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SEATTLE CHILDREN'S

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Title of Protocol:
A phase 1/2 study of a group model of psilocybin-assisted therapy for cancer-related anxiety in patients with metastatic cancer

Investigators List:		
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IND Number:
165562
Investigationant:
Psilocybin PEX010, Psilo Scientific Ltd.
IND Sponsor:
Anthony Back MD

Supported by:
Psilo Scientific Ltd is providing the investigational product.

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PROTOCOL SYNOPSIS

Protocol Title	**A phase 1/2 study of a group model of psilocybin-assisted therapy for cancer-related anxiety in patients with metastatic cancer**
Protocol Numbers	*RG1123316 (BACK002)*
IND Sponsor (if applicable)	*Anthony Back MD*
Funding Sponsor (if applicable)	*Steven and Alexandra Cohen Foundation*
Supplier of Investigational Product	*Psilo Scientific Ltd*
Trial Phase	*1/2*
Trial Type	*Interventional*
Clinical Indication	*Cancer-related anxiety*
Study Objectives	*1. To test the safety, tolerability, and feasibility of a group model for psilocybin-assisted therapy for patients with stable metastatic cancer with clinically significant anxiety.* *2. To explore the efficacy of the group model of psilocybin-assisted therapy on symptoms of anxiety, depression, demoralization, quality of life, and cancer-related post-traumatic stress.*
Study Design	*Single arm*
Population	*Stable metastatic cancer patients*
Primary Endpoints	*Potentially unattended psilocybin-related distress, which is defined as the occurrence of participant distress that needs 1:1 facilitator attention that cannot be met by the 4-person facilitation team*
Secondary Endpoints	• *Hospital Anxiety and Depression Scale, Symptoms of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) at 1 week, 8 weeks, 12 weeks, and 6 months post psilocybin-assisted group therapy.*
Exploratory Endpoints	• *Symptoms of depression using the Center for Epidemiologic Studies-Depression Scale (CES-D) at 1 week post psilocybin-assisted group therapy at 1 week, 4 weeks, 8 weeks, 12 weeks, and 6 months.* • *Measurement of quality of life using the Functional Assessment of Cancer Therapy – General (FACT-G) at 1 week, 4 weeks, 8 weeks, 12 weeks, and 6 months.* • *Measurement of demoralization using the Demoralization II (DS-II) scale at 4 weeks, 8 weeks, 12, weeks, and 6 months.* • *Measurement of psychosocial functioning using the NIH_HEALS) at 4 weeks, 8 weeks, 12 weeks, and 6 months.* • *Measurement of acceptance using the Peace, Equanimity, Acceptance in Cancer Experience (PEACE) instrument and the Watts Connectedness Scale at 1 week, 4 weeks, 8 weeks, 12 weeks, and 6 months.* • *Measurement of retreat experience using the Mystical Experience Questionnaire, Communitas Scale, Challenging Experiences Scale, Emotional Breakthrough Scale, and the Psychedelic Music Questionnaire on the day of the psilocybin*

	session.
Investigational Product	*Psilocybin PEX010*
Dose	*25 mg*
Route of Administration	*Oral*
Regimen	*Single dose + psychotherapy group and individual sessions*
Treatment Groups	*This is a small group psychosocial intervention in small groups, the size of which will be adjusted as the trial progress according to predefined adverse events.*
Treatment Schedule/Schema	*Prior to psilocybin session there are 3 sessions of weekly group therapy and 1 session of individual therapy. Day 0 = Psilocybin session. After the psilocybin session there are 3 sessions of weekly group therapy and 1 session of individual therapy.*
Efficacy Assessments	*1 week, 4 weeks, 8 weeks, 12 weeks, 24 weeks*
Number of Subjects	*Up to 56*
Estimated Duration of Trial	*1.5 years*
Duration of Participation	*6 months*

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1.0 INTRODUCTION TO THE PROTOCOL

1.1 Introduction

Psilocybin-assisted therapy is proving to be a potent treatment for the anxiety, distress and fear of recurrence experienced by people living with cancer. In randomized studies, psilocybin-assisted therapy conducted using an existing 2-therapist/1-patient model has shown impressive efficacy for cancer-related anxiety and existential distress.[1-3] Larger, multisite randomized trials are being launched now. In addition, psilocybin-assisted therapy is being tested for a number of other indications, including depression, substance use, obsessive-compulsive disorder, demoralization, and—in a study Dr Back is leading—symptoms of depression and burnout in doctors and nurses who developed these symptoms during their frontline work in the COVID pandemic.

For patients with metastatic, incurable cancer, unrelieved anxiety and existential distress cause profound suffering. Of patients with metastatic cancer, 25-50% have clinically significant anxiety.[4-6] These patients experience a sense of uncertainty, fear of future uncontrollable suffering, sense that they are burdens on the people caring for them, feelings of loneliness and isolation, and grief for the loss of their lives and opportunities missed. In longitudinal studies, existential distress and anxiety generally increases over time, and probably contribute to patients' pursuit of futile medical interventions at the very end of life.[7] Existing therapies are unsatisfactory.[8] For many of these patients, their anxiety and distress impedes their ability to participate in psychotherapy, many decline to take antidepressant medications because of the unwanted side effect of blunting positive emotions, and benzodiazepines do not seem to change the course of the anxiety.

1.2 Preclinical Data

Substantial data demonstrates the safety of psilocybin (mushroom-derived, and synthesized)

Studies in humans and nonhuman animals indicate that psilocybin has very low toxicity.[9,10] The LD_{50} ranged from 285mg/kg in rats and mice.[11] The maximum tolerated dose of psilocybin in humans has not been defined or established. The best estimate of a lethal dose for pure psilocybin in humans is about 19 grams. The full dose of psilocybin that will be administered in this study is 1/100 times of the established LD_{50} in nonhuman animals and in humans. A Phase I trial of psilocybin completed in 2019 at oral doses of up to 0.6 mg/kg demonstrated no serious adverse events.[12] Psilocybin is not associated with disease or damage to any organ or system.[10] More commonly, damage or disease to organs (as renal failure) is associated with mistakenly consuming poisonous mushrooms under the belief that they are psilocybin-containing mushrooms.[13]

Three cases of death possibly related to the direct toxic effects of Psilocybe mushrooms (the natural source of psilocybin) have been reported in the world literature. One fatality occurred in a post-cardiac transplant patient who ingested Psilocybe mushrooms.[14] It is not known however whether psilocybin was the proximal cause of death or whether death occurred secondary to the cardiac stimulant phenethylamine, which is also present in the mushrooms. In the French literature, another fatality linked to Psilocybe mushroom use was associated with far higher blood concentrations of the active metabolite of psilocybin than would be expected with the doses proposed in this study.[15] A final fatality from Psilocybe mushroom ingestion was mentioned in a 1961 review but was poorly characterized, with no psilocin concentrations were reported.[16]

In a review of other adverse effects of psilocybin from Psilocybe mushrooms, an additional 10 individuals were reported to have experienced accidental deaths associated with Psilocybe mushroom ingestion.[17] In most cases, these accidental deaths resulted from falls from buildings. Given the documented history of use of *Psilocybe* mushrooms in a variety of societies and cultures, that there are only 3 known fatalities at best indirectly linked to the physiologic effects of mushroom ingestion is an argument for the general safety of this natural product. Further, a recent review of

the potential harm of the ingestion of *Psilocybe* mushrooms by the Dutch medicinal advisory board found that the risk of acute orchronic toxicity was low.[17]

To date, over 2000 participants have received psilocybin under controlled conditions in scientific studies with no reports of the occurrence of a significant adverse event deemed to be associated with drug administration. The most commonly reported adverse events from the scientific literature are psychological in nature and include the induction of negative emotional states and paranoid/delusional thinking during psilocybin sessions, as well as far less frequent reports of Hallucinogen Persisting Perception Disorder (HPPD).[18] A review of studies conducted worldwide between 1999 and 2008 identified only one subject (out of 110) who experienced any persistent perceptual symptoms associated with HPPD and these symptoms were mild, brief, and resolved within three days of psilocybin exposure.[19] Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. As in the phase 2 studies, common physical adverse events associated with psilocybin administration include increased BP and heart rate, nausea, and headaches. In the phase 2 studies of cancer related anxiety and depression no cases of HPPD were identified and no participants developed any symptoms of paranoia or anxiety that required pharmacological interventionor anything more than reassurance from session facilitators.[1,2] In a survey of 1993 individuals in the context of unsupervised, illicit use of psilocybin-containing mushrooms, 11% put self or others at risk of physical harm. Of the respondents, 2.6% behaved in a physically aggressive or violent manner and 2.7% received medical help. Of those whose experience occurred >1 year before, 7.6% sought treatment for enduring psychological symptoms. 3 cases appeared associated with onset of enduring psychotic symptoms and 3 cases with attempted suicide.[20]

To date, there have no reports of physical harm in patients who have received psilocybin under controlled conditions, and no fatalities have been associated with its use in a controlled clinical trial. The difference in the side-effect profile between the unknown doses of psilocybin-containing mushrooms consumed in an uncontrolled setting and dose- controlled medically prepared oral psilocybin consumed in a controlled setting is thought to be in part due to the focus on the set and *setting* of the experience. The *set* refers to the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure, and the *setting* refers to the physical environment in which the exposure occurs.[21]

There are no confirmed reports of an overdose of synthesized or purified psilocybin meant for use in a clinical trial. In the United States, use of chemically synthesized psilocybin does not occur.[22] Although psilocybin in the form of mushrooms is sometimes used non-medically, medical emergencies due to psilocybin mushrooms are very rare (psilocybin is mentioned in only 0.1% of drug-related emergency department visits).[23] It can be anticipated that an overdose of psilocybin might present in a manner similar to “serotonin syndrome”. Removal of any residual gastric drug, supportive care, and cautious administration of a serotonin antagonist such as risperidone are reasonable interventions; however, to date no cases have described similar responses with respect to psilocybin, and the doses of psilocybin that might provoke these physiological effects would be many times greater than even the highest doses used in early human studies.

1.3 Clinical Data to Date

Psilocybin-assisted therapy can relieve anxiety and existential distress by disrupting patterns of thinking that are ruminative, catastrophic, and persistent. The lived experience of cancer patients who have participated in psilocybin-assisted therapy studies using individual models reveal that patients feel more able to examine their fears, find meaning in their lives, and connect more deeply the people they care about.[24] While scientific studies have yet to measure medical utilization, anecdotes describe a dramatic shift in decisions away from medical treatments that are invasive and isolating, such as mechanical ventilation in intensive care, and an increase in discussions related to advance care planning. The qualitative data, and many anecdotes published in the media, demonstrate that psilocybin-assisted therapy seems to allow many patients to hold a realistic appraisal of their

prognosis while at the same time experiencing a heightened appreciation of the parts of their lives they still enjoy and cherish—and these benefits have persisted in a 4 year followup study.[25] While other psychotherapeutic approaches have been reported as valuable, their benefits take much longer to be experienced, typically weeks to months, and long term followup is sparse. Thus psilocybin-assisted therapy appears to have unique promise as a modality to treat anxiety, existential distress, and demoralization for patients with life-threatening cancer. The study proposed here addresses a population of patients with metastatic cancer whose need for relief from suffering is high.

Established treatment models use a 2-therapist/1-patient therapy model that is extremely resource intensive, to a degree that will likely limit future access. For example, in two highly efficacious clinical trials, 2 therapists conducted 3 preparation sessions, a medication day sessions, and 3 integration sessions with a single participant. A single study participant required at least 30 hours of direct contact. [Assuming (3 x 90 min prep sessions) + (1 x 7 hour medication session) + (3 x 90 min integration sessions] x 2 therapists]. This 2 therapist/1 patient model is likely to become a barrier to expanding access. Many therapists consider 30 hours of direct contact to be a week of full time work. Thus a therapist who focused exclusively on psilocybin-assisted therapy could work with up to 48 people with cancer in a year (30 hours/week x 48 weeks). It is hard to imagine scaling up this level of resource intensity to provide access for the 602,000 people who died of cancer in the US 2020–if only 30% of those people wanted access, 12,541 therapists working full time would be required. If 8-person groups run by a facilitation team of 4 therapists were to be shown safe and efficacious, the number of required therapists would drop by 4-fold, to 3,135 therapists. (To date the most established training program, at the California Institute for Integral Studies, has trained 559 practitioners over its 6 year history, and only a fraction of their work will be with cancer patients; CIIS, personal communication May 2022).

Note that this protocol uses the term 'facilitator' rather than therapist, but for this protocol these terms both refer to the same role on the research team.

Limited scientific evidence is available that describes the safety and efficacy of a group model for psilocybin-assisted therapy. There is an extensive non-clinical experience with groups using psilocybin in a community or ceremonial setting. However, we very few studies involving prospective data collection from a group setting are available to inform a group model for clinical use.[26] In a University of California San Francisco (UCSF) study of psilocybin-assisted therapy with 18 long term HIV survivors (3 groups) showed clinically meaningful changes in demoralization.[27] This group study used group preparation and integration sessions, but used individual psilocybin sessions, so does not provide data to inform a group psilocybin administration model. Another recent experience is from the Aquilino Cancer Center, which uses groups of 4 cancer patients who receive mostly individual preparation; then the group members have 4 simultaneous individual psilocybin sessions each with a single therapist, with a backup therapist monitoring the sessions by video (Manish Agrawal, personal communication, April 2022). This model is less intensive than the 2-therapist/1-patient model, but does not provide data about group psilocybin administration. To our knowledge, there are no published studies involving use of group preparation, group medication sessions, and group integration sessions that report adverse events. Thus, there is a gap in scientific knowledge about group models of psilocybin-assisted therapy for use in the United States in 2022, and this proposal describes a substantial step forward in filling that knowledge gap.

Evidence from a large body of scientific evidence from psychosocial group interventions for cancer patients without psychedelics suggests that the benefits of group therapy plus psilocybin could be substantial. A large body of empirical research has reported the beneficial effects of cancer group psychosocial interventions on distress, anxiety and fear of recurrence. To date, numerous randomized studies have compared different group interventions, with results favoring manualized group therapy sessions that result improvements in distress and fear of recurrence without the use of psychedelics. The state-of-the-science cancer group intervention typically involves groups of 8 cancer patients and 2 facilitators, and since the COVID pandemic, these interventions have been conducted online. Interestingly, in addition to improved psychosocial outcomes, these randomized trials also

demonstrate improvements in physiologic parameters: immune function, neuroendocrine function, and even survival.[28-30]

Dr McGregor (a sub-investigator on this proposal) is currently a co-investigator on a National Cancer Institute-funded clinical trial of a manualized group intervention for ovarian cancer survivors, has extensive experience designing and facilitating these group interventions, and will bring this scientific knowledge to the study described in this proposal. This proposal would be the first study to combine this scientific knowledge about cancer group interventions together with the emerging psychedelic science.

In summary, there exists a gap in knowledge about whether the benefits of psilocybin-assisted therapy could be realized in a group model, and how those groups should be structured. This study aims to fill that gap with a phase 1/2 psilocybin-assisted therapy intervention study in which the preparation, psilocybin, and integration sessions are conducted with carefully screened patients in a group setting, using a Phase 1/2 design adapted from cancer clinical trials that would answer foundational questions about what group size is safe, feasible, and efficacious.

1.4 Study Agent

Psilocybin is a naturally occurring compound, found in a variety of mushroom species collectively called 'magic mushrooms' in lay publications. According to the most recent and comprehensive review, serotonergic psychedelic medications "are generally considered to be physiologically safe molecules" that chiefly alterconsciousness.[31] Recent reviews and searches of the literature indicate thatpsilocybin – either in the form of mushrooms, or synthesized psilocybin -- is not associated with harm or damage to any organ or system in the body.[18] Psilocybin can produce changes in blood pressure and heart rate, but these changes are not as strong or consistent as those seen after psychostimulants (amphetamines), and sometimes these changes only occur at one time point.[31] More consistently, psilocybin can produce rapid and intense changes in mood including periods of anxiety or panic. Both these physiological and psychological effects are transient and do not last beyond the duration of drug effects.

The psilocybin that will be used in this study, PYEX psilocybin, is a partially purified fraction of the extract of Psilocybe cubensis mushroom fruiting bodies that is produced by Psilo Scientific Ltd. (Vancouver BC), in a patented process that yields a pharmaceutical grade botanical drug that meets FDA guidance for a botanical drug suitable for a clinical investigation. The drug product to be used is PEX010, 25 mg psilocybin capsules, and it is manufactured under cGMP conditions. Further CMC information is available in the accompanying Investigator's Brochure describing PEX010. In a variety of studies, researchers leading clinical trials using pharmaceutical grade psilocybin at this dose took precautions similar to the ones we will use in this study, and observed no reactions requiring pharmacological intervention.[2,32] This preparation of psilocybin is being used in over 25 studies in North America, Europe, and Australia, including a series of ongoing studies at the University of California San Francisco.

1.5 Dose Rationale

The dose of psilocybin to be used in this study, 25 mg, has been shown to produce equivalent results to body-weight-based dosing in a review of experience at the Johns Hopkins Center for Consciousness Studies.[33]

1.6 Other Agents

There are no other pharmacologic agents used in this study. The study intervention includes psychotherapy sessions that are similar to established small group psychosocial interventions for cancer patients.[1,34,35]

1.7 Risks/Benefits

Expected benefits for participants include: reductions in symptoms of anxiety, depression, demoralization, existential anxiety; increases in feelings of well-being and spiritual connectedness. Possible benefits for society

include establishment of safe procedures for psilocybin-assisted therapy in groups, and the advancement of scientific knowledge in the area of psychedelic-assisted therapy.

The expected benefits outweigh the risks for study participants because: symptoms of depression, anxiety, demoralization, existential anxiety can lead to severe suffering for patients with metastatic cancer, and the existing treatment options have significant limitations. For example, about 30% of cancer patients with depressive symptoms respond to conventional antidepressant therapy. For patients with demoralization, antidepressants have no known efficacy. For patient with metastatic cancer, conventional psychotherapy has modest effects, yet requires a substantial investment of time and energy which can be difficult for patients with metastatic disease. While the evidence for psilocybin-assisted therapy is limited, existing randomized studies using an individual patient approach show responses that are larger in magnitude, more rapid, and more prolonged than existing antidepressant studies. Thus this study, which attempts to make psilocybin-assisted therapy more accessible, and is designed with multiple safety features, seems reasonable to propose to patients with metastatic cancer.

2.0 OVERVIEW OF CLINICAL TRIAL

This is a phase 1/2 study of psilocybin-assisted group therapy for cancer-related anxiety and distress that will measure safety, feasibility, and efficacy in order to establish evidence-based parameters for a group model of psilocybin-assisted therapy.

2.1 Study Objectives and Endpoints

2.1.1 **Primary Objective.** To test the safety, tolerability, and feasibility of a group model for psilocybin-assisted therapy for patients with stable metastatic cancer with clinically significant anxiety.

2.1.1.1 **Primary Endpoint.** The number of instances of 'Potentially unattended psilocybin-related distress', which is defined as the occurrence of participant distress during the psilocybin administration session on Day 0 that requires 1:1 facilitator attention that cannot be met by the 4-person facilitation team in small groups of different sizes that will vary over the course of the study; these occurrences will be identified by a study observer and validated with the study PI.

2.1.2 **Secondary Objective.** To explore the efficacy of the group model of psilocybin-assisted therapy on symptoms of anxiety and depression at 1 week, 4 weeks, 12 weeks,

2.1.2.1 **Secondary Endpoint.** The primary measurement of anxiety and depression will be Hospital Anxiety and Depression Scale at 1 week, 4 weeks, 8 weeks, 12 weeks, and 24 weeks.

2.1.3 **Exploratory Objective 1.** To explore the efficacy of the group model of psilocybin-assisted therapy on symptoms of demoralization.

2.1.3.1 **Exploratory Endpoint 1. Demoralization will be measured using the DS-II scale at** 1 week, 4 weeks, 8 weeks, 12 weeks, and 24 weeks.

2.1.4 **Exploratory Objective 2.** To explore the efficacy of the group model of psilocybin-assisted therapy on symptoms of quality of life.

2.1.4.1 **Exploratory Endpoint 2. Quality of life will be measured using the FACT-G and Adjustment Disorder scales at** 1 week, 4 weeks, 8 weeks, 12 weeks, and 24 weeks.

2.1.5 **Exploratory Objective 3.** To explore the efficacy of the group model of psilocybin-assisted therapy on psychosocial functioning and connectedness.

2.1.5.1 **Exploratory Endpoint 3. Cancer-related post-traumatic growth will be measured using the NIH-HEALS scale and the Watts Connectedness Scale at** 4 weeks, 8 weeks, 12 weeks, and 24 weeks.

2.1.6 **Exploratory Objective 4.** To explore the efficacy of the group model of psilocybin-assisted therapy on death anxiety.

2.1.6.1 **Exploratory Endpoint 4. Death anxiety will be measured using the Death and Dying Distress Scale at** 4 weeks, 12 weeks, and 24 weeks.

2.1.7 **Exploratory Objective 5.** To explore the quality of the group experience of the group model of psilocybin-assisted therapy.

2.1.7.1 **Exploratory Endpoint 5. The quality of the group experience will be measured using the Mystical Experience Questionnaire, Emotional Breakthrough Inventory, Communitas Scale, and Challenging Experiences Questionnaire, and the Psychedelic Music Questionnaire on the day of the psilocybin session only.**

2.2 Study Design

This study is designed to define the specifications for a new model of group psilocybin-assisted therapy. We describe the design as a Phase 1/2 study because it combines features of Phase 1 and Phase 2 studies. Phase I trials are often designed as 'dose-finding' studies for new drugs that focus on toxicities and adverse events as primary outcomes. For psilocybin the individual toxicities have already been well described by prior studies. The adverse outcome of interest in this study is related to episodes during the medication session when more participants require 1:1 attention at the same moment than can be provided by the 4-person facilitation team, which this study calls ***'potentially unattended psilocybin-related distress'—***which is somewhat similar to a 'dose-limiting toxicity' in a typical Phase 2 drug study. In this study, the adverse event of interest, potentially unattended psilocybin-related distress, is 'group-size-limiting toxicity'. (Please note that backup facilitators will be on hand to step in when this occurs). This adverse event is specific to the small group design used in this study. In addition, Phase 2 studies are often designed to measure efficacy of a therapy at different doses, and in this study efficacy will be measured at different group sizes by comparing these results to historical studies for cancer patients that provided the same number of preparation and integration therapy sessions. Thus we describe this study as Phase 1/2 because it will examine both adverse events and efficacy.

2.3 Estimated Accrual

This study will accrue up to 56 participants if the small group size over the course of the study increases to 8 participants per group.

3.0 INCLUSION AND RECRUITMENT

3.1 Eligibility of Women and Minorities

Individuals of any sex, gender, race, or ethnicity are eligible for this study.

3.2 Recruitment of Minority Groups

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

3.3 Inclusion Across the Lifespan

The study design and recruitment strategy aim to achieve representation of age groups that reflect the demographics of the affected population. Individuals ages 18 - 85 are eligible for this study**.** Children (age <18) are excluded because insufficient data is available on prospective benefits or adverse events. Adults older than 85 are excluded because insufficient data is available on prospective benefits or adverse events.

3.4 Study Population

Existing studies indicate that older age is associated with decreasing anxiety for patients with metastatic cancer, but the the risk of depression does not vary with age. These trends however were identified in studies of older adults, and studies of younger adults indicate that anxiety is a notable issue, although no studies examined associations with age within younger adults.

A 2021 study of Central Puget Sound demographics showed that 37% are people of color, and 63% are White non-Hispanic/Latino. Among people of color: Asians (14%); Hispanic (10%); Black (6%); American Indian/Alaska Native (1%); Native Hawaiian or Other Pacific Islander (0.8%)

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	3	3	6
Not Hispanic or Latino	25	25	50
Ethnic Category Total of All Subjects*	28	28	56
Racial Categories			
American Indian / Alaska Native	0	1	1
Asian	4	4	8
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	2	4
White	21	21	42
More Than One Race	0	0	0
Racial Categories: Total of All Subjects*	28	28	56

4.0 STUDY AGENT(S)

4.1 Primary Investigational Agent

Psilocybin, is a 4-hydroxy-N,N-dimethyltryptamine and occurs in nature in many species of mushrooms, including the genera Psilocybe, Conocybe, Gymnopilus, Panaeolus, and Strophparia. Its chemical formula is $C_{12}H_{17}N_2O_4P$. Psilocybin is a potent agonist at 5-HT2A/C, and their binding potency to these receptors correlates with human potency as hallucinogens [7]. Psilocybin has been

administered to normal volunteers to measure physiological and psychological parameters at doses ranging from 0.045mg/kg to0.43mg/kg [45; 51]. It has also been safely administered to patients with OCD at doses ranging from 0.025mg/kg to 0.3mg/kg.

Psilocybin PEX010 is a naturally occurring compound that after oral administration is metabolized to psilocin, which reacts antagonistically with serotonin type 2A (5-HT2A) receptors to produce the psychological and spiritual experiences that patients often report. Psilocybin PEX101 is a partially purified fraction of the extract of Psilocybe cubensis mushroom fruiting bodies that is produced by Psilo Scientific Ltd. (Vancouver BC), in a patented process that yields a pharmaceutical grade botanical drug that meets FDA guidance for a botanical drug suitable for a clinical investigation. PEX010 will be provided to Dr. Back for this study in 25 mg psilocybin capsules that have been manufactured under cGMP conditions.

4.1.1 The investigational agent will be shipped directly to Dr. Back (PI) at the Harborview Investigational Drug Service, who is working with Dr. Back on his current psilocybin study.

4.1.2 The investigational agent will be stored at room temperature at the Harborview Medical Center IDS, in a locked cabinet in the narcotics vault that has been inspected and approved for storage of psilocybin by the DEA and the Washington State Department of Health.

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria

5.1.1 A diagnosis of metastatic solid tumor, or incurable hematologic malignancy that has been accepted by a physician in a medical record.

5.1.2 Measurable disease is not required.

5.1.3 Previous treatment with chemotherapy: There are no minimum or maximum prior lines of chemotherapy.

5.1.4 18-85 years of age.

5.1.5 Required performance status, including the appropriate scale. ECOG 0-2.

5.1.6 Acceptable organ and marrow function includes:
Hematocrit >20, Plt >20K, Liver function tests 1.5x normal, Creatinine 1.5x normal.

5.1.7 Subjects of childbearing potential must be willing to use an effective contraceptive method from study enrollment until at least 1 month after receiving the investigational agent(s).

5.1.8 Must be at least 4 weeks after surgery or radiotherapy at study entry, but can be receiving oral or iv chemotherapy if those schedules can be adjusted around the medication session date;

5.1.9 Motivated to participate in a group study and able in the research team's judgment to participate in the small group effectively;

5.1.10 On pre-enrollment screening tests, they will have clinically significant anxiety or depressive symptoms as defined by a score of 11 or greater on the HADS-Total.

5.1.11 English speaking – able to understand the process of consent and the risk andbenefits associated with the study, and able to give written informed consent. This is a pilot study, and if future larger studies are designed, consideration will be given for non-english-speaking subjects.

5.1.12 Must be willing to sign a medical release for the investigators to communicate directly with their treating clinicians (mental health professional or oncologist) and doctors to confirm a medication and/or medical history.

5.1.13 Must provide at least one adult who is in contact with the participant at least once a day when the participant is at home who is able to verbally monitor participant-reported changes in the behavior and able to notify research staff of behavior changes that may require research staff assessment.

5.1.14 Has been off selective serotonin inhibitors for five half-lives of the drug plus 2weeks.

5.1.15 Must avoid taking any psychiatric medications or starting a new psychiatric medication during the study. Should participant's doctor recommend starting a new psychiatric medication, participant will be required to notify the study team and the subject would withdraw from the study. (Use of prn benzodiazepines is allowed but high dose chronic benzodiazepine use must be reviewed by the PI. Use of prn gabapentoids is allowed by high dose chronic gabapentoid use must be reviewed by the PI.)

5.1.16 Must provide a contact (relative, spouse, close friend, or other caregiver; can be the same person as in 5.1.13) who is willing and able to be reached by the research team in the event that the participant becomes suicidal.

5.1.17 If the potential participant is of childbearing potential, they must have a negative pregnancy test at baseline and prior to the medication dosing session, and must agree to use adequate birth control.

5.1.18 Are willing to commit to preparation sessions, medication dosing sessions, integration sessions, to complete evaluation instruments and commit to be contacted for all necessary telephone contacts.

5.2 Exclusion Criteria

5.2.1 Brain metastases that have not been treated.

5.2.2 Uncontrolled or concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5.2.3 Pregnancy, breastfeeding, or expecting to conceive or father children for the duration of the trial through 30 days after receipt of investigational agent(s).

5.2.4 Personal or immediate family history of schizophrenia, bipolar affective disorder, delusion disorder, paranoid disorder, or schizoaffective disorder;

5.2.5 Suicidal ideation with a C-SSRS $\geq$ 3;

5.2.6 Current substance abuse disorder (although prospective subjects will not be excluded for reasonable alcohol use that does not meet criteria for alcohol use disorder or marijuana use that does not meet criteria for substance use disorder);

5.2.7 Neuroleptic (including olanzapine, prochlorperazine, promethazine), and SSRI medications that cannot be tapered and discontinued in conjunction with the participant's prescribing physician (although ondansetron can be used for nausea);

5.2.8 Unstable neurological or medical condition; history of seizure, chronic/severe headaches;

5.2.9 Any use of psychedelic drugs in high doses (psilocybin >2 grams of dried mushrooms, LSD >200 micrograms) within the prior 12 months (microdosing will not require exclusion but participants would have to agree to discontinue microdosing 1 month before study entry);

5.2.10 Use of tramadol, due to the potential for serotonin syndrome with concomitant use of psilocybin.

5.2.11 Individuals who are on MOAI (monoamine oxidase inhibitors) or who have a known sensitivity to the drug or its metabolites. Psilocybin is contraindicated in medications that are known UGT (UDP-glucuronosyltransferase) enzymemodulators. The concurrent use of SSRI/SNRI meds 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.

5.2.12 A marked baseline prolongation of QT/QTc interval (e.g., demonstration on >1 ECG of a QTc interval >450 milliseconds (ms).

5.2.13 A history of additional risk factors for Torsade de Points (including but not limited to: heart failure, hypokalemia, family history of Long QT Syndrome) .

5.2.14 The use of concomitant medications that prolong the QT/QTc interval.

6.0 SUBJECT REGISTRATION

Subjects will be registered by the Fred Hutch/UW Study Coordinator and entered into the Clinical Trial Management System (CTMS, OnCore). A complete, signed study consent and HIPAA authorization are required for registration.

Subject IDs will be assigned by CTMS data entry.

Signed ICFs must remain in each subject's chart and must be available for verification by monitors or regulatory agencies at any time.

7.0 TREATMENT PLAN

7.1 Overview. This study is designed to define the specifications for a new model of group psilocybin-assisted therapy. We describe the design as a Phase 1/2 study because it combines features of Phase 1 and Phase 2 studies. Phase I trials are often designed as 'dose-finding' studies for new drugs that focus on toxicities and adverse events as primary outcomes. For psilocybin the individual toxicities have already been well described by prior studies. The adverse outcome of interest in this study is related to episodes during the medication session when more participants require 1:1 attention at the same moment than can be provided by the 4-person facilitation team, which this study calls ***'potentially unattended psilocybin-related distress'*** (note that backup facilitators will be on hand). This adverse event is specific to the small group design used in this study. In addition, Phase 2 studies are often designed to measure efficacy of a therapy at different doses, and in this study efficacy will be measured at different group sizes by comparing these results to historical studies for cancer patients that provided the same number of preparation and integration therapy sessions. Thus we describe this study as Phase 1/2 because it will examine both adverse events and efficacy.

7.2 Treatment Plan Schema

SCHEMA

Eligibility determination

↓

REGISTRATION

↓

3 Group Preparation Therapy visits
1 Individual Preparation Therapy visit

↓

Psilocybin Session

↓

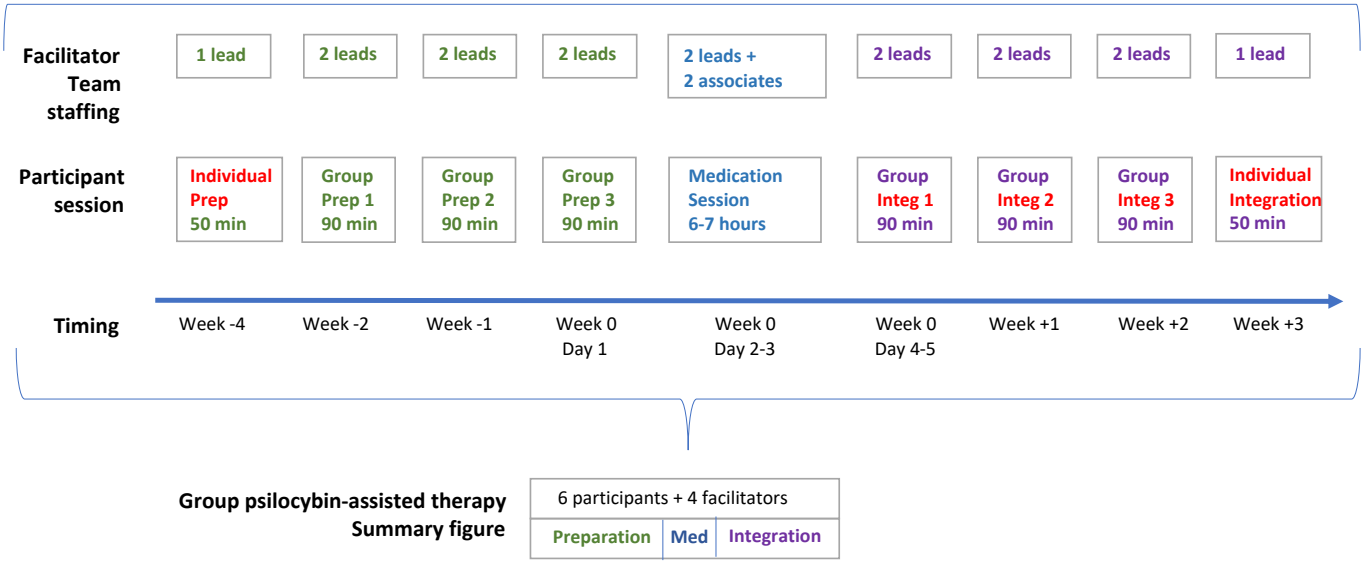
3 Group Preparation Therapy visits
1 Individual Preparation Therapy visit

(end of study treatments)

Outline Treatment Schedule	
Day	***Treatment***
-14 (+/8 days)	*Group Preparation First session (video)*
-7 (+/8 days)	*Group Preparation Second session (video)*
-1 (+/- 3 days)	*Group Preparation Third session (in person)*
-1 (+/-3 days)	*Individual Prep Visit (in person)*
0	*Psilocybin Session*

1 (+/3 days)	*Group Integration First session (in person)*
1 (+/-3 days)	*Individual Integ Visit (in person)*
8 (+/8 days)	*Group Integration Second session (video)*
15 (+/8 days)	*Group Integration Third session (video)*

The basic group intervention structure for psilocybin-assisted therapy designed for this study



7.3 Rationale. This group intervention structure is designed to allow for historical comparison to studies using individual models of psilocybin-assisted therapy. Published studies using individual models have generally used 3 preparation sessions, a medication session, and 3 integration sessions. The group model used in this study will add an individual preparation session and an individual integration session to the 3 group preparation sessions, medication session, and 3 group integration sessions. We acknowledge that many patients may wish to continue integration after the study ends, which we feel is an important research question that merits a future study. In the individual integration sessions, the facilitators will discuss when integration beyond what the study provides may be useful, and participants will receive resources on aftercare. In addition, participants will be able to contact the study facilitators for supportive calls.

7.4 Group size study considerations. An optimal group size for psilocybin-assisted therapy would have an acceptable incidence of adverse events attributable to the group nature of the intervention, **and efficacy that is comparable to individual psilocybin-assisted therapy**. For this study the adverse event of most interest will be an intense emotional experience during the psilocybin day that requires 1:1 facilitator attention. The efficacy measure will be the Hospital Anxiety and Depression score, already demonstrated to change in prior studies, which will allow historical data to be considered when assessing the potential efficacy of this group model. Since we are aware that demoralization is being used as a primary outcome in multicenter studies that are already funded, demoralization is included as another secondary outcome measure.

Our review of the group intervention literature combined with our experience with psychedelic-assisted interventions led us to conclude that a 6 person group with 4 study facilitators is an reasonable starting point for investigation. Research in cancer group psychotherapy was initiated by David Spiegel MD and Irvin Yalom MD at Stanford, and their work was based on extensive research in groups often done using approaches from depth

psychology. The state of the science now in cancer group psychotherapy that does NOT use psychedelics is a 6- to 8-person group with 2 facilitators, which gives each participant both time to speak and be heard, with minimal pressure to speak, in a 75 minute session.

Dr Back's experience in group interventions at a legal psychedelic retreat center in the Netherlands (Synthesis Institute) in 2021, (conducted with group preparation, medication day, and integration), suggests that a group of 6 – 8 would also work well for the same reasons, but also that more than 2 facilitation team members would be necessary to ensure that participant safety can be addressed (e.g. participants should be accompanied to the bathroom), and that intense emotional experiences can be addressed with periods of 1:1 attention during the medication session. Dr. Back observed that a safe and efficacious experience for participants did not require continuous 1:1 attention for the entire medication day, and that the facilitation team was able to distribute attention to participant episodes where 1:1 attention was needed under direction from a lead facilitator. Dr Back has been working as a group facilitator with the Synthesis Institute in the Netherlands (where psilocybin is legal in the form of 'truffles') at 5 legal psilocybin retreats in 2022 and also received Synthesis Institute training in emergency protocols and facilitation skills. In addition, Dr Back's group facilitation experience prior to his work with psychedelic-assisted therapy includes more than 20 years of group facilitation interventions in a series of studies funded by the National Cancer Institute.

Recent research studies from individual psychedelic medication day sessions provide useful data to estimate the rate of intense emotional experiences that would require 1:1 facilitator attention. For example, in the UCSF group psilocybin study of long term HIV survivors mentioned earlier, where group preparation and integration were used along with individual psilocybin sessions, there was a 44% rate of adverse events during the psilocybin session that were mostly time-limited episodes of fear and anxiety that were all addressed with facilitator verbal (e.g. coaching) and non-verbal interventions (e.g. presence, hand-holding) and did not require medication; the duration of these episodes was not described in the publication but none were more than 30 min (personal communication to Dr Back from the lead author Dr Anderson). A study at New York University (NYU) of psilocybin-assisted therapy for cancer patients reported a 17% rate of transient anxiety during the psilocybin sessions, also addressed by facilitator non-pharmacologic interventions; the duration of these episodes was not described but all were transient and self-limited (personal communication to Dr Back).

For the purposes of justifying the initial 6 participant group size (with 4 study facilitators) for this study, the USCF and NYU data are valuable. For a hypothetical 'worst case scenario': if this initial group of 6 participants has a 50% rate of adverse events (i.e., higher than either the UCSF group study or NYU cancer study) that are intense emotional experiences, *and* if those adverse events happen *simultaneously*, then 3 participants might need 1:1 attention for some period of time. But even in this 'worst case scenario', if 3 participants need 1:1 attention simultaneously, the 4-person facilitation team should be able to provide 1:1 attention to 3 participants easily.

It is possible that the above 'worst case scenario' may not cover all needs for 1:1 attention. In this study, there will be backup facilitators available on-site who will have been observing the group, who will be able to step in to provide additional assistance at any moment if the group monitor (who is a member of the research team but a separate role from study facilitator) and the PI decide in the moment that additional assistance is warranted.

7.5 Group size for the first group intervention. In this study, the group psilocybin-assisted therapy intervention will start with a group of 6 screened participants and a 4-person facilitation team. This will be referred to as the '6-person group level', and a 'series' of up to 4 groups will be conducted at this group size. Groups will be conducted sequentially, so that adverse events can be tabulated and analyzed for each group before starting the next group. While the number of participants in each group may vary, all groups will be run by a team of 4 study facilitators (who will have had prior specific training in psychedelic therapy and group facilitation). Dr Back and Dr McGregor will perform additional study-specific training for all facilitators, which will include ethics of consent during a psilocybin session and acceptable modalities of touch.

7.6 Rationale for facilitation team. The 4-person facilitation team is a clinically practical, adaptable model that could set a standard for future care. This team includes two lead facilitators and two associate facilitators.

--**Lead facilitator A** will (1) keep an eye on the room and allocate facilitator resources to participants who could benefit from attention, and (2) will guide participants with complex or intense emotional reactions to psilocybin. This role will be filled by the PI Dr Back for most of the groups. The lead facilitators (A and B) will be licensed healthcare providers with graduate-level professional training and clinical experience in psychotherapy. The lead facilitators (A or B) must be licensed to practice independently. Examples of acceptable professional credentials include clinical or counseling psychologist (PhD or PsyD), psychiatrist or other physician (MD or DO), Masters of Social work (MSW), licensed marriage and family therapist (LMFT), Masters Licensed Clinical Professional Counselor (LCPC), or licensed Psychiatric Nurse Practitioner (Psychiatric NP).

--**Lead facilitator B** will have the same responsibilities with the priorities reversed. The lead facilitators will work together to lead the team.

--**Associate facilitator C** responsibilities will focus on guiding participants with emotional reactions that are less complex or intense. The associate facilitators must have a bachelor's degree and at least 1 year of clinical experience in a licensed mental health care setting. In addition, a licensed physician be present on-site in the event of a physiological or psychiatric emergency.

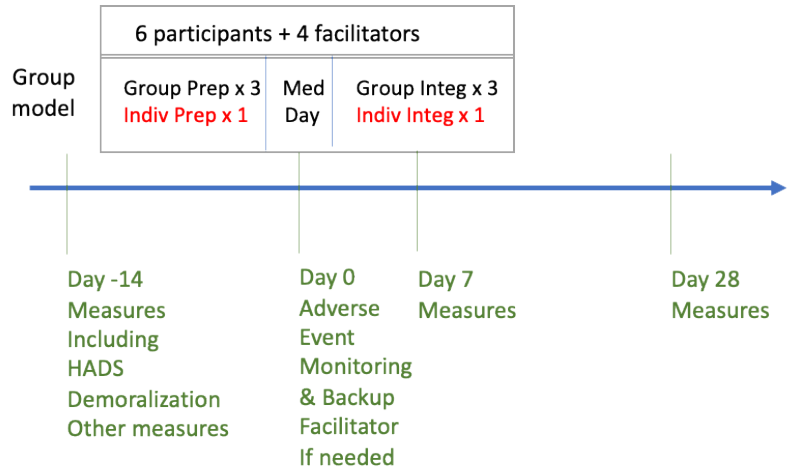
--**Associate facilitator D** responsibilities will share guiding responsibilities with A, and also provide logistical support for trips to the bathroom, water, blankets, and ways of providing comfort.

Note that this protocol uses the term 'facilitator' rather than therapist, but for this protocol these terms both refer to the same role on the research team.

7.7 The main adverse event that we anticipate is the occurrence of participant distress that needs 1:1 facilitator attention that cannot be met by the 4-person facilitation team, and we refer to this adverse event as ***'potentially unattended psilocybin-related distress'***. Three examples of this would be significant fear, intense sadness or anxiety related to ego disalusion. These conditions would all require one to one attention for a period of 10 to 40 minutes. This adverse event will be identified and recorded in real time by a group monitor who is separate from the 4-person facilitation team. If the group monitor identifies a participant who needs 1:1 attention and a member of the facilitation team is unavailable to handle the participant at the level of expertise required, the group monitor will record that occurrence as an adverse event. The groups will be videotaped so that these decisions can be reviewed later to validate the monitor's observations and decisions. In addition, the group monitor will check with the PI and will be empowered to bring in a backup facilitator to provide the participant with the attention needed, until the facilitation team can resume responsibility.

For a 6 person group, there will be 2 backup facilitators available so for any instances of 'potentially unattended psilocybin-related distress' our research team will have the capacity to provide 1:1 participant to facilitator attention all participants at all times. This design affords the ability for adverse events to be identified and recorded, while also ensuring that all group participants receive the attention they need even as group sizes are changed through the course of the study. We anticipate that 'potentially unattended psilocybin-related distress' will be most likely to occur during the 2-4 hours of peak psilocybin effect.

7.8 Timing of adverse event recording and outcome measurements for a single group



Other adverse events could challenge the capacity of the 4-person facilitation team to manage the safety of all group members adequately. For example, if more than 4 participants became seriously nauseated at the same time, at a level requiring assessment and intervention, a backup facilitator might be indicated.

Adverse events will be reviewed by the research team after each group. As the first series of 6-person groups are conducted, adverse events will be tabulated and reviewed after each medication day. These adverse events will be reviewed by the research team to determine if the next group should proceed at the same group size, or if the group size should be decreased. As a rough benchmark, we shall consider an observed adverse event rate of 10% or more as potentially too high to allow increase in group size or continued enrollment to the current group size.

7.9 Efficacy analyses will be conducted after 4 groups of the same size. The efficacy of the group psilocybin-assisted therapy intervention will be conducted after 4 groups have been conducted at one group size. The primary outcome for this analysis will be the HADS Total score, which in other studies has been shown to be responsive to psilocybin-assisted therapy in people with cancer. The primary outcome analysis from 4 groups will be informally compared to existing studies of psilocybin-assisted therapy in patients with cancer, in order to assess whether the efficacy of the group psilocybin-assisted therapy appears to be comparable to the results shown by prior published studies. The objective of this trial is not to statistically compare to historical numbers, but rather to see if the HADS values currently are roughly similar to the prior studies.[1-3]

Towards this end, we hope to see changes (pre- vs. post-psilocybin) in the HADS-Total score on the order of 1.0 standard-deviation (sd) unit. An observed effect size of 1.0 sd units or more would be largely considered to be at least comparable to previous studies and, depending on analysis of safety, could lead to an increase in the group size to see if both safety and potential efficacy can be maintained. This assessment will consider the totality of the data, not just simple the mean change in HADS and the proportion of adverse events. Other measures will be taken into account as will the demographics of the patient population and proximity to anticancer treatment.

In addition, we have included demoralization as a secondary outcome as we are aware that it is being used as a primary outcome in a multisite randomized study that will include cancer patients that is planned but are not yet recruiting participants.(Anderson, personal communication Dec 2022)

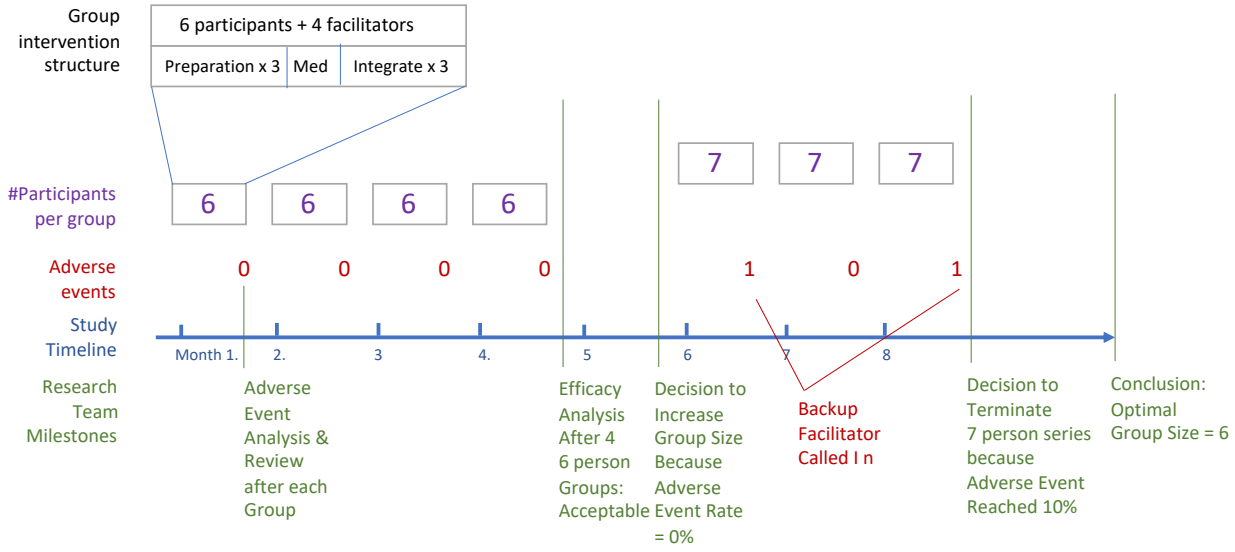
The judgment of our investigator team (that includes experience in psychedelic therapy, cancer group psychosocial interventions, and cancer clinical trial statistical analysis) is that the combination of statistical

analyses and expert judgment will result in reasonable decisions (in conjunction with a Trial Decision-Making Committee) to determine as the study progresses whether the group size should increase or decrease according to a set of Guiding Principles described below. Three examples of these decisions are described below.

7.10 Examples of how the study might proceed

Example 1 explanation. The study begins with 6 person groups, and 4 groups are conducted. No adverse events are recorded. The efficacy analysis indicates the decrease in anxiety is comparable to that seen in individual psilocybin-assisted therapy. The "Trial Decision-Making Committee" (explained further below) then decides that the group size should be increased to 7 person groups. After three 7-person groups, 2 instances of 'potentially unattended psilocybin-related distress' is recorded. Because the observed adverse event rate has reached 10%, the research team decides to terminate the study. The study recommendation would be for 6 participants with the 4-person facilitation team.

Example 1 graphic of how the study might proceed:



Two additional examples of how the study might proceed:

Example 2. The study begins with 6-person groups, and four groups are conducted. In the first four groups, 1 adverse event of a 'potentially unattended psilocybin-related distress' is recorded. The efficacy analysis of the primary outcome from these 4 groups (= 24 participants) suggests that efficacy is comparable. The Trial Decision-Making Committee makes a judgment that a group size of 8 is feasible to test. After 4 groups of 8 persons, 1 adverse event is recorded, and the efficacy analysis is comparable. The study recommendation would be that 8 person groups with a 4 person facilitation team is adequate *if* a backup facilitator is available.

Example 3. The study begins with 6-person groups, and each of the first 3 groups records 1 instance of a 'potentially unattended psilocybin-related distress'. The Trial Decision-Making Committee determines that the study continue with 5-person groups. Four 5-person groups are conducted, with zero instances of 'potentially unattended psilocybin-related distress. The efficacy analysis from the 5-person groups indicates the decrease in anxiety is comparable to that seen in individual psilocybin-assisted therapy. The study recommendation would be for 5-person groups with a 4-person facilitation team.

Trial decision-making committee

The Trial Decision-Making Committee is a specific feature of this proposal that will make decisions about how the trial should proceed with regards to group size changes over time. This committee is like a Data and Safety Monitoring Committee in that it will review adverse events data for each group, review statistical analyses of potential efficacy for each series of 4 groups, and will review individual adverse events with the investigators.

However, this committee is different from a Data Safety Monitoring Committee in that it will be composed of the study investigators and external experts (with expertise in legal group psilocybin experiences in the Netherlands, bioethics, psycho-oncology, and psychotherapy), and they will discuss changes proposed by the investigators to group size and vote on investigator proposals. The Trial Decision-Making Committee will have 5 members, including Dr Back, Dr McGregor, two study facilitators, two external experts (chosen for their expertise in group intervention clinical trials and psychedelic therapy) and one cancer patient who has experienced psychedelic therapy in a clinical trial. The PI will review trial progress and updates the committee after each group. If there are no adverse events, the committee may not meet until an efficacy analysis from a series of 4 groups at the same size is available. If there are adverse events, the committee will meet to discuss the adverse event, the outcome, and PI's proposal about how to proceed. Changes in group size of 1 or 2 participants will be allowed.

These examples define the following Guiding Principles that the Trial Decision-Making Committee will use in making decisions about group size as the study progresses:

Guiding Principle 1: Adverse group events that are directly related to exceeding the capacity of the 4-person facilitation team ensure participant safety and are critical for study determination of a safe and efficacious group size.

Adverse group events will be recorded and documented, but the study team will be able to respond to 'potentially unassisted psilocybin-related distress' within a short time (<15 min) so as to mitigate the impact on an individual study participant. As a rough benchmark, we shall consider an observed AE rate of 10% or more to be excessive.

Guiding Principle 2: Measured efficacy of the group-size-specific-outcomes is another important factor for reaching a study determination of optimal group size.

Optimal group size would have efficacy at least comparable to individual psilocybin-assisted therapy, or at least define the tradeoff in efficacy vs group size. Based on prior work, we consider benchmark for "at least comparable" to be a change in HADS-Total score from pre-psilocybin to post-psilocybin to be 1.0 sd units or more.

Guiding Principle 3: Assessment of adverse events should take into account participant-specific features and group-specific features.

A participant-specific feature might lead to refinement of screening criteria for participants rather than terminating conduct of another group at the same size. A group-specific feature might mean that 2 adverse events in a single group are given different weight than 1 adverse event in two successive groups.

7.11 Administration of Investigational Agent

The investigational agent in this study, Psilocybin PEX010, will be administered once, on Day 0, orally, with water.

7.12 Concomitant Medication and Supportive Care Guidelines

Adverse event management during the psilocybin session. Reviews of the published literature on synthesized and botanical psilocybin indicate that the physiological and psychological effects are transient. The patient will be monitored at all times by trained research and/or medical staff. The study facilitator team will remain in attendance during the entire session. On the medication day, participants will be reminded that they have agreed to remain supervised by the study facilitators until the acute effects of psilocybin have subsided, and all participants will be accompanied by a facilitator to dinner after the medication session, and then to their individual rooms for bedtime. There will be a study staff person available through the night for any concerns that a participant might raise after the medication session.

Most study procedures can and will be immediately stopped if participants request or if they are exhibiting significant distress. However during the psilocybin session, once participants have taken the psilocybin, the psychological effects cannot be immediately terminated and must be managed until the psilocybin effect has worn off. The medication day session with psilocybin will be performed in a

non-hospital setting that minimizes distraction and interruption, with a team of specially trained study facilitators and backup facilitators, and the participant will be monitored by specially trained facilitators who will have the skills to provide reassurance and a safe environment for the duration of the session.

If during the medication session, a participant does experience extreme distress, the PI may prescribe a designated 'rescue' medication in the event of symptoms that require it during or after the medication dosing session. Rescue medications may be a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment.

Following the Investigator's Brochure, although there have been no reports of their use in well-reported clinical trials with oral psilocybin, medications will be available for the treatment of causal symptomatic hypertension, agitation, or severe psychosis.

If any participant develops an adverse reaction to the psilocybin as reported by them or as assessed by a member of the research team, we will ensure that the participant receives appropriate medical or psychiatric care. The level and exact type of care will depend on whether the adverse event occurs during the medication session where study facilitators will be in attendance or after the medication session when the participant is at home. Finally, the participant may be withdrawn from the study if his/her withdrawal is in the best interests of either the participant or of the research (e.g., due to a medical condition making the procedures unsafe or any condition making interpretation of the results difficult).

***Overnight monitoring for safety if an adverse event is occurring*:** The PI and study facilitators will closely monitor the participant's medical status during all study interventions. The staff take whatever medical steps are safely possible to reduce the need for an additional holding period after the medication session is over. For the participants who opt to participate in this study at a rustic retreat center, staying overnight at the retreat center will be required, and a night call clinician will be available in-person throughout the first night after the medication session for participant concerns. For participants to opt to participate in this study at the urban day-retreat center, who return home at the end of each day, a night call clinician will be available by phone through the first night after the medication session. No published psilocybin study done since 2015 has reported the need for overnight hospital admission after a medication session involving psilocybin and while an overnight hospitalization will be available in this study, and the PI has not heard of any anecdotal cases of overnight observation being required in a clinical trial setting.

Emotional Responses and Discomfort During the Psilocybin Medication Session, or During Preparation or Integration Sessions: The study facilitators will be specially trained to work with cancer patients and also in working with group psilocybin experiences. The facilitator manual outlines first- and second-line interventions for emotional responses or any psychological reactions that may be experienced. In studies since 2000 conducted at academic research centers, no participants required 'rescue' medication for psychological reactions during the medication session or in preparation or integration sessions—emotional distress did occur, but was successfully managed with non-pharmacologic psychotherapeutic interventions.

Inappropriate Interactions with Study Facilitators. At all times during in-person preparation, medication day, and integration sessions, a therapist will not be alone and unmonitored with a participant during the psilocybin session at any time.

7.13 Duration of Therapy

Participants in this study will receive one psilocybin session, along with associated therapy sessions. The entire duration of this psilocybin-assisted therapy from Prep 1 through Integration 3 is approximately 6 weeks.

7.14 Duration of Follow-Up

Participants will receive questionnaires to complete at 1 week, 4 weeks, 8 weeks, 12 weeks, and 24 weeks after their psilocybin session.

7.15 Dosing Delays/Dose Modifications

Dosing delays are not applicable. If a subject develops a complication that requires them to withdraw from the study during the 6 weeks of therapy, we will need to re-enroll them in a new small group and they will start again from Prep 1.

Dose modifications will be not be done. The dose of psilocybin is fixed for all body weights at 25 mg, and this fixed dose has been shown to produce equivalent results in a large historical comparison to body weight dosing at the Johns Hopkins Center for Consciousness Studies.

8.0 SUBJECT EVALUATION

8.1 Clinical Evaluations

Clinical evaluations take place according to the Study Calendar (Appendix A).

8.2 Screening and Baseline Evaluations

Screening/Baseline Visits will occur within 2 months of the first zoom call. Procedures to be performed during the Screening/Baseline Visit are as follows:

- Physical Examination
- Neurological Exam
- Blood pressure
- Performance Status (specify appropriate performance scale)
- Labs (which may be done at outside labs within 2 months of the screening visit)
    - Hematology: CBC, differential, platelets
    - Serum Chemistries: including calcium, magnesium, SGOT, SGPT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, electrolytes, and glucose
- Baseline questionnaires

8.3 Psilocybin session

- Blood pressure at start of session and 1 hour after administration. If the 1 hour BP is elevated above 140/90 mm Hg, the BP will be repeated hourly until it returns to baseline
- Labs to be done at start of session
    - Urine pregnancy test for participants of childbearing potential
- At the end of the medication dosing session:
    - Participants will complete paper or computer-based questionnaires designed to assess acute subjective experiences associated with the medication dosing session within 24 hours of completing the session.
    - Study facilitators will assess the participant's mood and suicidality with the C-SSRS if indicated.
    - Participants will remain under observation by the facilitation and research team until the facilitation team judges that their perception, cognition, functioning, and judgment are adequate for them to go to bed safely.

8.4 Integration visit safety checks

- Facilitators will be alert to participant symptoms of anxiety or depression on integration visit safety checks and will reach out after the group session to any participant who may need additional support and assessment. An announcement will be made at the beginning of every session inviting any participant to send an individual chat message to the facilitator or to text the study coordinator if any concerns related to suicidality are arising. The study coordinator will then perform an C-SSRS assessment and contact the PI for further assessment.

8.5 Post-Treatment Follow-up Period (specify visits based on days after psilocybin session)

Subjects will have visits 14 days after EOT, 28 days after EOT, and 90 days after EOT. Assessments to be performed at these visits are as follows:

--Integration sessions are as follows:

Group Integration 1 is in-person, on Day 3 of the retreat
Individual Integration 1 is in-person, on Day 3 of the retreat
Group Integration 2 is about a week after leaving the retreat, is virtual, using a secure video platform
Group Integration 3 is a week after the prior session, is virtual, using a secure video platform

--Any participant who appears to display any warning signs of a worsening mood (more withdrawn, more hopeless, more helpless in any session will be contacted immediately after a session for an assessment including C-SSRS suicidality assessment. That C-SSRS would be done on a private phone or video call.

--Online questionnaires will be completed after the psilocybin session at:

2 weeks
4 weeks
8 weeks
12 weeks
24 weeks

Once these visits and assessments have been completed, the subject will be considered as having completed participation in the clinical trial. If a subject enrolls in another study or requires additional cancer treatment, the visit or assessment dates may be adjusted to accommodate the subject's schedule.

If a subject is unable/unwilling to return for any scheduled visits after the end of trial (EOT), the subject will be considered as having completed study requirements at the EOT.

8.6 Long-Term Follow-up Period (specify duration and timing)

Subjects will be contacted by site staff by telephone, email, or mail at 6 months after the psilocybin session to complete scheduled study questionnaires.

8.7 Plan of Action for A Participant Exhibiting Suicidality

For suicidality exhibited on a video call (preparation session or integration session):

--the study PI (a physician with training in assessing suicidality) or co-investigator (a PhD psychologist also trained to assess suicidality) will immediately call the participant individually, and will conduct a narrative assessment of suicidal wish, method, intent, and plan according to the FDA guidelines on assessing suicidality in clinical trials involving an IND. The assessment will also include administration of the C-SSRS, the instrument approved by the FDA for assessing suicidality in IND clinical trials.

--for a participant with active suicidal ideation (which may include method, or intent, or plan), the study PI will immediately consult the Attending Psychiatrist in the Harborview Emergency Room, who is available 24 hours/day to discuss the case.

--based on the Attending Psychiatrist's recommendations, the study PI may ask the participant to come to the Harborview Emergency Room immediately. If the participant lives a long distance from Harborview Medical Center, the study PI will contact the participant's medical provider (which the PI secures during the consent process) to find an appropriate local referral.

For suicidality exhibited at the retreat:
--the study PI (a physician with training in assessing suicidality) or co-investigator (a PhD psychologist also trained to assess suicidality) will immediately assess the participant individually in person, and will conduct a narrative assessment of suicidal wish, method, intent, and plan according to the FDA guidelines on assessing suicidality in clinical trials involving an IND (attached). The assessment will also include administration of the C-SSRS, the instrument approved by the FDA for assessing suicidality in IND clinical trials.
--for a participant with active suicidal ideation (which may include method, or intent, or plan), the study PI will immediately consult the Attending Psychiatrist in the Harborview Emergency Room, who is available 24 hours/day to discuss the case.
--If the Attending Psychiatrist recommends that the patient be seen in an Emergency Room, the study PI will discuss whether the best plan would be for the participant to be transported to the Harborview Emergency Room (a 2 hour drive) or to be seen locally at Mason General Hospital (a 15 min drive) which does not have a psychiatrist on call.

9.0 TOXICITY MONITORING

Both acute and chronic toxicities are recorded. Monitoring for acute toxicity takes place during and immediately following IP administration for a period of 8 hours at the study site. Subjects are observed for the development of an immediate localized allergic reaction or anaphylactic reaction or emotional reaction during this time.

A rare reported complication of psilocybin use is Hallucinogen Persisting Perceptual Disorder (HPPD), which results in visual perceptual distortions that are generally mild (this is sometimes described as the visual equivalent of tinnitus). This has not been reported in a recent clinical trial but this condition has been reported in anecdotes in the lay literature. Because this is a rare condition and there is no clear treatment, subjects will be warned about this in the consent process, reminded after the psilocybin session, and assessments will be individualized to the subject's symptoms.

There are no known unacceptable toxicity treatments. However, it should be noted that during the psilocybin session that emotional distress or fear or even paranoia is best treated first with facilitator attention and calming, with medical treatments like benzodiazepines or antipsychotics used as a last resort. In recent clinical trials with investigators at New York University and Johns Hopkins, these 'rescue' medications have never been used (personal communications, A. Back).

10.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion *except* during the psilocybin session. Subjects may also be removed from this protocol if they develop any untoward side effects from the study medications. In addition, there are stopping rules in place for lack of efficacy and excessive toxicity as detailed in the statistical section.

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Survival data are important to the integrity of the final study analysis. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

During the psilocybin session, the subject will be able to withdraw from the study once the study facilitators and PI have assessed the subject and determined that they are safe for discharge from the session.

Follow for subjects who withdraw will be dependent on their willingness to be in contact with the PI, but the PI will offer informal followup at the subject's convenience in order to detect and report adverse outcomes.

Subjects who withdraw will likely not be replaced unless they withdraw before the psilocybin session at a time when a new subject could be recruited to join the small group prior to the first Preparation session.

An explanation for discontinuing treatment is recorded for each subject discontinuing treatment on the appropriate CRF/eCRF. The Sponsor, or its designee, must be notified immediately if a subject discontinues treatment. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- if the Sponsor decides to stop the study;
- at Investigator's discretion;
- at the subject's request;
- if the subject enrolls in a trial of another investigational agent;
- Grade 4 or life-threatening toxicity (See Section 12, Adverse Events) attributable to study agent;
- toxicity reactions of Grade 3 or higher, according to the grading in Appendix XX - NAME Grading Scale as identified in Section 10
- pregnancy;
- any mental health emergent or urgent condition.

11.0 CONCOMITANT MEDICATIONS

- Subjects may take small amounts of topical or inhaled corticosteroids, as well as corticosteroids used as replacement therapy for adrenal steroids, e.g., <0.75 mg of dexamethasone, or equivalent.
- Subjects may take doses of nonprescription strength NSAIDS, acetaminophen (paracetamol), ibuprofen or acetylsalicylic acid (aspirin) for non-chronic headache, muscle pain, trauma, or prophylaxis as long the dosing regimens comply with the recommended dose in the product labeling.
- Subjects may receive antihistamine therapy for colds or allergies at non-prescription doses, but subjects should not take these medications within 5 days before or after IP administration.
- Subjects may take vitamin supplements within a dose range not associated with toxicity.
- Other treatments and medications that may affect immune function, that have known or suspected anti-tumor activity, or that could interfere with the imaging assessment of disease progression are not allowed for subjects prior to crossover. A list that gives examples of such therapies is included in the study manual.
- The use of other investigational agents is not permitted.
- Active immunotherapy is not allowed for any subject.

12.0 ADVERSE EVENTS

12.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

12.2 Serious Adverse Event

An AE is classified as a serious adverse event (SAE) if it meets one of the following criteria:

Fatal	The AE resulted in death.
Life threatening	The AE placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization	The AE required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	The AE resulted in a substantial and persistent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

12.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

12.4 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

Subjects who terminate early or who experience a non-serious AE considered to be possibly or definitely related to the investigational study agent will be contacted at the time intervals specified in the study for questionnaire assessments with an email asking them how they are doing. If the AE has persisted or has created complications, the PI will request a phone call to hear a more detailed report of the AE, including the information in the above list.

12.5 Grading Adverse Event Severity

All AEs will be graded in severity but this study will not use the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 because that grading scale is designed for anticancer agents. For this study we will use the following grading system that was approved by the FDA:
--Mild adverse event (does not affect patient activity)
--Moderate adverse event (mild disruption in usual activity)
--Severe (major disruption in usual activity)

12.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

Definite (must have all 4)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure
Probable (must have 3)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention
Possible (must have 2)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the participant's clinical state • Could not readily have been due to environmental or other interventions • Follows a known pattern of response to intervention
Unlikely (must have 2)	• Does not have a temporal relationship to the intervention • Could readily have been produced by the participant's clinical state • Could have been due to environmental or other interventions • Does not follow a known pattern of response to intervention • Does not reappear or worsen with reintroduction of intervention

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

12.7 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of first exposure to a study-related intervention in this study, through the date of the last questionnaire at 24 weeks. AEs with an onset date prior to the first exposure to a study intervention will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

12.8 Adverse Event Reporting Requirements

12.8.1 Reporting to the IRB

The investigator or designee must report events to the IRB of record in accordance with the policies of the IRB for expedited reporting and continuing review.

12.8.2 Reporting to the Coordinating Center [and/or Lead Investigator]

There are no external clinical sites. Thus the PI will be collecting all reports of AEs directly and an additional procedure is not required.

12.8.3 Reporting to FDA

The sponsor-investigator assumes responsibility for IND safety reporting to the FDA and participating investigators, in accordance with regulations under 21 CFR 312.32.

The sponsor-investigator will assess each reported event for seriousness, expectedness, and the relationship to the investigational product.

For determination of IND safety reporting, AE attribution will be assessed according to the suspected adverse reaction definition in 21 CFR 312.32, as an AE for which there is a reasonable possibility that the drug caused the adverse event, where "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reactions that are serious and unexpected will be reported to the FDA as an IND safety report.

SAEs that do not meet IND Safety Report criteria will be reported to the FDA as part of annual reporting responsibilities described under 21 CFR 312.33.

12.8.4 Reporting to Psilo Scientific Ltd

Psilo Scientific Ltd is providing the investigational product for use in the study. All SAEs occurring during the AE reporting period must be reported to Psilo Scientific within 5 days of study team awareness by the study PI.

13.0 CRITERIA FOR ENDPOINT EVALUATIONS

All the endpoint evaluations in this study are self-reported questionnaires addressing mental health symptoms, quality of life, and other symptoms. All the evaluation questionnaires are scientifically validated, are listed in the the Schedule of Evaluations (Appendix A) and are included in the IRO application.

14.0 ASSESSMENT OF EFFICACY

14.1 Efficacy and endpoint assessment

Note that the primary endpoint in this study is an adverse event, and efficacy is the secondary endpoint.

Primary Endpoint: Potentially unattended psilocybin-related distress, which is defined as the occurrence of participant distress that needs 1:1 facilitator attention that cannot be met by the 4-person facilitation team.

The secondary endpoint is the measurement of symptoms of depression and anxiety using the Hospital and Anxiety Depression Scale-Anxiety score (HADS) at 28 days (4 weeks) after the psilocybin session.

14.2 Method and Timing

Primary endpoint: Will be assessed by a study monitor, who will in attendance at the psilocybin session, and will note potentially unattended psilocybin-related distress, alert the PI or one of the lead facilitators immediately. When either the PI or lead facilitator confirms the study monitor's determination that a potentially unattended psilocybin-related distress event has occurred, the backup facilitator will be immediately brought in. This endpoint could occur at any time during the 6-8 hour psilocybin session but is most likely between hours 2-4, when the psilocybin is having its peak effect.

Secondary and exploratory endpoint: Questionnaires that will be completed online according to the study schedule in Appendix A.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design

This study was designed in close consultaton with Ted Gooley PhD, biostatistician, to adapt an approach used for Phase 2 dose-finding studies to this Phase 1/2 group-size-finding study.

15.2 Objectives and Hypotheses

Primary Objective: **To test the safety, tolerability, and feasibility of a group model for psilocybin-assisted therapy for patients with stable metastatic cancer with clinically significant anxiety.**

Hypothesis:. The number of participants per group in a small group model of psilocybin-assisted therapy administered by a 4-person facilitation team that demonstrates safety will be between 6 and 8 participants with stable metastatic cancer.

Secondary Objective: **To explore the efficacy of the group model of psilocybin-assisted therapy on symptoms of anxiety, depression, demoralization, quality of life, and cancer-related post-traumatic stress.**

Hypothesis: The small group model of psilocybin-assisted therapy with demonstrated safety will also demonstrate efficacy, defined as improvement in the Hospital Anxiety and Depression Scale—Total score (HADS-Total) that is comparable to historical data from studies using an individual model of psilocybin-assisted therapy.

15.3 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

Primary outcome analyses. Descriptive statistics will be used to analyze '***potentially unattended psilocybin-related distress'***, and will be tabulated after each group intervention (which will happen approximately every month). The Trial Decision-Making Committee will review adverse event reports after each group, and will make a recommendation about how the trial should proceed (e.g., proceed at same group size; proceed at smaller size; or if 4 groups at the same size have been conducted, proceed to efficacy analysis). Thus we will change the facilitator:patient ratio based on the observed number of 'potentially unattended psilocybin-related distress' events. (See examples in Section 7.10) In the same way that a 10% incidence of certain non-life-threatening drug-related toxicities are considered clinically acceptable in routine practice for anticancer agents, a 5-10% incidence of psilocybin-related distress in a group setting that requires calling in an extra facilitator may in the future be considered clinically acceptable if group psilocybin-assisted therapy is demonstrated to have that level of safety in this study.

Efficacy analyses of measures of anxiety and other symptoms. A pre-post analytic strategy will be used for a series of 4 groups, with the primary measure (HADS) compared at Day -14 (where the medication day = Day 0) and Day 28. We expect that we will see in improvement in the mean HADS value (day 28 vs. day -14), where "improvement" is meant as a mean change in HADS of less than zero. There is no comparison group in this trial, and for each group size, we'll be estimating the "effect size" of change in HADS, where effect size is defined as

the mean change divided by the standard deviation of change. To calculate standard deviation, we shall ignore the potential "group" effect and consider all individuals within an intervention group as independent from each other as well as independent from individuals from other intervention groups. While we are hoping to see changes in HADS that are at least comparable to previous studies and this assessment will be descriptive, we will formally test the null hypothesis that the mean change in HADS is statistically different from the fixed value of 0. With 24 subjects (4 6-person groups) and assuming independence between subjects, this study will have 90% power to observe a statistically significantly (at the one-sided significance level of 0.05) reduced change from the fixed value of 0 if the true distribution of change in HADS is 0.6 standard-deviation units from 0.

The Trial Decision-Making Committee will review efficacy analyses after each series of 4 groups at the same size, and will make a recommendation about how the trial should proceed (e.g., proceed at larger group size if efficacy comparable to historical data; proceed at smaller group size, if efficacy is not comparable; or conclude trial).

15.4 Randomization

All subjects in this study will be receiving psilocybin. A future study could compare group psilocybin-assisted therapy to individual psilocybin-assisted therapy with random assignment to each study arm.

15.5 Exploratory Analysis

Descriptive statistics will be used for the exploratory outcomes in order to allow for comparison to historical controls, as a secondary analysis of efficacy. A qualitative interview after Visit 8 and before Visit 9 will provide subject perspectives on the group experience, what might be improved in future studies, and the value of interacting with other group members during the therapy sessions and at the retreat.

16.0 DATA MANAGEMENT/CONFIDENTIALITY

16.1 Data Type

A. Types and amount of scientific data expected to be generated in the project:

This study will provide data from scientifically valid questionnaires and a qualitative interview completed by study subjects who provide ratings and descriptions of their symptoms, and experience with psilocybin-assisted group therapy. In addition, this study will collect data on blood pressure, subject distress, and subject adverse events during the psilocybin session.

The questionnaires include questions about mental health symptoms (including depressive symptoms, anxiety, demoralization, post-traumatic growth), suicidality, and future plans (advance care planning). A complete list of the questionnaires is in Appendix A.

B. Scientific data that will be preserved and shared, and the rationale for doing so:

The raw questionnaire data, interview data, and blood pressure, distress and adverse event data, and data for administrative linkages will be stored within a secure computing environment. All direct respondent identifiers (e.g., names and addresses) will be removed and maintained in a secure file for future contact purposes.

If this scientific data is shared in the future (no plans exist at this time, subject identifiers will not be shared.

C. Metadata, other relevant data, and associated documentation:

Documentation to be made publicly available to the research community will include a list of the questionnaires (which are publicly available), study procedures, qualitative codebook, and research procedures (such as components of the screening evaluation), as well as study-level meta-data.

16.2 Related Tools, Software and/or Code:
Scientific data will be processed and analyzed with SAS, SPSS, and Excel, as well as Dedoose for qualitative data.

16.3 Standards
To facilitate data use, the study will use standard processing and documentation protocols adopted by the Inter-university Consortium for Political and Social Research (ICPSR) for data formats and dictionaries as well as for variable names, descriptions, and labels.

Demographic, economic, and relationship questions will be based on NCI standards.

16.4 Data Preservation, Access, and Associated Timelines
A. Repository where scientific data and metadata will be archived:
Data and metadata will be archived on secure UW research servers. Access is restricted to authorized study staff.

B. Who will receive what records, where, and when.
Only authorized study staff will have access to identifier files, study databases, and CRFs. CRFs that are completed by hand during psilocybin sessions will be stored in a locked cabinet in the PI's office, and will be transferred to electronic data files stored on secure UW servers designed for research data.

C. Protections for privacy, rights, and confidentiality of human research participants:
Subjects' identifying information is only accessed by approved staff as part of the project duties within a secure computing environment. All questionnaire data will be identified only by a study code during collection and analysis.

The privacy, rights, and confidentiality of human subject participants in this study will be protected through the suppression of all direct respondent identifiers, the careful classification of any potentially identifying data as restricted access, and we have applied for a Certificate of Confidentiality.

16.5 Oversight of Data Management and Sharing:
Monitoring of and compliance with this Data Management and Sharing Plan will be the responsibility of the project's Principal Investigator. The plan will be implemented and managed by professional staff working under the direction of the PI.

17.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/UW/SC Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study

progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these committees and other institutional, state, and federal guidelines.

18.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and oversight of the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The PI must ensure that all subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to undergoing any study-related procedures.

19.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

19.1 Pre-Study Documentation

The following documentation required by the FDA must be received by the IND Sponsor, or its designee, prior to initiation of the trial: FDA Form 1572; curricula vitae of the PI and all Sub-Investigators; signed Protocol Agreement; copy of the correspondence from the IRB indicating approval of the protocol and Informed Consent Forms, signed by the IRB chairperson or designee; an IRB membership list containing the names and occupations of the IRB members; copy of the Informed Consent Forms that were reviewed and approved by the IRB.

19.2 Study Site Training

Before initiation of the study, the IND Sponsor or its designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, CRF/eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF/eCRF completion will be provided.

19.3 Documentation

The documentation of clinical data must be stored by the IND Sponsor according to legal requirements. The PI and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the IND Sponsor (if applicable), the FDA, and/or other applicable regulatory agencies at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the FDA (as needed), IRB, site, and IND Sponsor (if applicable)); and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

19.4 Access to Source Data

The PI will permit the Cancer Consortium representatives or, if applicable, IND Sponsor's representatives, to monitor the study as frequently as deemed necessary to determine that protocol adherence and data recording are satisfactory. The CRF/eCRF and related source documents will be reviewed in detail at each site visit. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for

participation in this study and other medical records as required to confirm information contained in the CRF/eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the IND Sponsor, IRB, and other committees, as well as screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

19.5 Data Collection

Electronic case report forms must be completed and submitted for each subject enrolled in the study. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the PI. All data fields in the CRF/eCRF must be completed to avoid queries.

19.6 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB approval and FDA authorization to proceed (if applicable). The IND Sponsor is responsible for submitting protocol amendments to the FDA as described in 21 CFR § 312.30 (Protocol Amendments) and other regulatory agencies according to national, state, or local requirements.

For this study, the IND Sponsor-Investigator, or its designee, is always available to answer protocol- or subject-related questions.

19.7 Study Monitoring and Data Collection

The IND sponsor-investigator will monitor adherence to the protocol, applicable FDA regulations and/or other regulatory agencies national, state, or local requirements, and the maintenance of adequate and accurate clinical records. Electronic case report forms are reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The IND Sponsor or its designee is permitted to access source documentation as needed to appropriately monitor the trial.

19.8 Disclosure of Data/Publication

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, and by the IRB.

19.9 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH E6 (R2) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

19.10 Informed Consent

The PI assumes the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies

available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The IND Sponsor or designee will review the informed consent prior to submission to the IRB. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the IND Sponsor or designee (if applicable) and approved by the IRB prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

19.11 Institutional Review Board

The PI will assure that an appropriately constituted IRB that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH E6(R2) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB for its review and approval.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB, and that no changes will be made to the protocol without prior IND Sponsor (if applicable) and IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

If the study is under an IND, copies of relevant study-related correspondence between the Investigator and the IRB may be provided to the IND Sponsor, or its designee, by the Investigator. The PI or designee must promptly notify the IRB of any SAE occurring at the site or of any safety reports received from the IND Sponsor or designee according to the requirements of the IRB of record. The Investigator or designee will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

19.12 Subject Privacy

The IND Sponsor and the Investigator affirm and uphold the principle of the subject's right to privacy. The IND Sponsor, its designees, and the Investigator shall comply with applicable national and local privacy laws.

To verify compliance with this protocol, the IND Sponsor or designee will require that the Investigator permit the IND Sponsor or designee's monitor to review the subject's original medical records. Should access to such medical records require a waiver or authorization separate from the statement of Informed Consent, the Investigator will obtain such permission in writing from the subject before the subject is entered into the study.

20.0 STOPPING THE STUDY

The Sponsor-Investigator may decide to stop the study at any point, for any reason. The following reasons will lead to premature termination of the trial:

- New convincing information leading to unfavorable risk-benefit assessment of the investigational agent, including occurrence of significant toxicity associated with the investigational agent.
- Sponsor-investigator's decision that continuation of the trial is unjustifiable for medical or ethical reasons.

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22.0 APPENDICES

Appendix A: Study Calendar
Appendix B: ECOG Performance Status Scale

Appendix A Study Schedule

Schedule for Activities For A Participant									
Purpose	**Screen visi**	**Group Prep #1**	**Group Prep #2**	**Group Prep #3**	**Medi-cation**	**Integra-tion #1**	**Integra-tion #2**	**Integra-tion #3**	**Follow -up**
Study day	**-15+**	**-14**	-7	**-1**	**0**	**1**	**8**	**15**	**28**
Visit number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Research activity									
Demographics	X								
Eligibility Determination	X								
Medical exam	X								
Informed consent	X								
Caregiver contact info	X								
Labs, ECG, urine tox review	X								
Pregnancy screen (if applicable)	X				**X**				
PI review of inclusion/exclusion	X								
Psychiatric evaluation	X								
Education re expectations	X	X							
Preparation Session (group)		X	X	X					
Preparation Session (individual)				X					
Medication (psilocybin)					X				
Medication dosing monitoring					X				
Integration psychotherapy						X	X	X	
Adverse event reporting		X	X	X	X	X	X	X	X
Research activity									
Measures									
Hosp Anxiety Depr Scale (HADS)	X	X					X		X
FACT-G		X					X		X
CES-D		X					X		X
Adjustment Disorder Questionnaire		X					X		X
Watts Connectedness Scale		X					X		X
Peace Acceptance (PEACE)		X					X		X
NIH-HEALS		X					X		X
Demoralization II (DS-II)		X					X		X
Death and Dying Distress Scale		X					X		X
Suicidality (C-SSRS)*	X	X	X	X	X	X	X		
Mystical Experience Questionnaire**					X				
Emotional Breakthrough					X				
Challenging Experiences Q**					X				
Communitas Scale**					X				
Psychedelic Music Questionnaire**					X				
Qualitative interview***									X
Adverse events	X	X	X	X	X	X	X	X	X

*Note that the C-SSRS, a clinician-administered instrument that is required at the screening visit. Visit 3 (the day before the psilocybin session), and Visit 5 (the day after the psilocybin session. At other visit, the C-SSRS will be done at the discretion of the facilitators and will require an individual call (it will not be administered during a group visit).
**The time window for completing the V4 questionnaires is 24 hours.
***The qualitative interview will be done during a time window starting after V8 up to V9.

Follow up measures for participants randomized to psilocybin			
Purpose	**Follow up**	**Follow up**	**Follow up**
Study Day	56 (8 wk)	84 (12 wk)	168 (24 wk)
Visit number	**V9**	**V10**	**V11**
Research activity			
Measures			
Hosp Anxiety Depr Scale (HADS)	X	X	X
FACT-G	X	X	X
CES-D	X	X	X
Adjustment Disorder Questionnaire	X	X	X
Watts Connectedness Scale	X	X	X
Peace Acceptance (PEACE)	X	X	X
NIH-HEALS	X	X	X
Demoralization II (DS-II)	X	X	X
Death and Dying Distress Scale	X	X	X
Adverse events	X	X	X

Please note that these "Visits" are not actually in-person or virtual visits but are questionnaire followups only, but we are calling them "Visits" for the purpose of data tracking and analysis.

*Note that the C-SSRS will not be done at Visits 9, 10, and 11 because those Visits do not involve clinician contact.

Appendix B ECOG Performance Scale

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead