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# Treatment with Psilocybin for Chronic Neuropathic Pain and Depression (TRANSCEND): An Open-Label Clinical Trial

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# STATEMENT OF COMPLIANCE

This clinical trial will be carried out in accordance with the following:

- International Conference on Harmonisation Good Clinical Practice (ICH GCP)
- Tri-Council Policy Statement 2018 (TCPS 2)
- ISO 14155:2020 for Medical Device Clinical Trials
- Personal Health Information Protection Act (PHIPA), 2004; Chapter 3 Schedule A (PHIPA) and applicable regulations
- Food and Drugs Act
  - Part C, Division 5 of the Food and Drug Regulations
- Institutional and REB policies and procedures

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Signature of PI Date

# LIST OF ABBREVIATIONS

| | |
|---|---|
| *AE* | *Adverse Event* |
| *ALT* | *Alanine aminotransferase* |
| *AST* | *Aspartate aminotransferase* |
| *ATC* | *Anatomical Therapeutic Chemical* |
| *ATHF* | *Antidepressant Treatment History Form* |
| *CAMH* | *Center for Addiction and Mental Health* |
| *CGI* | *Clinical Global Impression Scale* |
| *CIHR* | *Canadian Institutes of Health Research* |
| *CRF* | *Case report form(s)* |
| *C-SSRS* | *Columbia-Suicide Severity Rating Scale* |
| *DMT* | *5-Hydroxytryptamine* |
| *ECG* | *Electrocardiography* |
| *ECT* | *Electroconvulsive therapy* |
| *EDI* | *Equity, diversity, and inclusion* |
| *GAD-7* | *Generalized Anxiety Disorder 7-Item Scale* |
| *GCP* | *Guidelines for Good Clinical Practice* |
| *HamD-17* | *Hamilton Depression Rating Scale* |
| *HDPE* | *High-density polyethylene* |
| *HIPPD* | *Hallucinogen-induced persistent perceptual disorder* |
| *HPMC* | *Hydroxypropyl methyl cellulose* |
| *GCP* | *Good Clinical Practice* |
| *ICF* | *Informed consent form* |

| | |
|---|---|
| *IP* | *Investigational product* |
| *IPAC* | *Infection prevention and control* |
| *LANSS* | *Leeds Assessment of Neuropathic Symptoms and Signs* |
| *LSD* | *Lysergic acid diethylamide* |
| *MADRS* | *Mongomery-Åsberg Depression Rating Scale* |
| *MDD* | *Major depressive disorder* |
| *MDE* | *Major depressive episode* |
| *PAP* | *Psilocybin-Assisted Psychotherapy* |
| *PHI* | *Personal Health Information* |
| *PHIPA* | *Personal Health Information Protection Act* |
| *PI* | *Principal Investigator* |
| *PRN* | *Pro Re Nata* |
| *PROMIS-PI* | *Patient Reported Outcomes Measurement Information System-Pain Intensity Scale* |
| *PROMI-Interference* | *Patient Reported Outcomes Measurement Information System-Pain Interference Scale* |
| *QI* | *Qualified Investigator* |
| *RCT* | *Randomized controlled trial* |
| *REB* | *Research ethics board* |
| *rTMS* | *Repetitive Transcranial Magnetic Stimulation* |
| *SAE* | *Serious Adverse Event* |
| *SCID-5* | *Structured Clinical Interview for DSM-5* |
| *SETS* | *Stanford Expectations of Treatment Scale* |

*SHAPS* *Snaith-Hamilton Pleasure Scale*

*SSRI* *Selective Serotonin Reuptake Inhibitor*

*SUSAR* *Suspected unexpected serious adverse reaction*

*TASS* *Transcranial Magnetic Stimulation Adult Safety Screen*

*TCPS 2* *Tri-Council Policy Statement*

*TRD* *Treatment Resistant Depression*

*TSC* *Trial Steering Committee*

*WEMWS* *Warwick-Edinburgh Mental Wellbeing Scale*

*WHO-QoL-BREF* *World Health Organization Quality of Life Questionnaire – Brief Version*

*5D-ASC* *Five Dimensions of Altered States of Consciousness*

# CLINICAL TRIAL SUMMARY

| | |
|---|---|
| **Title** | Treatment with Psilocybin for Chronic Neuropathic Pain and Depression (TRANSCEND): An Open-Label Clinical Trial |
| **Short Title** | TRANSCEND |
| **Phase** | II Feasibility Trial |
| **Methodology** | Open Label Clinical Trial |
| **Clinical trial Duration** | 24-months to complete all recruitment, study procedures, and data analysis. |
| **Participating site(s)** | CAMH |
| **Objectives** | To assess the feasibility, tolerability, and preliminary efficacy of psilocybin therapy for adults with chronic neuropathic pain and co-morbid TRD to inform a larger RCT |
| **Number of Participants** | Sixteen participants diagnosed with treatment resistant depression and chronic neuropathic pain |
| **Study Intervention Reference Therapy/Comparator** | 25 mg of psilocybin taken in conjunction with psilocybin-assisted psychotherapy (PAP). |
| **Duration of Intervention** | One day: 5-6 hours |
| **Statistical Methodology** | Characteristics of the trial cohort will be summarized by mean (SD), median (minimum, maximum). Summary raw scores will be presented at each assessment time both numerically and graphically. The small sample size means that conservative nonparametric testing is required in order to address the primary and secondary objectives. Exact paired permutation t-tests will be used to determine whether psilocybin-assisted psychotherapy achieves a 50% reduction in MADRS and a reduction in both pain intensity and pain interference. |

# 1.0 INTRODUCTION

## 1.1 Background

Treatment-Resistant Depression (TRD) affects up to a third of all depressed individuals (Wiles et al., 2013). Major depressive disorder (MDD) is a leading cause of disability worldwide. Although depressive symptoms are amenable to pharmacotherapy, a high proportion of patients experience TRD, typically defined as not responding to two or more adequate antidepressant trials, or relapse during treatment (Gaynes et al., 2020; Rush et al., 2006). TRD is associated with a significant decline in social and occupational functioning and higher rates of death by suicide and all-cause mortality (Reutfors et al., 2018). Persistent symptoms in TRD often translate into substantial increases in work loss, healthcare resource utilization, and costs, compared to more responsive forms of illness (Li et al., 2020). Current pharmacotherapy for TRD, including augmentation of antidepressants with atypical antipsychotics, lithium, or ketamine have high rates of non-response (Carter et al., 2020) and can be associated with problematic adverse effects (e.g., sedation, weight gain, diabetes, tardive dyskinesia) leading to non-adherence (Ho et al., 2017). Electroconvulsive therapy (ECT) is the most efficacious intervention for TRD. However, many patients with TRD refuse ECT because of stigma, lack of access, and fears of cognitive adverse effects (Wilkinson et al., 2021). Transcranial magnetic stimulation (rTMS) is an alternative to ECT but its response and remission rates are similar to pharmacotherapy (Carter et al., 2020), leaving a large proportion of patients with TRD in need of novel interventions.

Chronic neuropathic pain is a debilitating condition that causes shooting, burning and stabbing sensations that are often constant and unrelenting in severity. The impact on quality of life is substantially more than in other chronic pain conditions, with 17% of neuropathic pain patients rating their condition as “worse than death”(Torrance et al., 2014). Unfortunately, the condition is common, affecting 10% of Canadians resulting in significant economic costs in terms of healthcare utilization and lost productivity (Schaefer et al., 2014; VanDenKerkhof et al., 2016). Despite the high prevalence and severe disease burden, few therapeutic options are available for individuals with chronic neuropathic pain. While guidelines and recommendations for medications to treat neuropathic pain exist, evidence demonstrates that even first-line agents have limited efficacy and poor tolerability(Derry et al., 2019; Ferreira et al., 2023; Moore et al., 2014). Another reason for the high rate of treatment resistance could be that an estimated 40-80% of patients with neuropathic pain also suffer from concurrent major depressive disorder (MDD)(Bair et al., 2003; Cherif et al., 2020).

Research has shown that co-morbid pain and MDD confers worse outcomes than either disease alone (Dhanju et al., 2019). Patients with pain and co-morbid MDD have more pain complaints, greater pain intensity, higher healthcare utilization and longer duration of pain(Bair et al., 2003). Despite the relatively high prevalence and severe disease burden, few therapeutic options are available for individuals with co-morbid chronic neuropathic pain and MDD. While antidepressants are often considered in the treatment of neuropathic pain, patients with co-morbid disease are more likely to have persistent

pain that is refractory to treatment (Burton et al., 1995; Emir et al., 2017). Therefore, a significant unmet need exists for novel therapies that effectively manage concomitant neuropathic pain and MDD.

## 1.2 Study Intervention

Psilocybin is a chemical compound that naturally occurs in certain species of mushrooms, (for example, in the psilocybe genus, among others). It belongs to a class of drugs referred to as 'psychedelics'. Psilocybin is a tryptamine that is chemically similar to the neurotransmitter, serotonin, and the essential amino acid, tryptophan (Johnson et al., 2019). It is considered a 5-hydroxytrptamineric (serotonergic) psychedelic along with other similar drugs such as dimethyltryptamine (DMT) and lysergic acid dieythamide (LSD). Psilocybin is a prodrug for the pharmacologically active ingredient psilocin, which readily crosses the blood-brain barrier and acts as a potential partial agonist at serotonin $5HT_{2A}$ and $5HT_{2c}$ receptors in the brain (Halberstadt et al., 2011; Madsen et al., 2019). Typical effects of psilocybin include significantly altered states of consciousness, experienced through visual and sometimes auditory effects, changes in perception, distortions of time, and a range of effects including a sense of awe, novel perspectives, existential and personal insight, dramatically heightened empathy and feelings of compassion, strong emotions, and unitive experience. These mystical experiences are correlated with improvements in mood in healthy volunteers and palliative patients with end-of-life distress

Psilocybin-assisted psychotherapy (PAP) has been gaining traction as a promising potential treatment for many mental illnesses, including end-of-life anxiety and treatment-resistant depression (Perkins et al., 2021). PAP procedures typically involve psychological preparation prior to therapist-supported psilocybin dosing sessions. These sessions are used to establish a therapeutic relationship, inform participants about what to expect, and set expectations for the dosing session. During the psilocybin dosing session, trained therapists support the individual through their experience and psychological integration therapy occurs after the dosing experience. Evidence from recent clinical trials suggest that PAP can help in the reduction of anxiety, depression, and substance use (Carhart-Harris et al., 2021; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Further, there is also preliminary data suggesting that psilocybin may be effective for a myriad of pain conditions (Castellanos et al., 2020; Goel et al., 2023). With proper screening and preparation, psilocybin has a safe physiological and psychological profile.

## 1.3 Preclinical Data to Date

Animal studies looking into the effects of psychedelics in rodents have found evidence for improvements in behavioral outcomes, assessed by measures of coping strategy and cognitive function. The long-term effects using LSD (Buchborn et al., 2014; Hibicke et al., 2020), psilocin (Horsley et al., 2018), psilocybin (Hibicke et al., 2020), and DMT (Cameron et al., 2019; Cameron et al., 2018) were comparable to traditional treatment antidepressants. Moreover, there is evidence suggesting improvements in dimensions of

cognitive function, such as enhanced associative learning (Buchborn et al., 2014; Harvey, 2003) which are commonly impaired in major depressive disorder (Castaneda et al., 2008). Similarly, psilocybin also has a high affinity for the 5-HT2A receptor. The intensity of psilocybin-induced perceptual changes is correlated with serotonin 2A receptor (5-HT2AR) activation (Madsen et al., 2019). In a study involving 8-week old mice exposed to a chronic multimodal stress paradigm, hedonic state was assayed with an appetize choice task: a two-bottle sucrose preference test comparing consumption of a 1% sucrose solution and water (Hesselgrave et al., 2021). Psilocybin injections restored preference for sucrose solution whereas mice given a saline injection retained low sucrose (Hesselgrave et al., 2021). In the second part of the study, researchers pre-treated the mice with a 5-HT2A/2C antagonist prior to the psilocybin or saline injection. The results indicated that the behavioural responses to the sucrose test were not prevented when the antagonist was administered (Hesselgrave et al., 2021).

Pre-clinical studies have demonstrated that both MDD and chronic pain share common biological pathways and neurotransmitters (Bair et al., 2003). The emerging evidence on the underlying mechanisms of psilocybin's therapeutic effects suggest that it could lead to improvements for patients experiencing chronic pain, especially neuropathic pain. While the exact pathways through which psilocybin produces its therapeutic benefits are not fully elucidated, pre-clinical studies have suggested several possibilities including anti-inflammatory effects via activation of the serotonin 5-HT2A receptor and disruption of spatiotemporal patterns of brain activity (Carhart-Harris et al., 2014; Kuner & Flor, 2016).

## 1.4 Clinical Data to Date

During the past decade, there has been a resurgence of interest in psychedelic compounds as novel treatments for mental disorders including TRD. In particular, psilocybin, the chemical component of "magic mushrooms" at doses of 20-30 mg, in conjunction with supportive psychotherapy, has shown large and sustained antidepressant effects in patients with MDD and TRD in contemporary open-label and randomized clinical trials (RCTs) (Carhart Harris et el., 2016; Carhart Harris et al., 2021; Davis et al., 2021). For instance, in an open-label trial of psilocybin-assisted psychotherapy (PAP), 63% of 19 participants with TRD responded 1 week after treatment, and 32% were not on any antidepressant or therapy for a further year (Carhart Harri et al., 2016). Similarly, an RCT of 24 participants with MDD showed large effect sizes for PAP at week 1 (Cohen d = 2.5) and week 4 (Cohen d = 2.6) post-treatment compared with waitlist control (Davis et al., 2021). A long-term follow-up study of the same participants showed response and remission rates of 75% and 58%, respectively, at 12 months (Gukasyan et al., 2022). More recently, a trial comparing PAP with escitalopram in 59 participants with non-refractory MDD showed that PAP was as effective as escitalopram in reducing depressive symptoms with no differences in adverse effects between groups (Carhart Harris et a;., 2021). Recently, an international phase II RCT of PAP for 233 patients with TRD was completed. Preliminary findings indicate that

psilocybin 25 mg led to a significant reduction in scores on the Montgomery-Abserg Depression Rating Scale (MADRS) for at least 6 weeks post-treatment, compared to psilocybin 1 mg (an active placebo), without significant differences in serious adverse events between groups (COMPASS, 2021).

Further, the improvements seen in mood in participants of previous psilocybin therapy trials may also lead to benefits in chronic pain especially those with co-morbid MDD (Bondesson et al., 2018). A recent review of proposed mechanisms for psychedelics (including psilocybin) to affect chronic pain, deemed that the strongest evidence for any therapeutic potential is for neuropathic pain states (Castellanos et al., 2020). Thus, there is established plausibility based on existing data that psilocybin could be particularly helpful for patients suffering with comorbid chronic neuropathic pain and MDD.

While these theoretical mechanisms demonstrate promise, the benefits have not yet been translated into clinical evidence. Our team conducted a scoping-review of studies examining the use of psychedelics to treat chronic pain conditions (Goel et al., 2023). After a systematic search, we identified 21 studies of which 13 included psilocybin. Further, only 3 case reports described a change in both mood and pain. Although the general trend was that psychedelics improved outcomes for patients with chronic pain, study designs with a high risk of bias and small sample sizes precluded conclusions about their therapeutic effects.

This vacuum of clinical evidence has unfortunately been occupied by a “psychedelic hype bubble” with some media communications touting psychedelics as a ‘miracle cure’ for a myriad of ailments (Yaden et al., 2022). Without evidence to guide therapeutic decisions, patients who are desperately seeking relief from their pain are particularly vulnerable and at risk of suffering adverse effects that range from financial costs to psychological deterioration (Yaden et al., 2022). In one study of 354 patients with chronic pain, 30% reported prior psychedelic use and the majority had a favorable view of psychedelics as a form of treatment (Glynos et al., 2023).

The mismatch between evidence and perception amongst pain patients, creates an urgent need for a feasibility trial to fill this significant gap in the field. While there is an exponential growth in the number of clinical trials proposed related to psychedelics and mental health, this is not true for chronic pain. A review of Health Canada’s Clinical Trial Database shows that there is only a single, industry-funded study examining the use of psilocybin for opioid-weaning in chronic pain patients in Canada (NCT05585229). However, this study has significant design flaws such as the fact that patients with a wide range of chronic pain condition from migraines to fibromyalgia can be included. Further, a search of Clinicaltrials.gov shows that there are no currently registered trials that will be examining psilocybin for general neuropathic pain. Thus, the proposed trial would be ground-breaking, representing a significant advancement towards understanding the role of psychedelics in chronic neuropathic pain therapy, in Canada and globally.

*We propose an open label, proof of concept study in 16 adult patients with chronic neuropathic pain and comorbid TRD where each participant will receive 25 mg of psilocybin.*

## 1.5 Risks/Benefits

Possible Benefits

As with any research study, no direct benefit can be promised to research participants. Clinical trials investigating psilocybin-assisted psychotherapy in depression cohorts have indicated rapid and dramatic reductions in participants' symptoms. Participants may also experience improvements in chronic pain symptoms. Therefore, participants may receive some benefit from the study if PAP is effective in improving depressive symptoms and symptoms of chronic pain. Participants may also benefit from close monitoring of their clinical conditions.

Psilocybin Risks

We do not expect any major risks to the safety of participants. Psilocybin-containing mushrooms have been used safely by indigenous cultures in Central and South America for hundreds of years (Carod-Artal, 2015; Johnson et al., 2018). Expert consensus indicates that psilocybin is safe in human pre-clinical and clinical trial research (Johnson et al., 2008). A meta-analysis of clinical trials of psilocybin and other serotonergic psychedelics found no significant differences in adverse events between those receiving psilocybin and placebo. (Galvão-Coelho et al., 2021). In recently conducted RCTs, these adverse events were transient, tolerable, and resolved within the timeframe of the 8-hour dosing session, including: transient anxiety; minor elevation in heart rate or blood pressure; and mild nausea upon initiating the dose. (Carhart-Harris et al., 2016; Davis et al., 2021; Griffiths et al., 2016; Grob et al., 2013; Ross et al., 2016). However, psilocybin, especially at higher doses, can be associated with more concerning psychological effects. Psilocybin given at a dose of 25mg is expected to alter mood, cognition, and perception. Common psychological and adverse effects of psilocybin include transient anxiety, changes in thought form or thought speed (slowing down or speeding up of thought processes), depersonalization, derealization, inattention, impaired concentration, labile mood, altered perception of time. These effects are both expected component of the therapeutic response. Psilocybin can produce sympathetic system activation resulting in physiological effects such as pupillary dilation and detectable, but moderate increases in blood pressure or heart rate, transient nausea, diarrhea, paresthesia, dizziness, fatigue and headache. In rare cases, hallucinogen-induced persistent perceptual disorder (HIPPD) where individuals experience the effects of psilocybin for longer than expected. These have not been any reported cases of this in modern clinical settings, but it has been rarely reported following recreational use. With proper screening and preparation, psilocybin has a safe physiological and psychological profile. As with any investigational product trial, there is a possibility that some participants may experience a worsening of their mental state after the drug experience. Reports of this are very rare and have not been seen in other similar studies. Published findings on harm profiles associated with

drugs most commonly used in the UK and Australia consistently rate 'magic mushrooms' as being one of the least harmful substances to one's self and to society (Nutt et al., 2010). In order to mitigate risks, a preparatory therapy session will be scheduled with each participant to prepare them for what to expect during the experience. It is important to assess psilocybin tolerability (Primary Aim) given the high rate of noncompliance with antidepressant treatment related to perceived adverse effects. (Nomi et al., 2017).

Medication Tapering Risks

There will be a washout period of a minimum of 2 weeks (4 weeks for fluoxetine) for participants taking any concomitant medications prior to Baseline (V2). Withdrawing from medications may result in difficulty sleeping, nausea, diarrhea, flu-like symptoms, and jitters. These symptoms are not dangerous and usually pass in a few days. In addition, tapering off antidepressant medications can result in the worsening of a participant's symptoms. During the tapering period, the participant will be seen clinically by the study physician. If the participant is not on any prohibited medication, a monitoring period of 2 weeks will apply, prior to the baseline visit.

Blood Draw

There may be mild temporary discomfort, minor bruising or irritation, and in rare cases there may be local infection at the vein site. The blood draws are required to establish safety and eligibility for the trial.

ECG

Skin irritation from the ECG electrode pads or pain when removing the sticky pads are possible side effects.

Assessment Measures

Assessment measures are designed to address various aspects of psychopathology and as such, may be distressing. Participants may experience emotional reactions to the questions and when providing responses about the material on the questionnaires and in the interviews. Any distress or discomfort encountered by participants will be addressed by a member of the study team. In addition, the assessments may cause fatigue. These risks will be mitigated by offering breaks throughout the study visits.

# 2.0 CLINICAL TRIAL OBJECTIVES

The overall objective is to conduct a

## 2.1 Primary Objective

To evaluate the feasibility and safety of administering psilocybin (25mg) in adults with TRD and chronic neuropathic pain by evaluating feasibility and safety.

Hypothesis 1a (feasibility): We will be able to recruit 16 participants within 18 months with a retention of >90%.
Hypothesis 1b (safety): Psilocybin 25mg will not be associated with serious adverse events (SAE's) or Serious Adverse Drug Reactions (SUADR's).

## 2.2 Secondary Objective

To evaluate antidepressant effects as measured by the change in the MADRS from Baseline (V2) to 1-week post-treatment (V5). Antidepressant effects will also be measured at Weeks 2 (V6), month 1 (V7), and month 3 (V8) post-intervention. Response will be defined as a reduction of 50% or more of the MADRS score and remission defined as a score of <7 on the MADRS from Baseline (V2) to Week 1 (V5).

## 2.3 Exploratory Objective

To evaluate effects on neuropathic pain as measured by the change in the PROMIS-PI and PROMIS-Interference from Baseline (V2) to 1-week post-treatment (V5). Pain relief effects will also be measured at Weeks 2 (V6), month 1 (V7), and month 3 (V8) post-intervention. A clinically meaningful response will be defined as a reduction of 4 points or more of the PROMIS_PI from Baseline (V2) to Week 1 (V5) (Yost et al., 2011) and a reduction of 2.5 points or more on the PROMIS-Interference score from Baseline (V2) to Week 1 (V5) (Chen et al., 2018).

# 3.0 CLINICAL TRIAL DESIGN

## 3.1 Overall Design

Overview of Study Design:
A member of the study team will obtain informed consent prior to any study related activities. If consent is obtained, participants will undergo a screening assessment where they will complete lab tests, and clinical and psychiatric assessments to determine. Following the screening visit, eligible participants will undergo a washout period where they will be tapered off concomitant medication over a period of 2-6 weeks. The length of the tapering period will depend on the type of medication the participant is being tapered off (based on the half-life of the medication) and the participant's preference for the length of the tapering period. Most medications will require a minimum of a 2-week tapering period before the baseline, with the exception of fluoxetine, which will require a minimum of 4-weeks. Additional time may be added at the discretion of the study investigator. During the tapering period, the study psychiatrist will see participants weekly (V1a, V1b, etc.) for at least 2 weeks to monitor for withdrawal, worsening of depressive symptoms and worsening of chronic pain symptoms and suicidality. Suicidality will be closely monitored using the Columbia Suicide Severity Rating Scale (C-SSRS). Participants and

their family members/carers will be educated on the signs and symptoms of worsening depression and suicidality and will be given contact details of the study team in case of major decline in mental state or worsening of chronic pain symptoms.

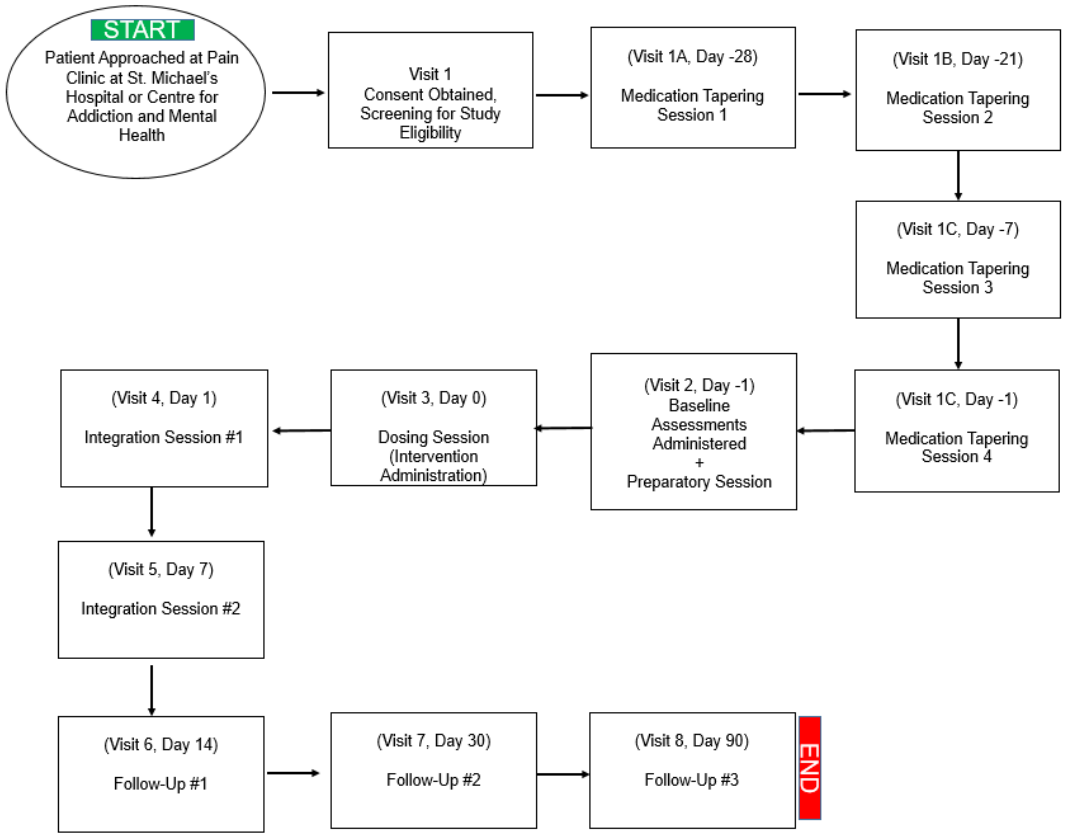
At the Baseline visit (V2), which occurs the day before the dosing session, participants will complete clinical measures, and undergo a preparatory session (up to 4 hours) with the study therapists. These sessions will build a therapeutic alliance, provide psychoeducation about, and set intentions for, the psilocybin session. To reduce participant burden, baseline can be broken up into multiple days, however all assessments must be completed within 7-days of the intervention. Ideally, baseline occurs the day before the intervention is administered.

The psilocybin session (Day 0 [V3]) will last 5-6 hours and will be conducted in the existing psychedelic treatment suite developed at the Centre for Addiction and Mental Health (CAMH) Mood Disorder Service by Dr. Husain (PI). Two trained study therapists will be supporting each participant during the dosing session. Participants will receive psilocybin 25 mg. All participants will receive 12-14 hours of manualized supportive psychotherapy (which includes the 5-6 hour dosing session). After 5 hours of dose administration, participants will be evaluated for safety by the study psychiatrist and discharged home.

After the dosing session, participants will be seen for two 1-hour integration sessions (Day 1 [V4], Week 1 [V5]). Thereafter, participants will be followed-up after 2 weeks [V6], 1 month [V7] and 3 months [V8] post-dosing (see Figure 1). A study psychiatrist will be available throughout the duration of the trial to respond to any concerns or changes in mental/physical state. Participants will not start other interventions for MDD or chronic pain during the study.

*Figure 1. Study Schematic:*

Timeline



## 3.2 Primary Endpoints

Feasibility endpoints will be evaluated by monitoring recruitment and retention rates.

Dropouts during three periods will be evaluated: 1) during preparatory medication tapering and washout period, 2) during the acute course of the study intervention, and 3) the one-month follow-up period. Throughout all three periods, we will also evaluate adverse events including psychological distress and serious adverse events (e.g., hospitalization, suicide attempt, death).

Safety endpoint is the number and severity of adverse events reported, it will be evaluated using standardized adverse events monitoring at all-time points. Adverse event monitoring will be prioritized to closely and thoroughly evaluate safety profile of the psilocybin. Constant observation by therapists will monitor for adverse events during the dosing sessions. An on-call psychiatrist will be available at all times to further assess as needed for acute concerns, as needed.

## 3.3 Secondary Endpoints

The antidepressant effects will be assessed by measuring changes from Baseline (V2) to Week 1 (V5) on MADRS. Baseline is defined as the assessment score obtained on Day -1 (V2). The primary time-point is Week 1 (V5). The changes in MADRS from Baseline to Day 1 (V4), and Week 2 (V6), 1 month (30 days) (V7), and 3 months (90 days) (V8) post-dosing will also be analyzed. Other clinical outcomes include response defined as a reduction of 50% or more of the MADRS score and remission defined as a score of <7 on the MADRS from Baseline (V2) to Week 1 (V5).

The effects on symptoms of chronic pain will be assessed by measuring changes from Baseline (V2) to Week 1 (V5) on PROMIS. Baseline is defined as the assessment score obtained on Day -1 (V2). The primary time-point is Week 1 (V5). The changes in PROMIS from Baseline to Day 1 (V4), and Week 2 (V6), 1 month (30 days) (V7), and 3 months (90 days) (V8) post-dosing will also be analyzed. Other clinical outcomes *include response defined as a reduction of 4 points or more of the PROMIS_PI from Baseline (V2) to Week 1 (V5) (Yost et al., 2011) and a reduction of 2.5 points or more on the PROMIS-Interference score from Baseline (V2) to Week 1 (V5) (Chen et al., 2018).*

## 3.4 Exploratory Endpoints

Other outcome measures will be changes from Baseline (V2) to Week 1 (V5) in the Clinical Global Impression (CGI) scale (Busner & Targum, 2007), World Health Organization Quality of Life Short Version (WHOQOLBREF) (Skevington et al., 2004), and the Generalized Anxiety Disorder scale (GAD-7) (Spitzer et al., 2006). Additional behavioural assessments will include measures of anhedonia (Snaith Hamilton

Anhedonia Pleasure Scale, SHAPS) (Snaith et al., 1995), wellbeing (Warwick-Edinburgh Mental Wellbeing Scale, WEMWS) (Tennant et al., 2007) and the experience after psilocybin administration (Mystical Experiences Questionnaire, MEQ) (Barrett et al., 2015).

# 4.0 PARTICIPANT SELECTION AND WITHDRAWAL

## 4.1 Target Population

The target population for this study are adults aged 18-65 who are diagnosed with major depressive disorder and experiencing a clinically significant depressive episode that has failed to respond to at least two adequate trials of antidepressants. Participants must also have a diagnosis of chronic neuropathic pain with no meaningful improvement from trial of at least two medications for pain management. Participants must meet all inclusionary/exclusionary study criteria as confirmed by the study investigator. In order to be eligible, these criteria must be met at the Baseline visit (V2). For participants on concomitant medications, confirmation of eligibility occurs after a successful washout period in which the participant has been tapered off concomitant medications for a period of at least 2-weeks prior to baseline (4-weeks for fluoxetine), as confirmed by the study investigator.

## 4.2 Participant Recruitment and Screening

The target sample size is 16 participants (N=16) diagnosed with treatment-resistant depression and chronic neuropathic pain. The study will take place at a single site: the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario.

The source of participants in this study will come from CAMH outpatient clinics and the St. Michael's Hospital Pain Clinic. Clinicians at CAMH and St. Michael's Hospital Pain Clinic may identify potential research participants and obtain verbal permission from these potential participants for a member of the research team to approach them. Potential participants that are interested in participating in the study will be prescreened by a member of the study team, as outlined below. After referral and consented to screening, I-Care will be used to confirm their eligibility.

Prescreening Procedures

Once a potential participant contacts the research team or is referred to the research team as an interested potential participant, a research team member will schedule a phone call. This phone call will be referred to hereafter as the Pre-Screening conversation. During the pre-screening conversation, a brief description of the study is provided to the potential participant and then, if the person agrees, the following eligibility criteria is obtained:

- Contact information (phone number and/or email)
- Partial date of birth

- Ability to read and speak English
- Whether they have a clinical diagnosis of major depressive disorder
- Whether they are currently experiencing a major depressive episode
- Whether they have a diagnosis of chronic neuropathic pain
- Treatments taken for chronic pain (frequency and type of treatment)
- Treatments taken for major depressive episode (frequency and type of treatment)
- Whether the potential participant has been diagnosed with psychotic disorder, bipolar disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder;
- Diagnosis of a substance use disorder (recreational use of tobacco, alcohol, cannabis, and prescribed opioids are permitted) within the previous 6-months;
- If they are currently undergoing therapy and if they are, the date that they started
- Whether the potential participant would be willing to discontinue current antidepressant medications
- Whether they are seeing a doctor on a regular basis for a medical problem
- If they are currently taking medications for the treatment of a physical health problem
- Difficulty with giving blood or needles
- Currently nursing or pregnant
- Willingness to take contraceptives for the duration of the study
- If they have been using contraceptives for at least the previous 3-months
- Currently enrolled in another study involving an investigational product or device
- If they are able to take medication orally
- If they have ever used psychedelic drugs

The information collected during this conversation will be recorded on the pre-screen form which will be reviewed by the study PI. If the potential participant does not meet any exclusionary criteria as listed on the Pre-Screen form, then the potential participant is called back to invite them to schedule a consent and screening visit.

If the person meets any exclusionary criteria during the pre-screening conversation or as determined by the study investigator, then the person is asked whether they would be interested in participating in any other studies (current or future) within our program. If they are interested in other studies within our department, their name and contact information will be transferred to a password protected log that is only accessible by the Mood Disorder Services and the Centre for Complex Interventions staff. If they fail the pre-screen and do not wish to be contacted, their pre-screen form will be discarded in the confidential shredding bin which will then be securely disposed of. However, their name will be kept in a password protected log along with the date and result (pass/fail) of their pre-screen so if they contact us again (e.g. to inquire about their eligibility) we can refer back to it.

Compensation

Participants will not be charged for research-only services for their participation in this study. All research-only services, such as clinical assessments, blood work, and the IP will be provided at no cost to the participant.

Participants will be reimbursed for the cost of parking incurred at each study visit. To receive reimbursement for parking expenses incurred at each study visit, participants must provide the research team with a parking receipt. In addition, TTC fare will be provided if the participant used public transit for transportation to and/or from study appointments. Participants will also be reimbursed for any taxi, Uber or Lyft costs due to travel to and from study appointments.

Participants will also be reimbursed for the time spent at study visits occurring after the screening and washout period where treatment (therapy or the intervention) is not administered. Participants will be reimbursed $10 per hour for each study visit that they attend (V6, V7, and V8). In total, if participants complete all study visits, they may be reimbursed up to $25 for their time. Compensation will be provided at the end of the sessions in the form of e-gift card, as follow-up sessions are conducted virtually. No payment will be provided in advance.

| Study Visit: | Duration: | Compensation: |
|---|---|---|
| Follow-Up: Visit 6 | ~1 hour | $10 |
| Follow-Up: Visit 7 | ~ 30 min. | $5 |
| Follow-Up: Visit 8 | ~1 hour | $10 |

## 4.3 Equity, Diversity and Inclusion Considerations

Equity, diversity, and inclusion (EDI) are important to ensuring the study design is ethically sound. No exclusions will be made based on race, ethnicity, religion, sex, or gender.

## 4.4 Eligibility Criteria

### 4.4.1 Inclusion Criteria

The participant must meet all of the inclusion criteria to eligible for this clinical trial:

1. Adults 18 to 65 years old;
2. Are outpatients;
3. Must be deemed to have capacity to provide informed consent;
4. Must sign and date the informed consent form;
5. Stated willingness to comply with all study procedures;
6. Ability to read and communicate in English, such that their literacy and comprehension is sufficient for understanding the consent form and study questionnaires, as evaluated by study staff obtaining consent;

7. Primary DSM-5 diagnosis of non-psychotic MDD, single or recurrent, based on the Structured Clinical Interview for DSM-5 (SCID-5) administered at the first screening visit;
8. Participants diagnosed with treatment-resistant depression defined as individuals with a baseline HamD-17 score > 14 and that have not responded to two or more separate trials of antidepressants at an adequate dosage and duration (an antidepressant resistance rating score of three or more is considered an adequate trial) based on the Antidepressant Treatment History Form (ATHF) (Sackeim & Sackeim, 2001); there is no upper limit on the number of treatment failures;
9. Diagnosis of chronic neuropathic pain as determined by a pain specialist and confirmed with the standardized Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire[25]
10. Moderate-to-severe neuropathic pain determined by Patient Reported Outcomes Measurement Information System (PROMIS) Pain Interference score of $\geq$ 60[26], as well as mean pain intensity scores $\geq$ 5 on a numeric rating scale[27]
11. Previous trials of at least two medications recommended in the Canadian consensus guidelines on the management of neuropathic pain with no self-reported meaningful improvement in symptoms
12. Ability to take oral medication;
13. Individuals with an eGFR above 40mL/min/1.73m$^2$ and all blood work on clinical laboratory tests assessed as not clinically significant by study delegate physician at Screening (V1)
14. Individuals who are capable of becoming pregnant: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation;
15. Individuals who are willing to taper off current antidepressant and antipsychotic medications for a minimum of 2-weeks (or more depending on the medication) prior to Baseline (V2) and for the duration of the study and whose physician confirms that it is safe for them to do so; and
16. Agreement to adhere to Lifestyle Considerations (section 4.5) throughout study duration.

### 4.4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this clinical trial:

1. Pregnant as assessed by a urine pregnancy test at Screening (V1) or individual's that intend to become pregnant during the study or are breastfeeding;
2. Treatment with another investigational drug or other intervention within 30 days of Screening (V1);
3. Have initiated psychotherapy in the preceding 12 weeks prior to Screening (V1);

4. Have a DSM-5 diagnosis of substance use disorder (recreational use of tobacco, alcohol, cannabis and prescribed opioids are permitted) within the preceding 6 months;
5. Have active suicidal ideation with intent and plan as determined by item 3 of the HamD-17;
6. Any DSM-5 lifetime diagnosis of a schizophrenia-spectrum disorder; obsessive-compulsive disorder, psychotic disorder (unless substance induced or due to a medical condition), bipolar I or II disorder, paranoid personality disorder, borderline personality disorder, or neurocognitive disorder as determined by medical history and the SCID-5 clinical interview;
7. Any first-degree relative with a diagnosis of schizophrenia-spectrum disorder; psychotic disorder (unless substance-induced or due to a medical condition); or bipolar I or II disorder as determined by the family medical history form and discussions with the participant;
8. Presence of a relative or absolute contraindication to psilocybin, including a drug allergy, recent stroke history, uncontrolled hypertension, low or labile blood pressure, recent myocardial infarction, cardiac arrhythmic, severe coronary artery disease, or moderate to severe renal or hepatic impairment.
9. Presence of baseline prolonged QTc or Torsade de Pointes as measured by the ECG or a history of long QTc syndrome or related risk factors;
10. Individuals who are currently taking methadone, buprenorphine or > 100 milligrams of morphine (or morphine equivalents).
11. Any other clinically significant physical illness including chronic infectious diseases or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if they take part in the study.

## 4.5 Lifestyle Considerations

During this clinical trial, participants are asked to:

- Abstain from alcohol for 24 hours before the intervention and for up to six hours after intervention administration.
- Abstain from the use of any prescribed opioids, benzodiazepines, or sleep aids (Z-drugs) within 12hrs prior to the intervention (V3) and for up to 6hrs after administration.
- Abstain from any illicit drugs (e.g. cocaine, ecstasy/MDMA, hallucinogens) and/or cannabis for the duration of the study.
- Abstain from driving or operating heavy machinery for up to 24hrs after the intervention.

## 4.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet one or more eligibility criteria required for participation. The screening period for participants in this study occurs before Baseline (V2) and eligibility for the study cannot be confirmed until the participant had tapered off any concomitant medication. In order to be eligible, the participant must meet all eligibility criteria as outlined in Section 4.4. The information collected about the participant during the screening process

including demography, screen failure details, eligibility criteria not met, and any AEs/SAEs will be used for the purposes of transparent reporting. Participants who are deemed ineligible will continue with their usual standard of care or may be referred to other research protocols for TRD and/or chronic pain.

## 4.7 Participant Withdrawal Criteria

### 4.7.1 When and How to Withdraw Participants

Participants are free to withdraw from participation in the clinical trial at any time.
An investigator will discontinue or withdraw a participant from the clinical trial for the following reasons:

- Pregnancy or if participants cease effective contraception;
- Significant study intervention non-compliance;
- If any adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the clinical trial would not be in the best interest of the participant;
- Disease progression which requires discontinuation of the study intervention;
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation; or

The reason for participant discontinuation or withdrawal from the study will be recorded within the participant's research record, and/or health record at CAMH.

Participants that are withdrawn from the study will be replaced using the same recruitment methods as outlined in Section 4.2: Participant Recruitment and Screening.

### 4.7.2 Follow-up for Withdrawn Participants

If a participant withdraws consent, the information that was provided by the participant and recorded by the study team before they withdrew consent will not be destroyed. However, once withdrawn from the clinical trial, no further research procedures or evaluations will be performed, or additional research-specific data collected on the participant. Reasonable effort will be made to obtain permission to document the reason for withdrawal.

Withdrawn participants will be seen clinically by the study investigator to ensure a plan for continued care outside of the study is established. If the participant is interested in hearing about other treatment options, they may be offered a referral to the CBT group at CAMH and/or a consultation with a psychiatrist to discuss pharmacotherapy options.

### 4.7.3 Early Termination Visit

If a participant withdraws from the clinical trial, every effort should be made to perform an Early Termination Visit.

<u>Participants that withdraw after the first dosing session:</u>

If the participant is willing to attend an early termination visit, the following information will be documented:

- Assessment of new and ongoing AEs;
- Assessment of any complications following the study intervention;
- Documentation of all concomitant medications;

The PI will also ensure the participant is appropriately transitioned/followed for any additional care as required.

### 4.7.4 Participants who are Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for 2 or more scheduled visits and is unable to be contacted by the research team.

The following actions will be taken if a participant fails to attend a required study visit:

- The research team will attempt to contact the participant and reschedule the missed visit 7 days, counsel the participant on the importance of maintaining the assigned visit schedule, and reconfirm whether the participant wishes to and/or should continue in the clinical trial.
- Before a participant is deemed lost to follow-up, the research team will make every effort to regain contact with the participant via 2 different methods of contact (e.g. telephone and email). These contact attempts should be documented in the participant's research record and/or legal health record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the clinical trial with a primary reason of lost to follow-up.

# 5.0 STUDY INTERVENTION

## 5.1 Description

Pharmacokinetics and Psilocybin Effects

Psilocybin is detectable in plasma 20 to 40 minutes after oral administration of 0.224 mg/kg (10-20mg total dose) (Hasler et al., 1997). Orally ingested psilocybin is metabolized in the liver, and primarily transformed into the active hydroxyl metabolite, psilocin. Psilocybin is essentially a prodrug and psilocin represents the pharmacologically active agent in systemic circulation. The elimination half-life of psilocybin is 50 minutes (Lindenblatt et al., 1998). Psilocin's half-life ranges between 2 and 3 hours and it detectable 6 hours after oral administration (Hasler et al., 1997; Hasler et al., 2004; Lindenblatt et al., 1998). Both psilocin and psilocybin are detectable in human urine, unmodified and particularly conjugated with glucuronic acid(Hasler et al., 2002). The majority of psilocybin recovered in urine is excreted within 3 hours after oral administration and is completely eliminated from the body within 24 hours (Hasler et al., 2002).

As a $5HT_{2A/2C}$ agonist, psilocin is regarded as a "classical" psychedelic; in humans, it commonly elicits significantly altered states of consciousness, experienced through visual and sometimes auditory effects, changes in perception, distortions of time, and a range

of effects including a sense of awe, novel perspectives, existential and personal insight, dramatically heightened empathy and feelings of compassion, strong emotions, and non-dual or unitive experience. A number of these 'peak' experiences have been associated with improved quality of life and improvement in mood (Griffiths et al., 2016; McClain et al., 2003; Visser et al., 2010). For a more detailed explanation on the effects of psilocybin and its mechanism of action, please refer to the investigators brochure.

Psilocybin-Assisted Psychotherapy

All participants will receive manualized psychotherapy in conjunction to their assigned pharmacological treatment. The participant will attend 1 preparatory session that occurs within 7-days of the first psilocybin dosing session (V3) to develop a therapeutic alliance, set intentions for the experience, and learn what to expect during the dosing session. In addition, the participant will undergo 2 integrative therapy sessions after the intervention (V4 & V5).

There will be an experienced clinical psychologist trained in PAP serving as a master trainer for the study. We will also use the Yale psilocybin-assisted therapy for depression manual to deliver psychotherapy and train each therapist (see manual attached). The therapy is closely related to Acceptance and Commitment Therapy, with a focus on "psychological flexibility" i.e. a person's ability to: 1) adapt to fluctuating situational demands; 2) reconfigure mental resources; 3) shift perspective; and 4) balance competing desires, needs, and life domains. The therapists' role is to witness the participant's therapeutic process and provide unconditional positive regard during the experience.

Therapy sessions will not be video recorded. A delegated physician will be available at all times during the dosage session to assess and manage any medical or psychiatric adverse events.

How the study intervention will appear:

The psilocybin will be provided by Filament Health Corporation (BC, Canada). The dose of psilocybin used in this study will be 25mg. The psilocybin will be administered in size 2 hydroxypropyl methyl cellulose (HPMC), white capsules.

## 5.2 Treatment Regimen

There will be one intervention day (V3 – Day 0) following Baseline (V2) and after the participant has been deemed eligible to participate. The procedures are outlined below:

Each participant will be assigned 1 treatment bottle containing 1 capsule of 25mg psilocybin. Under the supervision of a clinician, the 25 mg capsule of psilocybin will be taken orally with a glass of water. There will be no modifications to the dosage, each participant will receive the same dosage of psilocybin. In addition to the psilocybin, two study therapists trained in psilocybin-assisted psychotherapy will be supporting the participant during the dosing session. There will be 1 therapist present at all times

throughout the dosing session. The total treatment time will be 5-6 hours when the acute effects of the psilocybin have passed.

## 5.3 Method for Assigning Participants to Treatment Groups

All participants will be allocated to the 25 mg psilocybin group. The research pharmacist will dispense medication on the day of dosing.

## 5.4 Administration of Study Intervention

The IP will be prepared by the CAMH pharmacy and picked up by a trained research staff member. The IP will be given to the participant by a trained therapist who will supervise the participant. The participant will receive a capsule containing 25mg of psilocybin which will be taken orally, with water. The capsule should not be opened or chewed.

After taking the IP, the participant will lie down on a bed in a non-clinical environment. Therapists will encourage participants to focus their attention inward and stay with any experience that arises. To enhance inward reflect, a pre-selected music playlist will be played quietly. Two study therapists trained in PAP will be supporting each participant during the dosing session with at least one therapist being present at all times to respond to the emotional and physical needs of the participant. Constant observation by therapists will monitor for adverse events during the dosing sessions. At least one member of the dyad will be a clinician. An on-call psychiatrist will be available at all times to further assess as needed for acute concerns.

The effects of psilocybin usually start about 20 to 30 minutes after administration, becoming the most intense in the first 90 to 120 minutes and gradually subsiding in 5 to 6 hours. The participants will be asked to remain in the room for the duration of the session regardless of the intensity of the effects, preferably lying down and mostly silent unless they have a concern or need to communicate a discomfort or seek reassurance from the therapist, or use the restroom. The therapists will ‘check-in’ with the participant (i.e., ask how the participant is doing) in 30 to 60 minute intervals post-dosing. Light snacks will be provided, but participants are encouraged to bring in their own lunch.

About 5 to 6 hours after dosing, the trained therapists will discuss the IP administration experience with the participant. The participant will be discharged 5-6 hours post-dosing when, in the opinion of the investigator, the acute effects of psilocybin are resolved. The participant must be accompanied home by a caregiver who will remain with the participant for up to 24hrs after the intervention was given.

## 5.5 Participant Compliance Monitoring

The IP will be administered to the participant in front of study personnel. Thus, administration of the IP will be supervised by study personnel to ensure compliance.

## 5.6 Concomitant Therapy

All prescription and non-prescription medications (e.g. over-the-counter drugs and herbal supplements) that participants report taking during the 30 days prior to Screening (V1)

will be assessed and recorded at V1. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units, and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use. Where applicable, medication reports should be corroborated with participant medical records. All as-needed (*pro re nata,* PRN) prescriptions should be converted to reflect the actual number of pills or dose taken per day.

Concomitant medication refers to all drugs and therapies used from the time the ICF is signed through until the end of study participation. Changes, additions, or discontinuations to medications and/or therapy will be assessed, recorded, and verified with participants in the CRF during each study visit.

Permissible Medications

Medications for the management of concurrent anxiety and insomnia, or non-psychiatric medications that have a potential psychotropic effect are permitted within the following limitations.

For the initial Screening Visit (V1) through to the final study visit (V8), participants are permitted to use benzodiazepines (up to 2mg of lorazepam equivalent per day for insomnia and anxiety if it is not taken within 12 hours before the psilocybin dose (V3). Prescription and nonprescription medications with psychoactive properties that are used as needed for non-psychiatric conditions (e.g. pseudoephedrine for allergies or cold, zopiclone for sleep disorders) should be used no more than 2 times a week and not within 12 hours before any study assessment. Documentation of the use of adjunctive anxiolytics, hypnotics, or medication with potential psychotropic properties (including over-the-counter preparations) will be obtained at each visit.

Participants will be required to continue with their corresponding treatment for their chronic neuropathic pain disorder as prescribed by their chronic pain physicians. Participants will be asked to remain on stable doses of ongoing pain medications for 2 weeks prior and during the trial. Investigators will analyze all medications taken by the participants prior to the intervention as well as at each follow-up.

Permissible Contraceptive Methods

A woman/female or person who is not of childbearing potential is considered to be postmenopausal after at least 12 months without menstruation. The participant must be on a permissible contraceptive for a minimum of 3 months prior to screening and for the duration of the study. The following methods of contraception, if used properly and used for the duration of the study, are permissible:

- Combine estrogen-and progestogen-containing hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal

    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubual occlusion
- Vasectomized partner
- Sexual abstinence
- Tubal ligation/ occlusion

Periodic abstinence (e.g. calendar, symptothermal, or postovulation methods) is not an acceptable form of contraception for this study.

These methods of contraception also apply to partners of male participants.

The investigator (or delegate) and each participant will determine the appropriate method of contraception for the participant during the participation in the study. This will be documented at Screening (V1).

Prohibited Medications

Participants are to be discontinued from antidepressants and/or antipsychotic medications at least 2 weeks prior to Baseline (V2). Participants on fluoxetine will be taped off the medication at least 4-weeks prior to Baseline (V2). Additional time may be required as determined by the study investigator. Medications that must be discontinued include the following 2 classes of the Anatomical Therapeutic Chemical (ATC) Classification System: NO5A Antipsychotics & NO6A Antidepressants. Methylphenidate is also included in this list.

These medications should not be re-introduced until after month 3 (V8) when the study is complete. If the medications are re-introduced, the study investigator must be notified and the medications will be documented in the participant's CRF. Participants who require concomitant medication(s) specifically for the treatment of depression at any time through the duration of the study will be assessed for reasons of resuming their medications.

Rescue Medication

The decision to medicate a participant will depend on if the therapists and study investigator determine the safety of the patient and others can be maintained without medical intervention. The final decision will be made by the study investigator.

- Benzodiazepine anxiolytics
    - The preferred pharmacological intervention of choice in case of acute psychological distress (e.g. medications such as lorazepam or alprazolam

that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action).
    - The oral route is preferable because IV injection procedures may further exacerbate the participant's anxiety.
- Antipsychotic medications (e.g. risperidone) should be available in the event that an adverse reaction escalates to unmanageable psychosis.
- Management of blood pressure:
    - Asymptomatic with blood pressure (BP) < 180/100
        - Reassure, ensure lights are dim or off, tilt head of bed 15 degrees up and continue to monitor
        - Increase blood pressure measurement frequency to q15min until BP has partly normalized (sBP = 100-159; dBP = 60-99)
    - Asymptomatic with BP >180/100 for >30 minutes
        - Administer captopril* 12.5mg PO/SL x 1 with MD order
        - Increase blood pressure measurement frequency to q15min until BP has partly normalized (sBP = 100-159; dBP = 60-99)
    - Asymptomatic with BP persisting at >180/100 for >60 minutes post-dose, despite administering first captopril dose:
        - Consider potential transfer to ER – decision to be made by study investigator
        - Administer 2nd dose of captopril 12.5mg x 1 with MD order
    - Management of severe treatment emergent hypertension:
        - Consider potential transfer to ER – decision to be made by study investigator
        - Administer captopril 25mg PO/SL x 1
        - Call 911 immediately for patients experiencing symptoms of a hypertensive crisis (e.g., chest paint, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficit)
    - Note: if there are contraindications to captopril, substitute for hydralazine 10mg PO

In case of development of acute anxiety or psychotic symptoms requiring pharmacological intervention, the participant will be managed under the care of the onsite psychiatrist. The participant may be discharged from the clinic when, in the opinion of the investigator, the condition has stabilized. The participant will be accompanied home. The participant is to notify the site when they have returned home safely. In the absence of receiving a phone call, site staff will directly contact the participant.

Information for how to manage subjects during difficult psychological states are detailed in the Yale Manual for Psilocybin-Assisted Therapy of Depression. All therapists will undergoing training with the study investigator using this manual.

## 5.7 Packaging

The psilocybin will be provided by Filament Health Corporation (British Columbia, Canada). The dose of psilocybin used in this study will be 25mg. Filament Health Corporation will provide extra 20% of the capsules needed. The entire shipment for this trial will be sent in bulk. Psilocybin capsules will be packaged individually in high-density polyethylene bottles (30cc). The dose for each participant will be stored in individual boxes labelled with the protocol number, trial name, lot number, unique box number, and a statement that the drug is for clinical use only. The IP will only be removed from the safe for one participant at a time on the day of their session. Filament Health Corporation will be sent safety reports via email within 24 hours of team awareness.

## 5.8 Blinding of Study Intervention

N/A

## 5.9 Receiving, Storage, Dispensing and Return

### 5.9.1 Receipt of Study Intervention Supplies

Upon receipt of the study intervention supplies, an inventory will be performed and a receipt log filled out and signed by the person accepting the shipment. Designated research staff/pharmacy must count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study intervention in a given shipment (active drug or comparator) will be documented in the clinical trial files.

### 5.9.2 Storage

All IP will be kept in a locked area with limited access. The high-density polyethylene (HDPE) bottles of IP are to be stored as indicated in the investigators brochure. Bottles must be maintained at room temperature in a locked, secure location within research pharmacy. Deviations of storage temperature outside this required range should be documented and the study investigator should be notified immediately. Bottles of IP should not be frozen. If any component of the IP is damaged, the PI must be notified immediately. Any storage deviations will be reported to the REB as a protocol deviation.

### 5.9.3 Dispensing of Study Intervention

All participants will receive the same intervention. Each participant will be assigned 1 treatment bottle containing 1 capsule of 25mg of psilocybin. The IP will be dispensed and administered to the participants only by an appropriately qualified study physician. The study intervention will be administered orally, with water. Capsules should not be opened or chewed.

The investigator must keep an accurate accounting of the number of IP delivered to the site, administered to participants, and destroyed during and at the completion of the study.

The IP is to be used in accordance with the protocol by participants. The study team, overseen by the PI, should maintain records that adequately document that the participants were administered the IP dose specified by the protocol.

Regular study intervention reconciliation will be performed to document study intervention assigned, consumed, and remaining. This reconciliation will be logged on an accountability log (i.e. drug accountability log), and signed and dated by delegated research and/or pharmacy staff.

### 5.9.4 Return or Destruction of Study Intervention

At the completion of the clinical trial, there will be a final reconciliation of the study intervention shipped, consumed and remaining. This reconciliation will be logged on an accountability form, and signed and dated by delegated research and/or pharmacy staff. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study intervention. Intervention destroyed on site will be documented in the clinical trial's files.

# 6.0 RESEARCH PROCEDURES

## 6.1 Research Visits

**Description of Measures**

Screening Measures

*Structured Clinical Interview for DSM-5 (SCID-5).* The SCID-5 is a semi-structured diagnostic interview for ascertaining DSM-5 diagnoses (First, 2015). It will be administered by a trained study staff member.

*Hamilton Depression Rating Scale (HamD-17).* HamD-17 is a clinician-rated measure of depressive symptoms that consists of 17 items rated using a semi-structured interview. Eight of the 17 items are rated on a 5-point scale (0=absent; 1=doubtful or mild; 2=mild to moderate; 3=moderate to severe; 4=very severe), while the remaining 9 items are rated on a 3-point scale (0=absent; 1=doubtful or mild; 2=clearly present), yielding a minimum total score of 0 (least severe) and a maximum score of 52 (most severe) (Hamilton, 1960).

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). The LANSS is a two part (A and B), 7 item questionnaire that aims to identify the presence of neuropathic pain. Each item is rated between 3-5 points for yes and 0 points for no, with a total maximum score of 24. A score of 12 or above indicating the presence of neuropathic pain (Bennett, 2001).

Safety Measures

*Columbia-Suicide Severity Rating Scale (C-SSRS):* The C-SSRS will be used to assess suicide potential or tendency as a study entry criteria and monitored throughout the study to help rapidly identify this potential serious adverse event and intervene appropriately (e.g. further specialized assessment and hospitalization if needed). The C-SSRS is a semi-structured, clinician-rated interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period. The measurement of suicidal ideation is based on 5 "yes" or "no" questions with accompanying descriptions arranged in order of increasing severity. If the patient answers "yes" to either questions 1 or 2, the intensity of ideation is assessed in 5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. If any item(s) on the C-SSRS are answered "yes", the primary investigator or physician investigator must review the patient's responses in order to:

(a) During washout period and Baseline determine the patient's study eligibility and potential need for referral to a mental health professional, and
(b) During the study evaluate the patient's need for appropriate medical management such as a referral to a mental health professional.

Outcome Measures:

*Patient Reported Outcomes Measurement Information System-Pain Intensity Scale (PROMIS-PI)* is a single item questionnaire that aims to identify the intensity of pain experienced by the participant in the past seven days. Presented on a visual analogue scale of 0-10, scores range from 0= no pain to 10=worst imaginable pain. A score of 5 or greater indicates moderate to severe pain intensity(Karayannis et al., 2017).

*Patient Reported Outcomes Measurement Information System-Pain Interference Scale (Short Form) (PROMIS-Interference).* This is a six-item questionnaire which aims to identify how much an individual's physical pain has interfered with emotional, social and cognitive domains of living. All six items are rated on a scale of 1-5, with 1= Not at all, 2= A little, 3=somewhat, 4=quite a bit, 5=very much. Raw scores are converted to T-scores with a mean of 50 and a SD of 10. A T-score greater than 50 indicates higher pain interference than the general population (Amtmann et al., 2010; Bingham et al., 2021).

*Clinical Global Impression scale (CGI).* The CGI is a brief observer-rated instrument that measures the clinician's view of the patient's global functioning prior to and after initiating a study medication. It consists of two one-items measures that evaluate 1) severity of psychopathology from 1 ('normal – not at all ill, symptoms of disorder not present in the past seven days') to 7 ('among the most extremely ill patients – pathology drastically interferes in many life functions;) and 2) change from the initiation of treatment on a similar

seven-point scale (1 = 'very much improved' and 7 = 'very much worse'). It has been used in both research and clinical practice (Busner & Targum, 2007).

*Generalised Anxiety Disorder 7-item (GAD-7) scale.* The GAD-7 is a brief self-report measure of generalised anxiety, it consists of 7 items rated from 0 ('not at all sure') to 3 ('nearly every day'). It has good psychometric properties and is a widely used research instrument in assessing adult anxiety (Spitzer et al., 2006).

*Montgomery-Åsberg Depression Rating Scale* (MADRS;(Montgomery & Asberg, 1979)). The MADRS is a clinician-rated measure of severity of depressive symptoms. It consists of 10-items rated from 0 to 6. It is one of the most widely used clinician-rated assessments of depressive severity with well-established psychometric properties.

*Snaith-Hamilton Pleasure Scales (SHAPS).* The SHAPS is a 14-item self-report scale that measures hedonic capacity. Participants are asked to rate themselves on a Likert scale from 0 ('strongly disagree') to 3 ('strongly agree'). It is both a reliable and valid measure that is frequently used in research and clinical settings (Snaith et al., 1995).

*Stanford Expectancy of Treatment (SETS).* The SETS is an instrument to measure positive and negative treatment expectancies in clinical trials. It contains two subscales for both negative and positive expectancies. There are 6-items which are participant rated from 'strongly disagree' to 'strongly agree'. Items 7 to 10 are direct questions asked to the participant (Younger et al., 2012).

*World Health Organization Quality of Life Questionnaire – Brief Version (WHO-QoL – Bref).* This 26-item, self-report measure was developed by the WHO in order to assess quality of life in the following areas: physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs. Responses are rated on a 5-point Likert scale rating from 1 = (not at all, over poor, very dissatisfied, never) through to 5 = (very good, very satisfied, an extreme amount, completely, always).

*Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS).* The WEMWBS consists of a 12-item scale used to assess the mental wellbeing of people. The self-report scale consists of positively worded statements covering feelings and functioning aspects of mental wellbeing. Responses are rated on a 5-point Likert scale ranging from 1 ('none of the time') to 5 ('all of the time').

*Five Dimensions of Altered States of Consciousness (5D-ASC).* The 5D-ASC is a visual analogue scale of 94-items that consists of five subscales: 1) oceanic boundlessness; 2) anxious ego dissolution; 3) visionary re-structuralization; 4) auditory alterations; 5) reduction of vigilance (Dittrich, 1998; Studerus et al., 2010). It is well validated and widely

used to characterize the subjective effects of psychedelic drugs. This self-rated scale appears as at 10-item Likert scale ranging from 1 to 10.

*Mystical Experiences Questionnaire (MEQ).* The MEQ is a 30-item self-report measure that has been used to assess the experience after psilocybin administration. The scale consists of four factors: 1) mystical; 2) positive Mood; 3) transcendence of time and space and 4) ineffability. Responses are rated on a 6-point Likert scale rating from 0 = (none; not at all) through to 5 = (extreme).

**Outline of Study Procedures**

***Visit 1 (V1) – Screening Visit***

- Administered by trained study staff:
  - Informed consent
  - Review of medical history, family medical history, and demographics
  - ATHF
  - SCID-5
  - HamD-17
  - LANSS
  - Vital Signs (blood pressure, pulse)
  - Height and weight
- Clinician administered:
  - Review of prior and current medications; the participant will be tapered from prohibited medications (see Section 5.6), if any, under the supervision of the study clinician
    - The study clinician will discuss options of tapering off medications with the participant and their healthcare provider.
    - Participants will be given a choice of how quickly they would like to come off the medications, but participants must be off concomitant medications (see Section 5.6) at least 2 weeks prior to the Baseline Visit (V2). Some medications may require a longer tapering period.
  - Review of eligibility criteria, medical history, and family medical history
  - Review of assessments
  - Documentation of contraceptive method to be used by the participant
- Biological specimen collection and laboratory evaluations collected at the Queen Street CAMH laboratory:
  - Clinical laboratory tests:
    - Approximately 20 mL blood will be drawn to conduct the following evaluations:
    - *Haematology:* hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean

corpuscular hemoglobin concentration, white blood cell count (with differential), and platelet count.
- *Chemistry:* albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect, and total), calcium, chloride, creatine kinase, creatinine, gammaGT, glucose, lactate, dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, urea (blood urea nitrogen), and uric acid.

- Urine Samples:
  - *Urinalysis:* a dipstick urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen
  - *Urine drug screen:* for illicit drugs or drugs of abuse. Results of a positive drug screen will be reviewed by the study clinician for pattern of use.
  - *Urine pregnancy test* for all women of childbearing potential
- ECG: Standard 12-lead ECG to check heart function

***Washout Period: Minimum of 2-Weeks***

Participants who are on concomitant medications (Section 5.6) must be tapered off at least 2 weeks prior to Baseline (V2). The plan for tapering off medications will be determined at the first screening visit (V1) with the participant and the study physician. Participants who are not on any prohibited medications will still undergo a two week period between Screen (V1) and Baseline (V2). During the washout period, the study physician will have weekly appointments with the participant to check how they are doing and ensure they are safe. The weekly appointments can be scheduled in-person or remote (via telephone/WebEx) based on the participant's preference and at the discretion of the study physician. Participants will be assessed for suicidality with the C-SSRS, changes in pain intensity and interference via the PROMIS-PI and PROMI-Interference, and assessed for adverse events and serious adverse events at each contact/visit.

Any safety, pain and AE/SAE assessment visits during the washout period will be called V1a, V1b, etc. During these visits, the C-SSRS, the PROMIS-PI, the PROMIS-Interference, AE/SAE monitoring and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion.

***Visit 2 (V2) - Baseline Visit - Day -7 to Day -1***

The Baseline visit (V2) will occur approximately 3-6 weeks after the initial Screening (V1) when the participant has successfully been tapered off any concomitant

medication. At the Baseline Visit (V2), the participant's eligibility will be confirmed by the study investigator by reviewing the Inclusion/Exclusion Criteria (Section 4.4) and updating the medical history. The Baseline visit (V2) can occur within 7 days before the anticipated psilocybin session and may be split over multiple days to reduce the burden on the participant (additional study visits will be labelled V2a, V2b etc). The following procedures will be performed and recorded at the Baseline visit (V2):

- Administered by trained study staff:
  - Vital Signs (blood pressure, heart rate)
  - GAD-7
  - MADRS
  - SETS
  - SHAPS
  - WHOQOL-BREF
  - WEMWBS
  - PROMIS-PI
  - PROMIS-Interference
- Clinician administered:
  - C-SSRS
  - CGI
  - Confirmation of eligibility criteria
  - Review of assessments administered
- Preparatory session (up to 4 hours) with the study therapists which will involve building a therapeutic alliance, psychoeducation about the psychedelic experience, and setting intentions for the intervention.
  - Note: Therapists will have the option to schedule an additional preparatory session at their discretion.
  - For a more detailed explanation of the preparatory therapy session, please refer to the Yale Manual for Psilocybin-Assisted Therapy of Depression.

***Visit 3 (V3) – Intervention – Day 0***

The intervention will occur the day after Baseline (V2). The participant may have this session ≤7 days following the Baseline visit (V2). If the participant is out of the ≤7 day window, all baseline assessments are to be repeated. On the day of the intervention the following procedures will take place:

- Study intervention administration (Section 5.0): 1 oral dose of 25mg of psilocybin administered in conjunction with supportive therapy (PAP).
- Vital signs (body temperature, blood pressure and pulse) will be taken three times during this session (Once pre-dosing, once 3 hours after dosing and once at the end of dosing session) and documented in the data collection form.
- 
- At least one therapist will be present in the room at all times during PAP and be available to respond to participants' physical and emotional needs
- Participants will be instructed to lie on a bed in a non-clinical environment, and therapists will encourage participants to focus their attention inward and stay with

any experience that arises. To enhance inward reflection, a pre-selected music playlist will be played. Administration of questionnaires or other instruments to be completed at the end of the dosing session when the acute effects of psilocybin have resolved:

- Study team or therapist administered:
  - 5D-ASC and MEQ to assess the acute drug effects using 5 primary dimensions and respective sub dimensions after 5 hours of dose administration.
  - C-SSRS

- The participant will be discharged 5-6 hours post-dosing when, in the opinion of the study PI (or delegate), the acute effects of psilocybin are resolved. The participant must be accompanied home by a caregiver who will remain with them for up to 24hrs after the dose was administered.
- Rescue medications are permitted during this visit as outlined in Section 5.6.

***Visit 4 & Visit 5 (V4 & V5) – Post-Intervention – Day 1 & Day 7***

- Administered by trained study staff or therapist/clinician:
  - CSSRS
  - CGI
  - MADRS
  - SHAPS
  - PROMIS-PI
  - PROMIS-Interference

- Integrative psychotherapy session will occur with the study therapists. The participant will discuss their experience during the dose session including their thoughts, feelings, and experiences. For more detailed information on the integrative therapy sessions, please refer to the therapists manual (Yale Manual for Psilocybin-Assisted Therapy of Depression).

***Visit 6 (V6), Visit 7 (V7) & Visit 8 (V8) – Follow-Up: Week 2, Month 1 & Month 3***

Follow-up visits occur at Weeks 2 (V6), 3 (V7), and 4 (V8) after the intervention. The following assessments will occur at each visit:

- Administered by trained study staff or therapist/clinician:
  - CSSRS
  - CGI
  - GAD-7 (except Visit 7)
  - MADRS
  - SHAPS
  - PROMIS-PI
  - PROMIS-Interference
  - WHOQOL-BREF (except Visit 7)
  - WEMWBS (except Visit 7)
- Clinician administered:

        - Review of safety assessments
    - These scales will be administered in-person and/or via secure videoconference software (alternatives to in-person for COVID-19 or other travel restrictions). Study visits will be coordinated along with follow-up with the study psychiatrists to provide added security and screening for suicidality. All scales (both self-report and clinician-rated) will be administered using a tablet with the secure digital REDCap platform for results to be safely and instantly loaded to the study database, with paper versions available if there are technological difficulties.

## 6.2 Schedule of Events

| Procedures | Screening (Visit 1) | Washout period[1] (3-6 weeks) | Baseline[2] (Visit 2, Day -7 to Day -1) | **Intervention (Visit 3, Day 0)** | 1-Day Post-Intervention (Visit 4, Day 1) | 1-Week Post-Intervention (Visit 5, Day 7) | 2-Weeks Post-Intervention (Visit 6, Day 14) | 4-Weeks Post-Intervention (Visit 7, Day 30) | 3-months Post-intervention (Visit 8, Day 90) |
|---|---|---|---|---|---|---|---|---|---|
| Location of Visit | Clinic | Remote | Clinic | Clinic | Clinic | Clinic | Remote | Remote | Remote |
| Allowable Window | | Weekly | | ±7 days from Baseline | None | ±3 day | ±3 day | ±3 day | ±3 day |
| Informed Consent | ✓ | | | | | | | | |
| Demographics | ✓ | | | | | | | | |
| Medical history | ✓ | | ✓ | | | | | | |
| Prior/concomitant medication review | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inclusion/Exclusion Criteria Review | ✓ | ✓ | ✓ | | | | | | |
| ATHF | ✓ | | | | | | | | |
| CGI | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| CSSRS[3] | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| HamD-17 | ✓ | | | | | | | | |
| MADRS | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| SCID-5 | ✓ | | | | | | | | |
| Vital signs (blood pressure, pulse) | ✓ | | | ✓ | | | | | |
| Weight | ✓ | | | | | | | | |
| Height | ✓ | | | | | | | | |
| ECG | ✓ | | | | | | | | |
| Clinical laboratory tests[4] | ✓ | | | | | | | | |
| Urinalysis | ✓ | | | | | | | | |
| Urine drug screening | ✓ | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Urine pregnancy test[5] | ✓ | | | | | | | | |
| Documentation of birth control | ✓ | | | | | | | | |
| Preparatory/Integrative therapy & psychoeducation[6] | | | ✓ | ✓ | ✓ | ✓ | | | |
| Intervention (25mg of psilocybin) | | | | ✓ | | | | | |
| Adverse event and serious adverse event review and evaluation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| CRF completion | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 5D-ASC[7] | | | | ✓ | | | | | |
| MEQ | | | | ✓ | | | | | |
| GAD-7 | | | ✓ | | | | ✓ | | ✓ |
| SETS | | | ✓ | | | | | | |
| SHAPS | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| WEMWBS | | | ✓ | | | | ✓ | | ✓ |
| WHO-QOL-BREF | | | ✓ | | | | ✓ | | ✓ |
| LANSS | ✓ | | | | | | | | |
| PROMIS-PI | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PROMIS-Interference | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

1. Additional visits may be needed during the washout period to ensure adequate time for discontinuation of medication. Visits will occur on a weekly basis during this period (V1a, V1b, etc.). Review of medications and assessments for suicidality will occur in addition to other assessments at the discretion of the study investigator.
2. Baseline assessments can occur on separate days (-7 days from first dose) to reduce the burden on participants. These visits will be V2a, V2b etc.
3. The "Last 12 Months" version will be administered at Visit 1A and the "Since Last Visit" version will be administered at all other visits.
4. See Section 6.0: Research Procedures for complete list of required laboratory tests to be performed.
5. For women/females and people of child-bearing age only
6. Additional therapy visits may be scheduled at the discretion of the study therapists and/or the study investigator.
7. To be administered immediately after the acute effects of psilocybin have subsided.

Instruments:
ATHF: Antidepressant Treatment History Form; CGI: Clinical Global Impression; CSSRS: Columbia Suicide Severity Rating Scale; ECG: Electrocardiogram; GAD-7: Generalized Anxiety Disorder assessment form; HamD-17: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; SCID-5: Structured Clinical Interview for DSM-5; SETS: Stanford Expectations of Treatment Scale; SHAPS: Snaith Hamilton Anhedonia Scale; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale; WHO-QoL-BREF: World Health Organization Quality of Life abbreviated scale; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale.

# 7.0 STATISTICAL PLAN

## 7.1 Sample Size Determination

Sample size was based upon the rule of 12 for pilot studies (Julious, 2005).

Using an effect size of d=2 and 1% significance will require N=12 completers to achieve 95% power. This calculation is for a single-arm design (2-sided) assuming a Wilcoxon Signed Rank Test. This sample size is also sufficient to detect large correlations (r=0.7) between change scores with 5% significance and 80% power. We expect a dropout rate of 25%, and will recruit 16 participants to account for this.

## 7.2 Statistical Methods

In this pilot study, we will estimate rates and percentages for feasibility outcomes, along with lower one-sided 95% CIs where high percentages are desirable (e.g., enrollment rate) and upper one-sided CIs where low percentages are desirable (e.g., loss to follow-up). For clinical outcomes, statistical analysis will be descriptive in nature. Continuous data will be reported as means with standard deviations, or as medians and interquartile ranges if data is skewed. Categorical data will be reported as counts and percentages. Since this study is a pilot trial, its sample size is not designed to provide the statistical power to detect clinically meaningful differences in outcomes. Therefore, we will not formally test for statistical differences between baseline and follow-up visits; rather, estimates of will be reported with 95% confidence intervals.

# 8.0 SAFETY AND ADVERSE EVENTS

## 8.1 Definitions

**Adverse Event**

An **adverse event** (AE) is any untoward medical occurrence in a research participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) 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 related to the investigational product.

AE severity can be defined as:

- *Mild:* discomfort noticed but no disruption of normal activity
- *Moderate:* discomfort sufficient to reduce or affect normal daily activity
- *Severe:* interferes significantly with the participant's normal activity or course of illness

**Serious Adverse Event**
A **serious adverse event** (SAE) is any AE that is:

- Fatal;
- Life-threatening;
- Requires or prolongs hospital stay;
- Results in persistent or significant disability or incapacity;
- A congenital anomaly or birth defect; or
- An important medical event (events that may not be life threatening but are of major clinical significance, such as a drug overdose or seizure that did not result in in-patient hospitalization).

**Adverse Drug Reactions**
An adverse drug reaction is any noxious, unintended or undesirable response to a medicinal product related to any dose.

**Unexpected Adverse Reactions**
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure).

**Adverse Event Collection Period**
AEs occurring as of the first administered dose of the study intervention and 30 days after the last administered dose, or for a follow-up period of at least five half-lives of the study intervention will be collected. AEs recorded during this period will be followed through to resolution, or until the event is assessed as chronic or stable.

**Preexisting Condition**
A preexisting condition is one that is present at the start of the clinical trial. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At the Screening Visit (V1), any clinically significant abnormality will be recorded as a preexisting condition in the participant's CRF. Where applicable and at the consent of the participant, additional information from the participant's healthcare provider including medical records, may be requested. Throughout the clinical trial, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

**Post-study Adverse Event**
At the last scheduled visit, the PI and/or QI should instruct each participant to report any subsequent event(s) that the participant believes might reasonably be related to participation in this clinical trial. The PI and/or QI should notify Health Canada of any death or adverse event (meeting reporting criteria) occurring at any time after a participant has discontinued or terminated participation that may reasonably be related to this clinical trial. Health Canada and Filament Health Corporation should also be notified if the PI and/or QI should become aware of the development of cancer or of a congenital anomaly

in a subsequently conceived offspring of a participant that was involved in this clinical trial.

**Abnormal Laboratory Values**

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions are met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality;
- The abnormality suggests a disease and/or organ toxicity;
- The abnormality is of a degree that requires active management (e.g. change of dose, discontinuation of the study intervention, more frequent follow-up assessments, further diagnostic investigation, etc.); or
- Any laboratory abnormalities assessed as being clinically significant by a study physician or qualified individual.

## 8.2 Recording of Adverse Events

All adverse events occurring during the study period must be recorded. At each contact with the research participant, the research team must seek information on adverse events by specific questioning. Information on all adverse events should be recorded immediately in the participant's CRF and/or legal health record, and recorded in the adverse event log. All adverse events will be assessed the PI for relatedness, expectedness, seriousness, and severity in relation to the study intervention. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the CRF and/or legal health record and assessed by the PI in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs (severe unexpected adverse drug reactions) if needed. Adverse events related to the study drug will be reported to Filament Health Corporation at the end of the study. These reports should not contain PHI. For a full outline of the information required in the report, please review the agreement with Filament.

## 8.3 Reporting of Serious Adverse Events

### 8.3.1 Investigator Reporting: Notifying the Sponsor

There is no sponsor for this study, however Filament Health Corporation is the supplier of the psilocybin used in this trial. Filament Health Corporation will be sent safety reports as outlined in the 'Investigational Drug Supply Agreement' Safety reports on dosing information, AEs, and concomitant medications will be provided annually. Safety reports on demography, AEs, and concomitant medications will be provided at the end of the study. Safety reports on serious adverse events that have a causal relationship to the IP and on pregnancy will occur within 24hrs of the study team being notified. None of these safety reports will contain PHI and all data will be coded.

### 8.3.2 Investigator Reporting: Notifying the REB

The process for notification to the REB for applicable serious adverse events (SAEs) must be completed as per REB reporting requirements. SAEs and unanticipated events must

be recorded and reported to the REB in accordance with the REB's reporting requirements and timelines. Copies of each report and documentation of REB notification and REB receipt/acknowledgement must be kept in the Investigator Study Binder.

### 8.3.3 Sponsor Reporting of SUADRs: Notifying Health Canada

There is no sponsor for this study, thus the PI/QI is responsible for reporting the safety information to Health Canada as required. The SUADR report must be reported to Health Canada in the following cases:

- Where the ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- And within 8 days after having informed Health Canada of the ADR, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

### 8.3.4 Sponsor Reporting of SUADRs: Notifying Sites

Not applicable.

## 8.4 Reporting of Device Deficiencies

Not applicable.

## 8.5 Safety Management Plan

Safety of the participants (including data confidentiality) and the scientific integrity of the project will be ensured by the research team led by the PI. Participant safety will be monitored at each study visit by asking the participant about their experience and about any adverse events from the last study visit. All adverse events will be reviewed by the study PI and reported to the REB and/or Health Canada in accordance with the regulatory guidelines as outlined by each entity. Adverse events will be recorded and/or reported as outlined in Section 8.2 and 8.3. Safety reports on dosing information, AEs, and concomitant medications will be provided annually. Safety reports on demography, AEs, and concomitant medications will be provided at the end of the study. Safety reports on serious adverse events that have a causal relationship to the IP and on pregnancy will occur within 24hrs of the study team being notified. None of these safety reports will contain PHI and all data will be coded. A description of the reporting procedures can be found in the agreement with Filament Health Corporation. The study team will also use a published Suicide Risk Management Protocol to as*sess* and reduce suicide risk (Herbeck et al., 2015). Participants experiencing a serious adverse event will be immediately withdrawn from the study. In the case of increased suicidality, the study physician will conduct an urgent psychiatric assessment with the participant

The study investigator and study team will meet regularly to review the accrued data, data confidentiality, recruitment, and participants complaints. Participant confidentiality will be maintained through the use of code numbers to identify all participants. All research

records will be kept in a locked file and no participants will be identified in any published report.

Participants may be removed from the study at the discretion of the PI. Reasons for possible withdrawal from the clinical trial are outlined in Section 4.7.1.

Remote Assessment Safety Procedures

All remote assessments will be conducted in a private room. The research team will not require identification from the participant as the research team will already be familiar with the participant and will be able to identify them visually through WebEx. The sessions occuring over WebEx or over the phone will not be recorded. If the assessment requires screen sharing, the individual administering the assessment will ensure that any documents or windows on the desktop containing PHI or personal information will be closed. The individual administering the assessment will also have access to necessary communication technology in order to communicate with relevant research supports or emergency services in case of an emergent situation. When sending invitations for remote assessments or communicating via email, the research team will limit personal information in all emails by avoiding full names ot direct identifiers in the subject line of the email or meeting invitation.

## 8.6 Unblinding Procedures

N/A

## 8.7 Data and Safety Monitoring Board

N/A

# 9.0 CLINICAL TRIAL DISCONTINUATION AND CLOSURE

## 9.1 Clinical Trial Discontinuation

This clinical trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (i.e. closure based on PI decision, sponsor/funder decision, REB or other oversight bodies' decision; review of serious, unexpected and related AEs; noncompliance; futility). Notification, which includes the reason for study suspension or termination, will be provided by the suspending or terminating party to research participants, the PI, funding agency, CAMH, and regulatory authorities. If the clinical trial is prematurely terminated or suspended, the PI will promptly inform research participants, the REB, and the sponsor, and will provide the reason(s) for the termination or suspension. All communication with participants for this purpose will go through REB review and approval. Research participants will then be contacted, as applicable, and be informed of changes to the study visit schedule.

# 10.0 DATA HANDLING AND RECORD KEEPING

## 10.1 Source Documents & Case Report Forms

Source data will be collected on paper data collection forms (i.e. source documentation).

We will also collect health card information from all participants that will be securely transferred to ICES, which is a prescribed entity under section 45 of Ontario's Personal Health Information Privacy Act that is permitted to collect personally identifiable information for the purposes health system management and evaluation without individual consent or research ethics approval. The purpose of this transfer will be to link the individual's clinical data with health administrative databases to study long-term safety and efficacy outcomes.

REDCap

Data for this clinical trial will be managed using REDCap electronic case report forms. This system is maintained on central CAMH servers, with data backed up daily, and is supported by the Research Informatics department.

## 10.2 Protocol Deviations

No deviations from or changes to the protocol will be implemented without approval from the REB, unless to eliminate an immediate hazard to a participant. All study staff will monitor the study procedures to detect any potential protocol deviations. All potential protocol deviations will be reviewed by the study PI. The protocol deviation will be reported to the REB if any of the following criteria are met:

- Deviations that, in the opinion of the PI, jeopardize the safety of research participants, or that jeopardize the research efficacy or data integrity
- Any change in the approved process for obtaining consent
- Any deviations that lead to a serious adverse event or unanticipated problem
- Any unauthorized collection, use, or disclosure of personal health information (PHI)

## 10.3 Record Retention

Research records pertaining to this clinical trial will be retained for 15 years.

## 10.4 Clinical Trial Registration

In accordance with TCPS 2, a description of this trial will be registered on www.clinicaltrials.gov before the start of recruitment activities, and the content will be updated throughout the duration of the clinical trial. All results, including negative results should be entered at the completion of the clinical trial.

# 11.0 STUDY MONITORING, AUDITING, AND INSPECTING

## 11.1 Study Monitoring Plan

Site monitoring is conducted to ensure that the rights and well-being of research participants are protected, the reported trial data are accurate, complete, and verifiable, and the conduct of the clinical trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirement(s). Reference the study monitoring plan for specific monitoring information.

## 11.2 Auditing and Inspecting

The PI and site will permit study-related audits, and inspections by the REB, CAMH, sponsor, and applicable granting agencies or regulatory bodies, including access to all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The PI will ensure the capability for audits/inspections of applicable study-related facilities (e.g. research pharmacy, clinical laboratory, imaging facility, etc.).

# 12.0 ETHICAL CONSIDERATIONS

## 12.1 Research Ethics Board (REB) Approval

Research Ethics Board (REB) approval will be obtained prior to beginning any research-specific procedures. Following initial ethics approval, ongoing ethical approval will be maintained and the clinical trial will undergo REB review at least annually, in accordance with regulatory and REB requirements. The clinical trial will be conducted in accordance with the REB-approved study documents and the determinations (including any limitations) of the REB, and in compliance with REB requirements. Any amendments to the protocol will require review and approval by the REB before the changes are implemented in the clinical trial, unless to eliminate an immediate hazard to the participant.

Whenever new information becomes available that may be relevant to participant consent, a consent form and/or consent for addendum will be presented to the REB for review and approval prior to its use. Any revised written information will receive REB approval prior to use.

## 12.2 Informed Consent Process & Documentation

Informed consent is a process that is initiated prior to the individual agreeing to take part in the clinical trial and continues throughout their participation.

Informed consent will be obtained from each participant prior to their participation in the clinical trial. Informed consent will be obtained by appropriately trained and qualified CAMH research personnel who do not have an existing clinical relationship with the

participant or caregiver The PI will not obtain participant consent. Informed consent will be obtained in-person.

Each participant will be provided with a current copy of the REB approved ICF prior to the consent discussion. Research personnel will explain the clinical trial to the participant and answer any questions that may arise. This discussion will include an explanation of the clinical trial purpose, procedures, potential risks and benefits, confidentiality considerations and participant rights (e.g. participants will not be penalized or lose any benefits regardless of what they decide and they have the right to withdraw from the clinical trial at any time). Participants may take as much time as they need to make their decision, and may consult with others (e.g. family members, other health care providers, etc.) if they like. Following the consent discussion, and once the participant has decided to take part, the participant, and the person conducting the consent discussion will personally sign and date the ICF. Each participant will be provided with a complete (fully signed) copy of the ICF. The original ICF(s) and the informed consent process will be documented in the source documents.

Each study visit occurring onsite, including the consent visit, will follow the most current institutional IPAC guidelines put forth by CAMH to ensure staff and participants are protected against COVID-19 and other infectious diseases (e.g. participant screening upon entry, frequent hand-washing, masks for participants and staff).

# 13.0 PRIVACY AND CONFIDENTIALITY

All clinical trial-related documents and data will be held in strict confidence and stored at CAMH or on CAMH servers, and will follow CAMH policies and procedures to ensure participant privacy and confidentiality.

All research activities will be conducted in as private a setting as possible. The study team (including the PI), the study monitor, representatives of the REB, and Health Canada may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records and pharmacy records for the participants in this clinical trial. The participant's contact information will be securely stored at CAMH for internal use during the clinical trial. At the end of the clinical trial, all records will continue to be kept in a secure location in accordance to applicable institutional and regulatory requirements. Safety reports on dosing information, AEs, and concomitant medications will be provided annually. Safety reports on demography, AEs, and concomitant medications will be provided at the end of the study. Safety reports on serious adverse events that have a causal relationship to the IP and on pregnancy will occur within 24hrs of the study team being notified. None of these safety reports will contain PHI and all data will be coded. A description of the reporting procedures can be found in the agreement with Filament Health Corporation.

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Breach of confidentiality will be minimized by the research staff who will maintain research data (identified only by participant code number not related to name,

or date of birth). A list of participant names, their ID numbers, and information about how they can be reached will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. To minimize the risk of breach of confidentiality formal training sessions for all research staff emphasizing the importance of confidentiality will be conducted and formal mechanisms limiting access to information that can link data to individual participants will be monitored and established by study personnel. All information obtained from participants will be kept as confidential as possible. Computer-based files/data will be entered into password-secured databases (details below) and paper-based files will be stored in a secure location. These data will only be accessible to personnel involved in the study and they will abide by confidentiality regulations of the REB.

In unusual cases, a participant's research record may be released in response to a court order. If the research team learns that a participant or someone with whom the participant is involved with is in serious danger or harm, an investigator will inform the appropriate agencies.

Data from this study will be entered into a secure REDCap database. At point-of-entry, data values will undergo consistency edits (e.g., ID validation, range verification, duplicate detection) and personnel will be required to correct errors. Reports will be created via the REDCap program. Data management staff will run logic error programs to check for accuracy and irregularities within and across data structures and within and across sites. Quality assurance checks will be conducted regularly by study personnel. Although unlikely, instances may occur where REDCap is not available. In the case that this happens, we will follow the CAMH REDCap Downtime Procedures.

# 14.0 CLINICAL TRIAL FINANCES

## 14.1 Funding Source

This study is funded by the University of Toronto.

## 14.2 Conflict of Interest

The research team does not have any conflicts of interest to disclose.

# 15.0 PUBLICATION POLICY/DATA SHARING

In the publication of the results of research, the investigators are obliged to preserve the confidentiality of all research participants. Participants will not be identified in any publication of research results. The results of this study will be published as group data without the use of characteristics that would identify individual participants. The study investigator will hold the primary responsibility for the publication of the results of the clinical trial. All publications will follow CAMH policies associated with publications.

Safety data (i.e., pregnancy reports, adverse events and SAE's) will be reported to Filament Health Corp, the provider of the investigational product for this study.

### 15.1 Future Secondary Use of Data

De-identified data from this project may be used for future research by internal and/or external project collaborators in the future. The research team may share de-identified data with other researchers at CAMH or with collaborators around the world. Coded data that has been collected may also be combined with data collected from other people on other studies or it may be saved in a database. This is an optional part of the study for participants. On the ICF, participants can indicate whether they consent to allowing their data to be shared and/or pooled in the future.

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