications by a licensed physician on the study team.

Because there is a potential for interaction of psilocybin with other concomitantly administered drugs through the cytochrome P450 system, the study team will review the concurrent use of all other drugs, over-the-counter medications, or alternative therapies at every visit. The PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.5. Criteria for Taking a Participant Off Protocol Therapy

The planned duration of therapy is a 2 to 4 weeks, including 2 preparation sessions, 1 dosing session with a single intake of the study agent and 2 integration sessions. Treatment will be halted in the setting of:

- Inability to ingest study medication on the dosing day (V3)
- Intercurrent illness that prevents administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen, the psychotherapy support regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant

unacceptable for treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6. Duration of Follow Up

Participants will be followed for 6 months (24 weeks) after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7. Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Investigators discretion

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

There will be no modifications to the dose of psilocybin given to study participants.

Modifications of the number, length, content and day of preparation and integration sessions will be allowed after the first few patients, as finding the most feasible, safe and effective dose of psychotherapeutic support and refining the treatment manual are major objectives of this study. Decisions to modify the psychotherapeutic protocol will be made by the PI and the study psychiatrist. Changes and reasons for changes will be documented.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting. **Because this study is being completed in patients with terminal illness, medical events or deaths due to the primary diagnosis (e.g. cancer) are expected.**

The research team will not require expedited reporting to the DF/HCC IRB for primary diagnosis-related medical events or deaths (see section 7.4.4 below).

The principal investigator will be responsible for monitoring and reporting all adverse events to the DFCI IRB for this study, but in the event that the principal investigator is unavailable, the co-investigators will assume this responsibility. The role of the responsible person is to 1) identify the concern, 2) develop the appropriate response to the concern with the use of consultants if necessary and 3) ensure proper reporting of concerns to the IRB.

All potential adverse events will be reported to the PI. The PI in consultation with Co-investigators will classify events according to level of severity. Details will be recorded on an adverse case report form as well as logged on a secure spreadsheet for reporting to the IRB.

The adverse event case report form will include a description of all undesirable experiences, required interventions, and an assessment of the subject after the event if possible. An estimate of the extent of injury, and prevention strategies will be reported. The principal investigator will classify the relationship of the study protocol to the event as follows:

- Unrelated: The event is clearly related to factors such as the subject's clinical state, not with the study protocol.
- Unlikely: The event was most likely related to factors such as the subject's clinical state, not with the study protocol.
- Possible: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with events related to responding to queries about stress/drug craving but is possibly related to factors such as the subject's clinical state.
- Probable: The event follows a reasonable temporal sequence associated with participating in the study and/or is consistent with events related to dosing of psilocybin in the study and cannot be reasonably explained by factors such as the subject's clinical state.
- Definite: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

The severity of an adverse event in both groups is defined as a qualitative assessment of the degree or intensity of an adverse event as determined by the principal investigator following CTCAE Version 5.0 severity ratings:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a

Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

7.1. Adverse Events and Potential Risks

Previous studies in healthy volunteers and cancer participants (advanced and non-advanced cancer) have shown oral psilocybin to be well-tolerated in a controlled setting. No drug-related serious adverse events were reported. Overall, the most commonly reported adverse events associated with psilocybin administration are psychological in nature and include transient anxiety, negative emotional states and paranoid/delusional thinking during psilocybin sessions.[35,66,67] Such transient episodes of fear or anxiety respond well to reassurance and have not required pharmacological intervention. In previous clinical experience, acute psychological events were resolved by the end of the dosing day. Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%.
Cardiovascular changes including increased BP and heart rate, mild and transient nausea, and mild and transient headaches are also reported with psilocybin administration.

These events are therefore examined further in this section in the population of patients with cancer who participated in recent psilocybin trials.

The Harbor-UCLA Study was a randomized, double-blind, placebo-controlled crossover design study (NCT00302744) to evaluate the efficacy of psilocybin in 12 adults (11 females) with advanced-stage cancer (various types) and reactive anxiety.[68] The dosing sessions were spaced several weeks apart, and participants would receive either oral psilocybin (0.2 mg/kg) or oral placebo (niacin, 250 mg) in a randomized order. Assessments included monitoring for temperature, heart rate and blood pressure, and dosing sessions concluded with self-reported participant outcomes. The duration of follow-up was six months following the second dosing session.

No serious adverse events were reported during the study, and no adverse psychological effects arose from treatment. Adverse events were collected during study administration and solicited during monthly follow-up phone calls. No untoward cardiovascular sequelae was observed, though treatment with psilocybin produced transient increases in blood pressure (BP) and heart rate as compared to placebo. In response to psilocybin, mean maximum systolic BP increased from 117 ± 4.3 mm Hg to 138.9 ± 6.4 mm Hg, mean maximal diastolic BP increased 69.6 ± 2.7 mm Hg to 75.9 ± 3.4 mm Hg, and mean maximal heart rate increased from 70.4 ± 4.3 beats per minute to 81.5 ± (5.8) beats per minute. No additional information on adverse event reporting was available.

The John Hopkins Study was a randomized, double-blind, crossover study (NCT00465595) to investigate the effects of psilocybin dose (low vs high dose) on a variety of outcome measures relevant to anxiety or depressive disorders exacerbated by cancer diagnosis.[8] Participants were initially randomized to either the low dose oral psilocybin (0.014 mg/kg or 0.042 mg/kg), meant to act as placebo, or high dose oral psilocybin (0.31 mg/kg or 0.43 mg/kg), followed by crossover approximately five weeks later. The low dose was permanently

adjusted to 0.014 mg/kg due to concern that a 0.042 mg/kg dose might not serve effectively as an inactive placebo, and the high dose was similarly adjusted from 0.43 mg/kg to 0.31 mg/kg after two of the first three participants to receive the 0.43 mg/kg dose were discontinued from the study. Monitoring for adverse events occurred during dosing days up to six hours post-dose, and participant reported outcomes were solicited for up to six months following the second dose.

No serious adverse events were attributed to psilocybin. The most frequent adverse events occurring during psilocybin dosing sessions (both low dose and high dose) are shown in Table 7.1-1. With the exception of headache, all adverse events had resolved fully by the end of the sessions. The most frequent adverse events were transient moderate increases in systolic and/or diastolic blood pressure (DBP) after psilocybin, psychological discomfort, anxiety, and physical discomfort. Episodes of elevated systolic blood pressure (>160 mm Hg) occurred in 18 of 53 (34%) high dose sessions, as compared to 17% (N = 9) of the low dose "placebo" sessions. Episodes of elevated diastolic blood pressure (>100 mm Hg) occurred in 7 of 53 (13%) high dose sessions, and 1 of 52 (2%) of the low dose sessions. One participant experienced a transient peak blood pressure (214/114 mm Hg) during the high dose session that met severity criteria, but not the duration (15 minutes) criteria for pharmacologic intervention, and therefore no intervention was delivered.

Psychological discomfort was reported in 17 of 53 (32%) of high dose sessions and 6 of 52 (12%) low dose sessions. Anxiety was reported in 14 of 53 (20%) of high dose sessions, and 8 of 52 (15%) low dose sessions. Episodes of physical discomfort (any type) occurred in 21% of high dose sessions and 8% of low dose sessions.

One instance of mild headache was reported during a high dose session. Toward the end of this study, the study team became interested in documenting the occurrence of delayed headache after psilocybin sessions. Of the 11 (of 53) participants queried, two (18%) reported moderate headache following their high dose sessions.

Table 7.1-1: Adverse events reported during dosing sessions

Adverse Event Description*	Low Dose (N = 52)	High Dose (N = 53)
Elevated Diastolic Blood Pressure (> 100)**	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)**	9 (17%)	18 (34%)
Elevated Systolic (> 160) and/or Diastolic Blood (> 100)	10 (19%)	18 (34%)
Elevated Heart Rate (> 110)**	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11(21%)
Anxiety during session	8 (15%)	14 (20%)

* AE during sessions refer to one or more instance(s) of the AE that occurred on session days after capsule administration; in all cases, the AE had resolved by the end of the session day.

** In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes. In all cases blood pressure returned to normal levels by the end of the session.

Spontaneously reported adverse events that occurred following psilocybin sessions that were judged to be possibly related to drug administration were rare, with four occurring following the low dose session and one occurring following the high dose session (Table 7.1-2). The reported adverse events judged to be possibly related to drug administration following lower-dose sessions included instances of a feeling of fullness in the chest (n=1), anxiety (n=1), insomnia (n=1) and decreased appetite (n=1). One instance of leg pain occurred following a

higher-dose session. There were no cases of hallucinogen persisting perception disorder (HPPD) or prolonged psychosis.

Table 7.1-2: Adverse events reported after the psilocybin dosing session

Adverse Event Description*	Number of Instances	Causality
Death due to disease progression	2	Unrelated
Fullness in chest (post low-dose session)	1	Possible
Anxiety (post low-dose session)	1	Possible
Insomnia (post low-dose session)	1	Possible
Decreased appetite (post low-dose session)	1	Unrelated
Suicide after dropping out of study (did not receive high dose)	1	Unlikely
Eye infection (post low-dose session)	1	Unrelated
Coronary Artery blockage	1	Possible
Leg pain (post high-dose session)	1	Possible
Breast biopsy	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up; detailed event reports are appended

The New York University Study was a randomized, double-blind, placebo-controlled crossover study (NCT00957359) to investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression in adults who received a cancer diagnosis.[9,28] Participants were initially assigned to receive oral psilocybin (0.3mg/kg) or placebo (niacin, 250 mg), administered during an 8-hour treatment session. Crossover to the other arm occurred seven weeks after the first administration. Adverse events were monitored throughout the trial, including during and after dosing sessions. Primary outcomes of potential improvement of participant anxiety and depression were measured through 26 weeks after the second dosing session.

The most common adverse events that occurred during the psilocybin dosing sessions (before and after crossover, N = 28) included elevated systolic (>160 mm Hg) and diastolic BP (>100 mm Hg), headache and migraine, anxiety, and nausea. None of the elevated BP episodes required pharmacological intervention. One participant died as a result of cancer disease progression. Four subjects were withdrawn from the study due to disease progression and passed away shortly after withdrawal from the study. These serious adverse events were not attributed to psilocybin. Adverse events that occurred outside the dosing sections were collected, and causality from psilocybin was assessed (Table 7.1-3). Three of 11 events (27%) were determined to be possibly related to psilocybin administration.

Table 7.1-3: Adverse events not occurring during the psilocybin dosing sessions

Adverse Event Description*	Number of Instances	Causality
Community Acquired Pneumonia	1	Unrelated
Death due to disease progression	1	Unrelated
Hypotension	1	Unrelated
Lumbar Spinal Surgery	1	Unrelated
Migraine	1	Unrelated
Ocular Migraine	1	Unrelated
Experience of Thought Disorder	1	Possible
Neurosurgery	1	Unrelated
Visual Field Impairment	1	Possible
Vasovagal Syncopal Event	1	Possible
Vomiting	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up.

The University of California San Francisco study was single-arm, open-label, pilot study of psilocybin-assisted group therapy (NCT02950467). Participants were Gay-identified older long-term AIDS survivor (OLTAS) men ≥ 50 years old, recruited from the community, who suffer from moderate-to-severede moralization (DemoralizationScale-II≥8). They receive 8-10 open-label group therapy sessions over 8 weeks and one open label psilocybin individual session (0.3 mg/kg or 0.36 mg/kg po). Safety was evaluated with multiple measures. Every study visit included an adverse events assessment interview and the Columbia Suicidality Severity Rating Scale (C-SSRS) interval interview. Adverse events assessments during the medication visit included spontaneous participant self-report, events observed by clinicians, and symptoms derived from the Challenging Experiences Questionnaire[57] administered the next day. During psilocybin sessions, blood pressure and heart rate were assessed at regular intervals of 30 min for the first two hours, and then 60 min thereafter. At end-of-treatment, participant perceptions of benefits and harms from the intervention were assessed by a 7-point Likert scale (1= none at all; 7=extremely). The Schedule of Attitudes towards Hastened Death (SAHD) was administered at baseline, end-of-treatment and 3-month follow-up. The Montreal Cognitive Assessment (MoCA) was performed at enrollment and end-of-treatment. Because they were added after Cohort 1 completed the study, only Cohorts 2 and 3 completed the Alcohol Use Disorder Identification Test (AUDIT) and Drug Use Disorders Identification Test (DUDIT) at baseline and at the 3-month follow-up with a 'last 3 month' recall period.

Overall, zero serious adverse reactions and two unexpected adverse reactions to psilocybin were detected, and seven participants experienced self-limited, severe expected adverse reactions. Serious adverse events and adverse events are detailed in the following table.

Table 7.1-4: Adverse events during the UCSF study

Adverse events.

Serious Adverse Events (SAE)				
SAE Primary Term	# Participants (%), *n* = 18	Highest severity observed	Expectedness	Relatedness to Psilocybin
DURING INTERVENTION				
Renal Cell Carcinoma Recurrence, Metastatic[a]	1 (5·6%)	Severe	Unexpected	Unrelated
Pneumothorax[a]	1 (5·6%)	Severe	Unexpected	Unrelated
DURING FOLLOW-UP				
Stimulant-induced psychosis[b]	1 (5·6%)	Potentially life-threatening	Unexpected	Unrelated
Suicide attempt[b]	1 (5·6%)	Potentially life-threatening	Unexpected	Unrelated
Cholecystitis	1 (5·6%)	Severe	Unexpected	Unrelated
Medication Visit Adverse Events (AE)				
AE Primary Term	# Participants (%), *n* = 18	Highest severity observed	Expectedness	Relatedness
Hypertension		Severe	Expected	Related
Severe (SBP≥180 or DBP≥110 mmHg)	4 (22·2%)			
Moderate (160≤SBP<180 or 100≤DBP<109)	8 (44·4%)			
Anxiety/Anxiety Exacerbation (moderate-severe)	8 (44·4%)	Severe	Expected	Related
Nausea	6 (33·3%)	Severe	Expected	Related
Headache	5 (27·8%)	Moderate	Expected	Related
Paranoia/Ideas of Reference	4 (22·2%)	Mild	Expected	Related
Motor Agitation / Restlessness	4 (22·2%)	Moderate	Expected	Related
Unsteady Gait / Ataxia	4 (22·2%)	Moderate	Expected	Related
Tachycardia	2 (11·1%)	Mild	Expected	Related
Thought Disorder	1 (5·6%)	Moderate	Expected	Related
Urinary Incontinence	1 (5·6%)	Moderate	Expected	Related
Visual Changes (complaint)	1 (5·6%)	Mild	Expected	Related
Post-Medication Visit Psilocybin-Related Adverse Events				
AE Primary Term Associated AEs	# Participants (%), *n* = 18	Highest severity observed	Expectedness	
Headache	8 (44·4%)	Mild	Expected	
Fatigue	2 (11·1%)	Moderate	Expected	
Insomnia	2 (11·1%)	Mild	Expected	
Anxiety Exacerbation	1 (5·6%)	Severe	Expected	
Methamphetamine Relapse		Moderate	Unexpected	
Post-traumatic Stress Flashback Tinnitus, nausea, panic and insomnia	1 (5·6%)	Moderate	Unexpected	
Nausea	1 (5·6%)	Mild	Expected	

Adverse events were classified by the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events v2.0.
[a] Same participant.
[b] Same participant.

7.2. Adverse Events list for psilocybin

Based on the studies presented in the previous section, the following adverse events might be expected after subjects are given the study agent.

7.2.1. Psychological adverse events

- Anxiety
- Negative emotional states
- Paranoid/delusional thinking

7.2.2. Physical adverse events

- Increased blood pressure
- Increased heart rate
- Nausea
- Headaches
- Fatigue
- Insomnia

7.3. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the study agent that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4. Adverse Event Reporting

7.4.1. In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Principal Investigator.

7.4.2. Investigators **must** report to the Principal Investigator any adverse event (AE) that occurs after initial dose, during treatment, or within 30 days of last treatment on the local institutional SAE form (eCRF).

7.4.3. DF/HCC Adverse Event Reporting Guidelines

Site investigators will report AEs to the sponsor per DF/HCC requirements, and the Dana-Farber Cancer Institute IRB per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor Investigator, Dr. Beaussant.

Attribution	DF/HCC Reportable Adverse Events(AEs) to sponsor-investigator				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	5 calendar days	5 calendar days	5 calendar days	5 calendar days*	24 hours*

Possible Probable Definite	5 calendar days	5 calendar days	5 calendar days	5 calendar days*	24 hours*
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.					

7.4.4. Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Prolongation of Hospice stay	Attribution	Comments
Gastrointestinal disorders	**Nausea**	**1,2**	**Up to Day 1**	**Related**	The primary effects of the psilocybin are psychological and can bring about a very broad range of changes in perception and mood during the hours the drug is active. At times, subjects may experience anxiety, panic, or paranoia. The majority of reactions from psilocybin change rapidly, are easily managed with proper guidance and resolve by the end of the dosing session (7-10 hours). In many patients, they may be associated with the therapeutic effect of psilocybin-assisted therapy. Therefore, such expected effects do not require expedited
	Vomiting	**1**			
Nervous system disorders	**Ataxia**	**1,2,3**			
	Cognitive disturbance	**1,2,3**			
	Depressed level of consciousness	**1,2,3**			
	Dizziness	**1,2,3**			
	Headache	**1,2**			
	Lethargy	**1,2**			
	Tremor	**1,2,3**			
Psychiatric disorders	**Agitation**	**1,2,3**			
	Anxiety	**1,2,3,4**			
	Confusion	**1,2,3**			
	Delirium	**1,2,3**			
	Delusions	**1,2,3**			
	Depression	**1,2,3**			
	Euphoria	**1,2,3**			
	Hallucinations	**1,2,3**			
	Insomnia	**1,2,3**			

	Psychosis	**1,2,3**			reporting to the Principal Investigator or the DFCI IRB as long as they follow the natural arch of the psilocybin effect.
	Restlessness	**1,2,3**			
Other AE or SAEs related to underlying terminal condition		**1,2,3,4,5**	**GIP**	**Unrelated**	The context of this study – hospice – is defined by the potential for rapid clinical deterioration in enrolled patients. Should such deterioration occur and appear clearly related to the underlying terminal condition in the judgement of the investigators, they do not require expedited reporting to the Principal Investigator or the DFCI IRB

7.5. Reporting to the Food and Drug Administration (FDA)

The Sponsor will be responsible for all communications with the FDA. The Sponsor will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6. Reporting to Local Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.7. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Principal Investigator on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.8. Reporting to drug manufacturer

The sponsor will promptly report all adverse events related to the Investigational Drug to Usona as agreed per the contract and set forth below.

Format of Transfer
Data should be transferred in one of the following formats if possible:

- CDISC ODM XML file (preferred)
- Comma Separated Value file

If the study's data collection procedures do not enable export in one of these formats, the Investigator agrees to work with Usona to identify a mutually agreeable format in which required data can be transferred to Usona.

Data Requirements

Category	Timing	Minimum data to be reported
Dosing Information	End of Study	Dates and times of doses Treatment received Dose received
Adverse Events (AEs)	End of Study	AE Name Discovery (spontaneous or solicited) Start date End date or ongoing Severity Relationship to study drug Action taken Resolution Seriousness
Concomitant Medications	End of Study	Medication Dose Dose frequency Start date End date Indication
Serious Adverse Events (SAEs)	Immediate (within 5 days of knowledge)	Full case report enabling completion of MedWatch Form 3500. Transmit to: usonasae@ usonainstitute.org; tel. +1 608-210-6005
Pregnancy	Immediate (within 5 days of knowledge) & follow-up through 30-days post-delivery or first well-child visit	**Initial report** Gravidity Parity Estimated delivery date Prenatal care (including initiation relevant to gestation) Pregnancy complications and dates

		Medications used during pregnancy **Follow-up report: Delivery** Gravidity Parity Estimated delivery date Pregnancy outcome Date of delivery Duration of labor Type of delivery Postpartum complications Infant birth weight Apgar scores (1 min, 5 min) NICU admission Complications of newborn during hospitalization Date of hospital discharge or death Birth defects noted at birth **Follow-up report: Well Child Visit** Summary of diagnostic tests Complications Updates on past findings/anomalies

A serious adverse event (SAE) is an adverse drug or biologic or device experience occurring during any study phase (i.e., screening, admission, treatment, or follow-up), and at any dose of the study drug, comparator or placebo, that results in one or more of the following criteria:

- Results in death
- Is life-threatening*
- Requires in-patient hospitalization (i.e., admission) or prolongation of existing hospitalization
- Results in persistent or significant disability** or incapacity
- Is a congenital abnormality or birth defect (in an offspring)
- Is an important medical event that may not result in death, be life-threatening, or require or prolong hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of important medical events include events requiring intensive treatment in an emergency department, or convulsions that do not require in-patient hospitalization, or the development of drug dependency or drug abuse.

*** Life-threatening SAE:** Any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**** Definition of disability:** A substantial disruption of a person's ability to conduct normal life functions.

8. PHARMACEUTICAL INFORMATION OF PSILOCYBIN

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Sections 7.1 and 7.2.

8.1. Psilocybin background

Psilocybin 3-[2-(dimethylamino) ethyl]-1H-indol-4-yl] dihydrogen phosphate is a natural product produced by numerous species of Psilocybe mushrooms. The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which, for its behavioral effects, is the 5-HT2A receptor.[1,2] Psilocybin was first isolated from Psilocybe mushrooms in 1957, followed by de novo synthesis in 1958. It was marketed worldwide in the 1960s as Indocybin™ for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substance in the U.S., placed in Schedule I in 1970, and effectively removed from clinical use or scientific study. Psilocybin, and similar drugs such as lysergic acid diethylamide (LSD) and mescaline, fall into a pharmacological class that we refer to in this application as "classic psychedelics" to differentiate them from other psychoactive substances (ex. 3,4-methylenedioxy-methamphetamine; MDMA) that have different psychological/behavioral effects and different adverse effect profiles and risk/benefit ratios than psilocybin.

Several lines of evidence suggested that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically-beneficial behavior change in a variety of psychiatric conditions and in individuals with psychological distress associated with a serious medical illness.

8.2. Importance of a Supportive Set and Setting Protocol

Due to the psychoactive nature of psilocybin, the safety of participants in clinical trials can be enhanced by testing psilocybin within a "set and setting" protocol (Lyons & Carhart-Harris, 2018).[69] By addressing the set (the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure) and setting (the physical environment in which the exposure occurs) of the experience, the risk of the subject reporting an event which was distressing or injuring themselves can be reduced. This approach generally incorporates three components: 1) preparation, 2) drug session, and 3) post session meetings to integrate the classic hallucinogen experience.

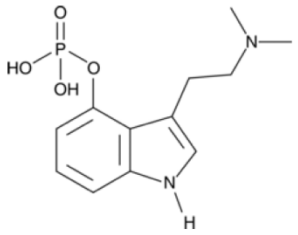
In the first phase, participants undergo pre-exposure preparation sessions designed to build rapport with the facilitators who would be present during the drug exposure session and to identify personal themes and struggles that might be especially likely to impact the session experience. In the second phase, the drug session itself is conducted by two facilitators who are present throughout the session. Sessions are typically conducted in a room designed to be quiet,

comfortable, and aesthetically pleasing, and participants are encouraged to wear eyeshades and listen to a program of music through headphones during the drug exposure to aid them in focusing their attention inward. In the third phase, participants are engaged in a series of drug-free interview meetings of variable frequency, sometimes over a period of several weeks, to discuss their session experience thoroughly with the goal of maximizing its therapeutic benefit.

8.3. Description

Psilocybin is a tryptamine derivative. Its chemical name is [3-[2-(dimethylamino)ethyl]-1H-indol-4- yl] dihydrogen phosphate. The molecular structure is the following:

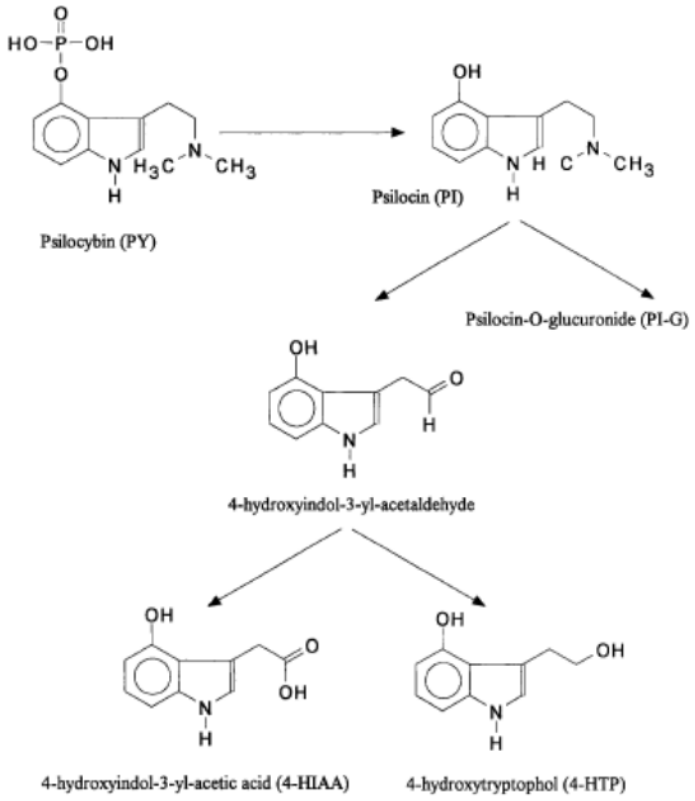
Figure 8.1-1: Molecular structure of psilocybin



Following oral administration (0.224 mg/kg) of psilocybin, average blood concentration of the active metabolite psilocin was calculated to be 8.2 ± 2.8 ng/mL after 105 ± 37 minutes, yielding an estimated dose-normalized bioavailability of psilocybin to be 52.7 ± 20% (N = 3). Psilocin typically appears in plasma within 15 minutes after oral administration. Psilocin half-life following oral administration of psilocybin was found to be approximately 3 ± 1.1 hours and is detectable for up to 24 hours after administration.[3,4] The levels of psilocin peaked at approximately 80 minutes, but the peak psilocin concentration was more gradually attained in some subjects than in others, suggesting metabolism rates can vary between individuals.[3]

Psilocin is metabolized to 4-hydroxyindole-3-acetic acid by deamination and demethylation via liver enzymes such as monoamine oxidase, and aldehyde dehydrogenase (Figure 8.1-2).[4] Psilocin is also extensively glucuronidated by the UDP- glucuronosyltransferase (UGT) family of enzymes, with the highest glucuronidation activity demonstrated by UGT1A10.[70] The amount of psilocin glucuronide-excreted renally has been shown to exceed that of psilocin over a 24-hr time period, and analysis of psilocin in urine over 24 hours after a single dose has shown that less than 4% of the overall clearance of psilocin occurs through renal excretion.[71]The pharmacokinetics of psilocybin (as psilocin) are linear over the dose range of 0.3–0.6 mg/kg.[3,71]

Figure 8.1-2: Metabolism of psilocybin



8.4. Form

For use in Usona sponsored clinical studies, psilocybin is provided as 25 mg capsules (size 2, hydroxypropyl methyl cellulose (HPMC), white)

8.5. Storage and Stability

Psilocybin capsules are packaged individually into high-density polyethylene bottles (30 cc). Bottles must be maintained at room temperature.

Psilocybin presents as a white crystalline solid with a melting point of 220-228°C. It is stable over extended periods in dark storage at controlled room temperature. Psilocybin is soluble in 20 parts boiling water or 120 parts boiling methanol.

8.6. Compatibility

Not applicable

8.7. Handling

Psilocybin is a controlled substance listed in Schedule I. Capsules of psilocybin will be maintained in a locked, substantially constructed cabinet in a secured location, in accordance with Drug Enforcement Agency (DEA) regulations. In accordance with these requirements, the

Schedule I license holder, and pre-defined authorized individuals trained by the license I holder, will be responsible for storing, dispensing, and administering the psilocybin.

8.8. Availability

Psilocybin will be provided by Usona Institute at no cost and the study sponsor (Yvan Beaussant, MD, MSc) will order the drug once all regulatory requirements are approved. The study will cover the shipping costs.

8.9. Preparation

Not applicable

8.10. Administration

Capsules will be administered orally, with water, per the associated clinical protocol. Capsules should not be opened or chewed.

In case a patient vomit after the drug is administered, assuming the pill was swallowed and entered the stomach (not just gagging on the capsule and spiting an intact capsule back out) – we will not administer another capsule because in theory they might have ingested some portion of the Investigational Product. We will record whether the capsule is present in the emesis and make note of that in patient's records. This then would be an exception in dosing practices and likely will be an outlier.

8.11. Ordering

Psilocybin is not commercially available. It will be obtained through Usona Institute, a non-profit medical research organization founded in 2014. Usona Institute conducts and supports biochemical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines. Usona has developed psilocybin for oral administration (25 mg, single-dose) in conjunction with a supportive set and setting protocol for major depressive disorder (MDD). Additional information about Usona can be found at www.usonainstitute.org and in the Investigator Brochure.

The study drug will be shipped to and logged at Care Dimensions facility (Lincoln house). Authorized individuals will dispense the study drug after the order is transmitted from the study psychiatrist with name, date of birth and medical record number of the study participant. Dispensed drug will be obtained by the study team who will sign a log kept in the same cabinet the study drug is stored to ensure that all study drug is accounted for.

8.12. Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the study drug in a drug accountability record form along with any DEA required forms

8.13. Destruction and Return

Expired or unused supplies of psilocybin will be returned to Usona or destroyed according to controlled substance disposal and institutional guidelines. Return or destruction will be documented on the drug accountability record form and any DEA-required forms.

9. CONCOMITANT MEDICATIONS AND TAPERING INSTRUCTIONS

If the participant is being treated with psychiatric drugs at the time they are recruited into the study, they will discuss medication tapering with the study psychiatrist and the hospice physician. If needed, the drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first Experimental Session to avoid the possibility of any drug-drug interaction (the interval will be at least five times the particular drug and active metabolites' half-life).

The therapists will request information about any changes in medication just prior to all intervention sessions. The study psychiatrist will be responsible for reviewing and confirming all medications collected during the study.

All medications, over the counter (OTC) and prescription will be collected from screening through V5. Throughout the protocol all medications used to treat AEs will be collected and all changes including discontinuations or additions to psychiatric medications will be collected. Medications will be recorded on the concomitant medications CRF.

In general, any MAOi will require a washout of at least 14 days or five half-lives of the medication or active metabolite (whichever is greater) plus one week for symptom stabilization. The Medication Tapering Table includes phenelzine, an example MAOi, (half-life of 11.6 hours) with a minimum of 14-day washout as requested. However, this table is not exhaustive. The washout time for any drug not listed on the table will be at least 5 times the half-life of the drug or active metabolite, plus 1 week for symptom stabilization.

Participants must be willing to refrain from taking any contra-indicated psychiatric medications during the active portion of the study.

As we expect individuals on hospice to be receiving medications to control symptoms such as pain, nausea and anxiety, all efforts will be made to not disrupt a patient's medication regimen unless the medication is contraindicated or carries a risk of interfering with psilocybin. Medications, such as opioids, may be given to patients during the trial to control pain, with efforts being made to not administer medications during the peak effect of psilocybin.

Medication Tapering Table

Generic Name	Brand Name	Half-life (hours) Including Active Metabolites	Days for Washout
alprazolam	Xanax	11	3
aripiprazole	Abilify	75	16
atomoxetine	Strattera	5-24	5
bupropion	Wellbutrin	21	5
citalopram	Celexa	35	8
clonazepam	Klonopin	30-40	8
diazepam	Valium	20-70	15
duloxetine	Cymbalta	12	3
escitalopram	Lexapro	32	7
fluoxetine	Prozac	7-9 (days)	45
imiprimine	Tofranil	6-18	4
lamotrigine	Lamictal	25	6
lorazepam	Ativan	12	3
mirtazapine	Remeron	20-40	8
olanzapine	Zyprexa	21-54	11
paroxetine	Paxil	21	5
phenelzine	Nardil	11.6	14
prazosin	Minipress	2-3	1
quetiapine	Seroquel	6	2
risperidone	Risperdal	3-20	4
sertraline	Zoloft	26	6
temazepam	Restoril	8-12	3
trazodone	Desyrel	9	2
venlafaxine	Effexor	12	3
ziprazidone	Geodon	7	2
zolpidem	Ambien	2.5	<1

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the Experimental Session (e.g. insomnia or severe anxiety that does not respond to other non-pharmacologic management outlined in the treatment manual). Rescue medications may be a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment. SSRIs, SNRIs, and MAOIs should not be used as rescue medications.

10. RISKS AND MITIGATION STRATEGY IN RESPONSE TO THE SARS-COV2 PANDEMIC

Care Dimensions has taken the following steps to ensure the safe delivery of care:

- Additional mandatory staff education on infection prevention procedures, the COVID-19 virus, and Care Dimensions precautions and procedures, so all staff have the latest information.

- Employees and volunteers are required to stay home when feeling sick. They must be fever free for 24 hours before returning to work.

- Employees and volunteers are being strongly discouraged from travelling internationally. Those returning from a CDC Level 3-defined country or certain US communities with widespread ongoing disease and travel restrictions may not return to work or see patients until 14 days after their return.

- Employees and volunteers who have had prolonged close contact to someone with confirmed or presumed diagnosis with COVID-19 or who has traveled to the countries or communities listed above, must report this to their manager to assess whether they need to self-quarantine for 14 days.

- Employees are not permitted to attend any conferences and have been instructed to avoid large public gatherings.

- Patient visits in most facilities have been reduced to nurses, social workers, chaplains, and hospice aides to comply with DPH guidelines.

- Working with each hospital and nursing facility to comply with their individual regulations and screening of our staff.

- Visitors to the hospice houses (in particular the Care Dimensions Hospice House in Lincoln where V3 of this study occurs) have been restricted to immediate family members (as defined by the patient) only, with **a** maximum of 2 visitors at at time and 6 per patient, per day. Visitors are screened upon entrance for temperature, symptoms and potential COVID-19 exposure to assess need for further precautions, and must wear a mask at all times while in the hospice house. Common areas of the houses are closed and visitors must stay in patient rooms.

- Cleaning services at our offices and hospice houses include enhanced disinfection of all high-touch surfaces such as doorknobs, handles, counters and railings and common equipment.

- All in-person support groups, trainings and meetings with non-staff members at our facilities have been suspended. Some support groups have started to meet online.

- Routine work-related meetings are being held virtually with video and teleconferencing and staff are prohibited from working at more than one Care Dimensions location.

- Care Dimensions equips clinical staff with a supply of hand sanitizer, anti-bacterial wipes and personal protective equipment (PPE) such as masks, gowns and goggles.

- Care Dimensions has a comprehensive Emergency Operations Plan, which has been activated and will be amended as this crisis response progresses.

In order to mitigate the risk of SARS-CoV-2 virus transmission during the study, the Principal Investigator, Study Team Members, and Study Subjects will adhere to Care Dimensions

guidelines. All study activities that don't necessitate in-person interaction with patients, families and/or staff, or within the study team, will be conducted remotely.

11. STUDY CALENDAR

	Full screenning + enrollment	Preparation session 1	Preparation session 2	Psilocybin session	Integration session 1 (Day 1)	Integration session 2 (Day 7)	F/U (HOME)	EDC Timepoints
Visit	V0	V1	V2	V3	V4	V5	V6a,b,...,f	N/A
Timing	At least 48h prior to the psilocybin session (V3)	Baseline ≤ 3 weeks prior to Day 0	≤7 days prior to Day 0	Day 0	Day 1	Week 1 Day 7	Week 3 Monthly after Week 3 Until Week 24 or death	
Allowable Window					Up to Day 3	Up to Day 14	±14 Day	
Location	Home/Remote	Home/Remote	Home/Remote	Hospice	Home/Remote	Home/Remote	Home/Remote	
Psilocybin				25 mg				V3
Psychotherapy - min (staff)		60 (LT-CT)	60 (LT-CT)	7h30 (LT-CT)	60 (LT-CT)	60 (LT-CT)		Psychotherapy notes should be captured after V1, V2, V3, V4 and V5
Assessment - min (staff)	60 (LT-RA)	30 (LT-RA)	15 (LT-RA)	30 (LT-RA)	15 (LT-RA)	30 (LT-RA)	30 (RA)	N/A
Clinical Assessments and Procedures								
Informed consent patient	✓							N/A
Informed consent cargiver	✓							N/A
Demographics	✓							V0
Medical and psychiatric history	✓							V0
Inclusion/exclusion criteria	✓							V0
PPS	✓	✓	✓	✓	✓	✓	✓	During all visits
CAM	✓	✓	✓	✓	✓	✓		V0, V1, V2, V3, V4, V5
C-SSRS (1)	✓	✓	✓	✓	✓	✓		V0, V1, V2, V3, V4, V5
Vital signs (2)	✓			✓				V0, V3
Physical examination (2)	✓			✓				V3
Prior/concomitant medication	✓	✓	✓	✓	✓	✓		N/A
Medication taper (if applicable)	✓	✓	✓					NA
AE/SAEs		✓	✓	✓	✓	✓	✓	During all visits
Session recording		✓	✓	✓	✓	✓		NA
Qualitative interview patient						✓		NA
Qualitative interview caregiver (3)						✓		NA
Qualitative interview hospice staff							✓	NA
Participant Completed Assessments (8)								
DS-II	✓	✓	✓	✓	✓	✓	✓	During all visits
HADS A and D (4)		✓	✓	✓	✓	✓	✓	During all visits
FACIT-Pal 14		✓				✓	✓	V1, V5, V6a,b,...,f
PIS (6)		✓				✓	✓	V1, V5, V6a,b,...,f
LAP-R		✓				✓	✓(7)	V1, V6a
SIS		✓				✓	✓	V1, V5, V6a,b,...,f
FACIT-sp		✓				✓	✓	V1, V5, V6a,b,...,f
MEQ-30 (5)				✓				V3 or V4
CEQ (5)				✓				V3 or V4
SAHD		✓				✓	✓(7)	V1, V6a
RRPQ						✓		V4 or V5
CarGOQoL (3)		✓				✓	✓	V1, V5, V6a,b,...,f

Abbreviations. LT: Lead Therapist; CT: Co-Therapist; RA: Research Assistant; DS-II: Demoralization Scale-II; HADS A and D: Hospital Anxiety and Depression Scale Anxiety and Depression; FACIT-Pal 14: Functional Assessment of Chronic Illness Therapy - Palliative Care 14; PIS: Pain Interference Scale; LAP-R: Life Attitude Profile – revised, Death acceptance subscale; SIS: Social Isolation Scale; FACIT-Sp 12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12; MEQ-30: Mystical Experience Questionnaire; CEQ: Challenging Experience Questionnaire; SAHD: Schedule of Attitude toward Hastened Death; C-SSRS: Columbia-Suicide Severity Rating Scale; CAM: Confusion Assessment Method;PPS: Palliative Performance Scale; RRPQ-R: Reactions to Research Participation Questionnaire Revised; CarGOQoL: CareGiver Oncology Quality of Life questionnaire .

(1) The "Last month" version will be administered at Screening (V1) and the "Since Last Visit" version will be administered at all other visits.

(2) Obtained from hospice clinician and/or patient chart

(3) Care Giver only

(4) These assessments will also be completed by the participant's cargiver at V1, V5 and V6a,...f

(5) To be administered immediately after the psilocybin session or the day after.

(6) Only if the patient indicates pain at a given assessment period.

(7) Only at V6a

(8) We anticipate that given their terminal condition, participants might not be able to complete these questionnaires or may only be able to complete part of them. To reduce administrative burden, we will not report those missing questionnaires as protocol violations.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1. Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2. Responsibility for Data Submission

Responsibility for Data Submission: Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2. Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1. Primary outcome variables

This study is an open label, single center, concurrent mixed-methods phase 2 trial. The primary objective is to pilot test a novel protocol of psilocybin-assisted therapy in patients receiving hospice care. Primary outcomes will relate to the following features of feasibility:

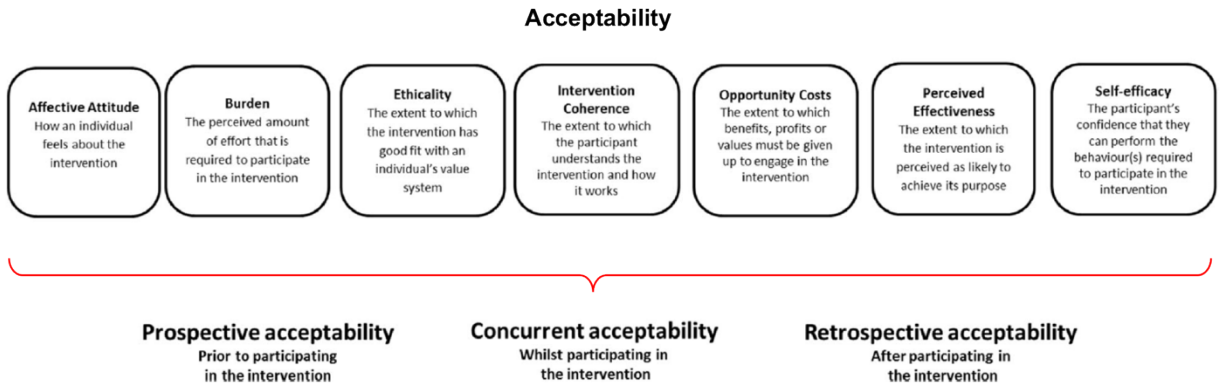
- **Enrollment:** number screened per month; number enrolled per month; average time delay from screening to enrollment

- **Retention:** number of sessions completed; retention rates for study measures; reasons for dropouts
- **Completion of assessment:** proportion of planned assessments that are completed; duration of assessment visits; reasons for dropouts
- **Acceptability:** acceptability ratings; qualitative assessments; reasons for dropouts

Benchmark for feasibility: treatment and week 1 assessments will be successfully completed in at least 60% of recruited subjects.

Benchmark for acceptability: ≥ 80% of subjects who completed Week 1 assessment will evaluate favorably (agree or strongly agree) acceptability on the global evaluation factors of the RRPQ (See section 5.1)

To guide our evaluation of acceptability in the proposed project, we will use seven component constructs as defined in the following figure: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-efficacy.[72]



Theoretical framework of acceptability (from Sekhon et al., 2017)

13.2. Secondary outcome variables

13.2.1. Safety outcomes:

- **Changes in vital signs:** During psilocybin session, monitoring of heart rate, blood pressure, respiratory frequency and oxygen saturation.
- **Adverse events (AEs) and serious adverse events (SAEs):** Longitudinal follow-up and analysis of the relationship with psilocybin-assisted psychotherapy (see section 7).
- **Suicidal risk:** suicidal ideations or plans will be assessed via the C-SSRS at each visit (see section 5.1)
- **Delirium:** signs of delirium will be assessed through the CAM (see section 5.1)

13.2.2. Efficacy outcomes

- **Global quality of life:** FACIT-Pal 14
- **Physical domain:** PIS

- **Psychological domain:** HADS A and D; LAP-R; CEQ
- **Social domain:** SIS
- **Spiritual domain:** FACIT-sp; DS- II; SAHD; MEQ-30
- **Caregiver quality of life and psychological distress:** CarGOQoL; HADS A and D

13.3. Sample size and statistical plan

13.3.1. Sample size justification

Patients with a PPS score of 50% and above have a median survival of 43 days or greater.[73] We anticipate that we will need to treat at least 10 patients for feasibility data to be relevant. To account for patients who are unable to complete the intervention because of clinical decline, we plan to recruit 15 patients.

Assuming that treatment and week 1 assessment will be completed on 10-15 patients, the 90% exact binomial confidence intervals for the feasibility rate will be between (30.3%-85.0%) – for 10 patients - and (36.0%-81.0%) – for 15 patients.

Assuming that between 6 (out of 10) and 9 (out of 15) patients will be able to assess the acceptability, the 90% exact binomial confidence intervals for the acceptability rate will be between (41.8% - 99.1%) – for 10 treated patients, out of which 60% deem the procedure "feasible" - and (57.1% - 99.4%) – for 15 treated patients, out of which 60% deem the procedure "feasible".

We will use the treatment effect size calculated for this study to inform the sample size of the upcoming corresponding confirmatory trial.

Accrual targets are as follow:

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	1	=	3
Not Hispanic or Latino	6	+	6	=	12
Ethnic Category: Total of all subjects	8 (A1)	+	7 (B1)	=	15 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	2	+	1	=	2
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	5	+	5	=	10

Racial Category: Total of all subjects	8 (A2)	+	7 (B2)	=	15 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

13.3.2. Safety analysis

The Safety Population will consist of all enrolled participants who receive study treatment. This population will be used for all summaries of participant accountability, demographic and baseline data, and safety information, including AE incidence.

The Full Analysis Set (FAS) will consist of all participants who receive the dose of psilocybin and will be used for all summaries of efficacy.

The Per Protocol (PP) population will consist of all participants in the FAS who do not have a major protocol deviation which is defined as a deviation which may significantly affect efficacy for that participant. Major protocol deviations will be reviewed and determined prior to database lock.

13.3.3. Efficacy analysis

Since this is a single treatment open-label study, no statistical testing will be performed. We will use descriptive statistics and thematic coding to analyze quantitative and qualitative data respectively, and joint display for the integration of the two.

Qualitative analysis will deploy thematically coding of interview transcripts using content analysis, an inductive and deductive approach. At least two investigators with experience in qualitative analysis will independently code the first four interviews. They will compare their coding, refine common theme, identify new themes, and iteratively refine the codebook. Discrepancies will be resolved through discussion with other investigators until consensus is reached. We will use Dedoose qualitative analysis software to support content analysis.

The FAS and PP populations will be used for each secondary efficacy endpoint (change in respective scores from baseline (V1) to Week 1 (V5), Week 3 (V6a) and subsequent monthly visits until death or Week 24), if the two sets are not identical. For each of the secondary endpoints, measuring change from Baseline, a repeated measures analysis will be performed. Comparisons with baseline will be performed at the 0.05 testing level. Secondary endpoints that are dichotomous variables (for example, proportion of participants who are responders, remitters and sustained remitters) will be summarized as frequencies. Scores for all efficacy endpoints will be summarized over time using descriptive statistics for all visits during the observation period.

14. PUBLICATION PLAN

The results will be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of

Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A STUDY MEASUREMENT SCALES

A1 – Patient demographic data

1. **How old are you?** _____ years old

2. **What is your current gender identity?**
   - ☐ Male
   - ☐ Female
   - ☐ Transgender Male/Trans Man/ Female-to-Male
   - ☐ Transgender Female/Trans Woman/Male-to-Female
   - ☐ Genderqueer, neither exclusively male nor female
   - ☐ Other (please specify): _____

3. **Which of the following most closely describes your race?**
   - ☐ White
   - ☐ African American or Black
   - ☐ Hispanic or Latino
   - ☐ Asian or Asian American
   - ☐ Native American or Alaska Native
   - ☐ More than one race
   - ☐ Other (please specify): _____
   - ☐ Prefer not to answer

4. **Which of the following most closely describes your current relationship status?**
   - ☐ Single, never married
   - ☐ Living with someone as if married/long-term partner
   - ☐ Married
   - ☐ Divorced/Separated
   - ☐ Widowed/Loss of a long-term partner
   - ☐ Other (please specify): _____

5. **What is your highest level of education?**
   - ☐ 11th grade or less
   - ☐ High school graduate or GED
   - ☐ 2 years of college/associate degree/technical school
   - ☐ College graduate (BS or BA)
   - ☐ Masters degree
   - ☐ Doctorate/Medical degree/Law degree

A2 – Family caregiver demographic data

1. **How old are you?** _____ years old

2. **What is your current gender identity?**
   - ☐ Male
   - ☐ Female
   - ☐ Transgender Male/Trans Man/ Female-to-Male
   - ☐ Transgender Female/Trans Woman/Male-to-Female
   - ☐ Genderqueer, neither exclusively male nor female
   - ☐ Other (please specify): _____

3. **Which of the following most closely describes your race?**
   - ☐ White
   - ☐ African American or Black
   - ☐ Hispanic or Latino
   - ☐ Asian or Asian American
   - ☐ Native American or Alaska Native
   - ☐ More than one race
   - ☐ Other (please specify): _____
   - ☐ Prefer not to answer

4. **Which of the following most closely describes your current relationship status?**
   - ☐ Single, never married
   - ☐ Living with someone as if married/long-term partner
   - ☐ Married
   - ☐ Divorced/Separated
   - ☐ Widowed/Loss of a long-term partner
   - ☐ Other (please specify): _____

5. **What is your highest level of education?**
   - ☐ 11th grade or less
   - ☐ High school graduate or GED
   - ☐ 2 years of college/associate degree/technical school
   - ☐ College graduate (BS or BA)

- ☐ Masters degree
- ☐ Doctorate/Medical degree/Law degree

6. Which of the following were you doing last week with regards to your current job?

- ☐ Working full-time
- ☐ Working part-time
- ☐ Not currently working but going to school
- ☐ Retired
- ☐ On layoff or unemployed
- ☐ Not currently working for health reasons
- ☐ Not currently working to take care of house, family, or the care recipient
- ☐ Other (please specify): _____

7. How long have you been the caregiver of your loved one?

_____years (mark "0" if less than a year) _____ months

8. What is your relationship to the care recipient (patient)?

- ☐ I am a spouse or partner of care recipient
- ☐ I am a child of care recipient
- ☐ I am a sibling of care recipient
- ☐ I am a parent of care recipient
- ☐ I am a friend of care recipient
- ☐ Other relationship (please specify) _____

9. In an average week, how many hours do you provide care or assistance to the care recipient?

- ☐ Up to 8 hours per week
- ☐ 9-19 hours
- ☐ 20-39
- ☐ 40 or more
- ☐ Don't know/not sure

A3 – Palliative Performance Scale

PPS Level	Ambulation	Activity & Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal activity & work No evidence of disease	Full	Normal	Full
90%	Full	Normal activity & work Some evidence of disease	Full	Normal	Full
80%	Full	Normal activity *with* Effort Some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable Normal Job/Work Significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable hobby/house work Significant disease	Occasional assistance necessary	Normal or reduced	Full or Confusion
50%	Mainly Sit/Lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or Confusion
40%	Mainly in Bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or Drowsy +/- Confusion
30%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Normal or reduced	Full or Drowsy +/- Confusion
20%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Minimal to sips	Full or Drowsy +/- Confusion
10%	Totally Bed Bound	Unable to do any activity Extensive disease	Total Care	Mouth care only	Drowsy or Coma +/- Confusion
0%	Death	-	-	-	-

A4 – Demoralization Scale – II (DS-II)

DS-II

*For each statement below, please indicate how much (or how strongly) you have felt this way **over the last two weeks** by circling the corresponding number.*

	Never	Sometimes	Often
1. There is little value in what I can offer others.	0	1	2
2. My life seems to be pointless.	0	1	2
3. My role in life has been lost.	0	1	2
4. I no longer feel emotionally in control.	0	1	2
5. No one can help me.	0	1	2
6. I feel that I cannot help myself.	0	1	2
7. I feel hopeless.	0	1	2
8. I feel irritable.	0	1	2
9. I do not cope well with life.	0	1	2
10. I have a lot of regret about my life.	0	1	2
11. I tend to feel hurt easily.	0	1	2
12. I feel distressed about what is happening to me.	0	1	2
13. I am not a worthwhile person.	0	1	2
14. I would rather not be alive.	0	1	2
15. I feel quite isolated or alone.	0	1	2
16. I feel trapped by what is happening to me.	0	1	2

A5 – Hospital Anxiety and Depression Scale

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

A6 – Functional Assessment of Chronic Illness Therapy - Palliative Care 14

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
Sp21	I feel hopeful	0	1	2	3	4
GE1	I feel sad	0	1	2	3	4
Pal4	I feel like a burden to my family	0	1	2	3	4
Pal5	I am constipated	0	1	2	3	4
Pall14	I am able to openly discuss my concerns with the people closest to me	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4

A8 – PROMIS® Pain Interference Scale

In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
How often did you feel emotionally tense because of your pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your close personal relationships?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain feel like a burden to you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How irritable did you feel because of pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did pain make you feel discouraged?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did pain make you feel anxious?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did pain make you feel depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often was pain distressing to you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

A9 – Life Attitude Profile – revised, Death acceptance subscale

Life attitude profile revised (LAP-R) – Death Anxiety

SA	A	MA	U	MD	D	SD
Strongly Agree	Agree	Moderately Agree	Undecided	Moderately Disagree	Disagree	Strongly Disagree

1.	I think I am generally much less concerned about death than those around me.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
2.	Death makes little difference to me one way or another.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
3.	Even though death awaits me, I am not concerned about it.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
4.	I would neither fear death nor welcome it.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
5.	Since death is a natural aspect of life, there is no sense worrying about it.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
6.	Some people are very frightened of death but I am not.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
7.	The thought of death seldom enters my mind.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**
8.	I accept death as another life experience.	**SA**	**A**	**MA**	**U**	**MD**	**D**	**SD**

A10 – Social Isolation Scale-6a

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
UCLA11x2	I feel left out.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA13x3	I feel that people barely know me.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA14x2	I feel isolated from others	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA18x2	I feel that people are around me but not with me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Iso-CaPS1	I feel isolated even when I am not alone.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Iso-CaPS2	I feel that people avoid talking to me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

A11 – Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Sp1	I feel peaceful	0	1	2	3	4
Sp2	I have a reason for living	0	1	2	3	4
Sp3	My life has been productive	0	1	2	3	4
Sp4	I have trouble feeling peace of mind	0	1	2	3	4
Sp5	I feel a sense of purpose in my life	0	1	2	3	4
Sp6	I am able to reach down deep into myself for comfort	0	1	2	3	4
Sp7	I feel a sense of harmony within myself	0	1	2	3	4
Sp8	My life lacks meaning and purpose	0	1	2	3	4
Sp9	I find comfort in my faith or spiritual beliefs	0	1	2	3	4
Sp10	I find strength in my faith or spiritual beliefs	0	1	2	3	4
Sp11	My illness has strengthened my faith or spiritual beliefs	0	1	2	3	4
Sp12	I know that whatever happens with my illness, things will be okay	0	1	2	3	4

A12 – Mystical Experience Questionnaire

instructions: looking back on the entirety of your psychedelic session, please rate the degree to which at any time during that session you experienced the following phenomena. Answer each question according to your feelings, thoughts, and experiences at the time of the psychedelic session. In making each of your ratings, use the following scale: ***0*** *none/not at all;* ***1*** *so slight cannot decide;* ***2*** *slight;* ***3*** *moderate;* ***4*** *strong (equivalent in degree to any other strong experience);* ***5*** *extreme (more than any other time in my life and stronger than* ***4)****.* Feel free to use *'half-point in-between scores'* if these are applicable.

		0	***1***	***2***	***3***	***4***	***5***
1	Loss of your usual sense of time. *(T)*						
2	Experience of amazement. *(P)*						
3	Sense that the experience cannot be described adequately in words. *(I)*						
4	Gain of insightful knowledge experienced at an intuitive level						
5	Feeling that you experienced eternity or infinity.						
6	Experience of oneness or unity with the objects and/or persons perceived in your surroundings.						
7	Loss of your usual sense of space. *(T)*						
8	Feelings of tenderness and gentleness. *(P)*						
9	Certainty of encounter with ultimate reality (in the sense of being able to 'know' and 'see' what is really real at some point during your experience).						
10	Feeling that you could not do justice to your experience by describing it in words. *(I)*						
11	Loss of your usual sense of where you were. *(T)*						
12	Feelings of peace and tranquillity. *(P)*						
13	Sense of being 'outside of' time, beyond past and future. *(T)*						
14	Freedom from the limitations of your personal self and feeling of unity or bond with what was felt to be greater than your personal self.						
15	Sense of being at a spiritual height.						
16	Experience of pure being and pure awareness (beyond the world of sense impressions).						
17	Experience of ecstasy. *(P)*						
18	Experience of the insight that "all is One".						
19	Being in a realm with no space boundaries. *(T)*						
20	Experience of oneness in relation to an "inner world" within.						
21	Sense of reverence.						
22	Experience of timelessness. *(T)*						
23	You are convinced now, as you look back on your experience, that in it you encountered ultimate reality (that you 'knew' and 'saw' what was really real).						
24	Feeling that you experienced something profoundly sacred and holy.						
25	Awareness of the life or living presence in all things.						
26	Experience of the fusion of your personal self into a larger whole.						
27	Sense of awe or awesomeness. *(P)*						
28	Experience of unity with ultimate reality.						
29	Feeling that it would be difficult to communicate your own experience to others who have not had similar experiences. *(I)*						
30	Feelings of joy. *(P)*						

scores/%'s: ***transcendence (T) = /30 = %; positive mood (P) = /30 = % ineffability (I) = /15 = %; mystical = /75 = %; total score = /150 = %.***

A13 – Challenging Experience Questionnaire

Instructions: Looking back on the entirety of your session, please rate the degree to which at any time during that session you experienced the following phenomena. Answer each question according to your feelings, thoughts, and experiences at the time of the session. In making each of your ratings, use the following scale:

0 – none; not at all

1 – so slight cannot decide

2 – slight

3 – moderate

4 – strong

5 – extreme (more than ever before in my life)

_____ 1. Isolation and loneliness

_____ 2. Sadness

_____ 3. Feeling my heart beating

_____ 4. I had the feeling something horrible would happen

_____ 5. Feeling my body shake/tremble

_____ 6. Feelings of grief

_____ 7. Experience of fear

_____ 8. Fear that I might lose my mind or go insane

_____ 9. I felt like crying

_____ 10. Feeling of isolation from people and things

_____ 11. Feelings of despair

_____ 12. I had the feeling that people were plotting against me

_____ 13. I was afraid that the state I was in would last forever

_____ 14. Anxiousness

_____ 15. I felt shaky inside

_____ 16. I had the profound experience of my own death

_____ 17. I felt my heart beating irregularly or skipping beats

_____ 18. Pressure or weight in my chest or abdomen

_____ 19. I experienced a decreased sense of sanity

_____ 20. I felt as if I was dead or dying

_____ 21. Panic

_____ 22. Experience of antagonism toward people around me

_____ 23. Despair

_____ 24. I felt isolated from everything and everyone

_____ 25. Emotional and/or physical suffering

_____ 26. I felt frightened

A14 – Schedule of Attitudes toward Hastened Death

T F	1. I feel confident that I will be able to cope with the emotional stress of my illness .
T F	2. I expect to suffer a great deal from emotional problems in the future because of my illness.
T F	3. My illness has drained me so much that I do not want to go on living.
T F	4. I am seriously considering asking my doctor for help in ending my life.
T F	5. Unless my illness improves, I will consider taking steps to end my life.
T F	6. Dying seems like the best way to relieve the pain and discomfort my illness causes.
T F	7. Despite my illness, my life still has purpose and meaning.
T F	8. I am careless about my treatment because I want to let the disease run its course.
T F	9. I want to continue living no matter how much pain or suffering my disease causes.
T F	10. I hope my disease will progress rapidly because I would prefer to die rather than continue living with this illness.
T F	11. I have stopped treatment for my illness because I would prefer to let the disease run its course.
T F	12. I enjoy my present life, even with my illness, and would not consider ending it.
T F	13. Because my illness cannot be cured, I would prefer to die sooner, rather than later.
T F	14. Dying seems like the best way to relieve the emotional suffering my illness causes.
T F	15. Doctors will be able to relieve most of the discomfort my illness causes.
T F	16. Because of my illness, the idea of dying seems comforting.
T F	17. I expect to suffer a great deal from physical problems in the future because of my illness.
T F	18. I plan to end my own life when my illness becomes too much to bear.
T F	19. I am aggressively pursuing all possible treatments because I'll do anything possible to continue living.
T F	20. I am able to cope with the symptoms of my illness, and have no thoughts of ending my life.

A15 – Columbia-Suicide Severity Rating Scale

Screen Version

SUICIDE IDEATION DEFINITIONS AND PROMPTS	**Past month**	
Ask questions that are bolded and underlined.	**YES**	**NO**
Ask Questions 1 and 2		
1) Wish to be Dead: Person endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?***		
2) Suicidal Thoughts: General non-specific thoughts of wanting to end one's life/commit suicide, "*I've thought about killing myself"* without general thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?***		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) Suicidal Thoughts with Method (without Specific Plan or Intent to Act): Person endorses thoughts of suicide and has thought of a least one method during the assessment period. This is different than a specific plan with time, place or method details worked out. "*I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it….and I would never go through with it.*" ***Have you been thinking about how you might kill yourself?***		
4) Suicidal Intent (without Specific Plan): Active suicidal thoughts of killing oneself and patient reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them.*" ***Have you had these thoughts and had some intention of acting on them?***		
5) Suicide Intent with Specific Plan: Thoughts of killing oneself with details of plan fully or partially worked out and person has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***		
6) Suicide Behavior Question: ***Have you ever done anything, started to do anything, or prepared to do anything to end your life?*** Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc. **If YES, ask: *How long ago did you do any of these?*** Over a year ago? Between three months and a year ago? Within the last three months?		

A16 – Confusion Assessment Method

Acute Onset

1. Is there evidence of an acute change in mental status from the patient's baseline?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Inattention

(*The questions listed under this topic are repeated for each topic where applicable.*)

2A. Did the patient have difficulty focusing attention (for example, being easily distractible or having difficulty keeping track of what was being said)?

_____ Not present at any time during interview

_____ Present at some time during interview, but in mild form

_____ Present at some time during interview, in marked form

_____ Uncertain

2B. (*If present or abnormal*) Did this behavior fluctuate during the interview (that is, tend to come and go or increase and decrease in severity)?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

2C. (*If present or abnormal*) Please describe this behavior.

_____

_____

Disorganized Thinking

3. Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable, switching from subject to subject?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Altered Level of Consciousness

4. Overall, how would you rate this patient's level of consciousness?

_____ Alert (*normal*)

_____ Vigilant (*hyperalert, overly sensitive to environmental stimuli, startled very easily*)

_____ Lethargic (*drowsy, easily aroused*)

_____ Stupor (*difficult to arouse*)

_____ Coma (*unarousable*)

_____ Uncertain

Disorientation

5. Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Memory Impairment

6. Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Perceptual Disturbances

7. Did the patient have any evidence of perceptual disturbances, such as hallucinations, illusions, or misinterpretations (for example, thinking something was moving when it was not)?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Agitation

8A. At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent, sudden changes in position?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Retardation

8B. At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space, staying in one position for a long time, or moving very slowly?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Altered Sleep-Wake Cycle

9. Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Scoring:

For a diagnosis of delirium by CAM, the patient must display:

1. Presence of acute onset and fluctuating discourse

AND

2. Inattention

AND EITHER

3. Disorganized thinking

OR

4. Altered level of consciousness

A17 – Reactions to Research Participation Questionnaire Revised

This questionnaire asks for your opinions about what it was like for you to participate in this study. Your responses will be used to help us understand more about what it is like to be a research participant.

I. From the list below, please rank the top three reasons why you decided to participate (1= most important 2= second most important 3= third most important).

____ I was curious	____ I don't know	____ Felt I had to
____ To help others	____ Thought it might improve my access to health care	____ For the money
____ To help myself		____ I didn't want to say no

____ Other (Please explain _____

II. **The following questions deal with your reactions to participating in this study. Please circle the number that best describes your response.**

	Strongly disagree (No)	Disagree	Neutral (Maybe)	Agree	Strongly agree (Yes)
1. I gained something positive from participating.	1	2	3	4	5
2. Knowing what I know now, I would participate in this study if given the opportunity.	1	2	3	4	5
3. The research raised emotional issues for me that I had not expected.	1	2	3	4	5
4. I gained insight about my experiences through research participation.	1	2	3	4	5
5. The research made me think about things I didn't want to think about.	1	2	3	4	5
6. I found the questions too personal.	1	2	3	4	5
7. I found participating in this study personally meaningful.	1	2	3	4	5
8. I believe this study's results will be useful to others.	1	2	3	4	5
9. I trust that my replies will be kept private.	1	2	3	4	5

	Strongly disagree (No)	Disagree	Neutral (Maybe)	Agree	Strongly agree (Yes)
10. I experienced intense emotions during the research session and/or parts of the study.	1	2	3	4	5
11. I think this research is for a good cause.	1	2	3	4	5
12. I was treated with respect and dignity.	1	2	3	4	5
13. I found participating beneficial to me.	1	2	3	4	5
14. I was glad to be asked to participate.	1	2	3	4	5
15. I like the idea that I contributed to science.	1	2	3	4	5
16. I was emotional during the research session.	1	2	3	4	5
17. I felt I could stop participating at any time	1	2	3	4	5
18. I found participating boring.	1	2	3	4	5
19. The study procedures took too long.	1	2	3	4	5
20. Participating in this study was inconvenient for me.	1	2	3	4	5
21. Participation was a choice I freely made.	1	2	3	4	5
22. Had I known in advance what participating would be like I still would have agreed to participate.	1	2	3	4	5
23. I understood the consent form.	1	2	3	4	5

A18 – CareGiver Oncology Quality of Life questionnaire

Answer each question by checking the case that comes closest to what you thought or felt **during the last four weeks.** Some of the questions concern your private life. These questions are necessary to evaluate every aspect of your quality of life. However, if you do not know how to respond to a question or if a question does not concern you, skip to the next question.

	During the last four weeks, in connection with the person you help, have you …	Never Not at all	Rarely A little	Sometimes Moderately	Often A lot	Always Enormously
1	Been worried, anxious?	❑	❑	❑	❑	❑
2	Been sad, depressed?	❑	❑	❑	❑	❑
3	Been emotionally tired, worn out?	❑	❑	❑	❑	❑
4	Been stressed?	❑	❑	❑	❑	❑
5	Felt a lack of freedom?	❑	❑	❑	❑	❑
6	Been bothered by the feeling of being confined?	❑	❑	❑	❑	❑
7	Been bothered by the fact that your life was entirely devoted to the care recipient?	❑	❑	❑	❑	❑
8	Been embarrassed to be the only person to provide assistance?	❑	❑	❑	❑	❑
9	Been satisfied with information given by health care providers (doctors, nurses…)?	❑	❑	❑	❑	❑
10	Been reassured by the health care providers (doctors, nurses…)?	❑	❑	❑	❑	❑

Quality of Life Questionnaire : CarGOQoL

	During the last four weeks, in connection with the person you help, have you …	Never Not at all	Rarely A little	Sometimes Moderately	Often A lot	Always Enormously
22	Felt you made a difference for the person you are helping?	❑	❑	❑	❑	❑
23	Felt useful?	❑	❑	❑	❑	❑
24	Could rest, relax?	❑	❑	❑	❑	❑
25	Could take care of yourself, pay attention to your own health?	❑	❑	❑	❑	❑
26	Been assisted, supported, understood by your family?	❑	❑	❑	❑	❑
27	Been assisted, supported, understood by your friends?	❑	❑	❑	❑	❑
28	Had difficulties in your intimate, emotional life?	❑	❑	❑	❑	❑
29	Had a satisfying love and sexual life?	❑	❑	❑	❑	❑

Thank you for your participation

Quality of Life Questionnaire : CarGOQoL

	During the last four weeks, in connection with the person you help, have you …	Never Not at all	Rarely A little	Sometimes Moderately	Often A lot	Always Enormously
11	Felt that your role as caregiver was recognized by health care providers (doctors, nurses…)?	❑	❑	❑	❑	❑
12	Had financial difficulties (lodging, transportation…)?	❑	❑	❑	❑	❑
13	Had other difficulties (lodging, transportation…)?	❑	❑	❑	❑	❑
14	Encountered difficulties in the administrative process (health insurance paperwork and other paperwork related to the cancer illness?	❑	❑	❑	❑	❑
15	Experienced feelings of guilt?	❑	❑	❑	❑	❑
16	Been bothered by a feeling of helplessness against disease?	❑	❑	❑	❑	❑
17	Felt a feeling of injustice, anger, or rebellion?	❑	❑	❑	❑	❑
18	Had sleeping difficulties?	❑	❑	❑	❑	❑
19	Had problems with your appetite?	❑	❑	❑	❑	❑
20	Been physically tired, worn out?	❑	❑	❑	❑	❑
21	Had the impression that your health was fragile?	❑	❑	❑	❑	❑

Quality of Life Questionnaire : CarGOQoL

During the last four weeks, in connection with the person you help, have you ...		Never Not at all	Rarely A little	Sometimes Moderately	Often A lot	Always Enormously
22	Felt you made a difference for the person you are helping?	☐	☐	☐	☐	☐
23	Felt useful?	☐	☐	☐	☐	☐
24	Could rest, relax?	☐	☐	☐	☐	☐
25	Could take care of yourself, pay attention to your own health?	☐	☐	☐	☐	☐
26	Been assisted, supported, understood by your family?	☐	☐	☐	☐	☐
27	Been assisted, supported, understood by your friends?	☐	☐	☐	☐	☐
28	Had difficulties in your intimate, emotional life?	☐	☐	☐	☐	☐
29	Had a satisfying love and sexual life?	☐	☐	☐	☐	☐

Thank you for your participation