# Does Psilocybin Require Psychedelic Effects to Treat Depression? A 4-Week, Double-Blind, Proof-of-Concept Randomized Controlled 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* |
| *DSMB* | *Data Safety & Monitoring Board* |
| *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* |

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|---|---|
| *ICF* | *Informed consent form* |
| *IP* | *Investigational product* |
| *IPAC* | *Infection prevention and control* |
| *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* |
| *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* |

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|---|---|
| *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

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|---|---|
| **Title** | Does Psilocybin Require Psychedelic Effects to Treat Depression? An 4-Week, Double-Blind, Proof-of-concept Randomized Controlled Trial |
| **Short Title** | PSI-RIS |
| **Phase** | Phase II |
| **Methodology** | Double-blind randomized clinical trial |
| **Clinical trial Duration** | 36-months to complete all recruitment, study procedures, and data analysis. |
| **Participating site(s)** | CAMH |
| **Objectives** | To assess the tolerability, feasibility, and clinical effects of risperidone and psilocybin administered in combination with supportive therapy to adult participants with treatment-resistant depression. The main objective is to evaluate the feasibility and tolerability of administering psilocybin with risperidone by evaluating recruitment, retention, tolerability and safety. The secondary and exploratory aims are to measure the psychedelic effects by the 5-dimensional altered states of consciousness rating scale (5D-ASC) and antidepressant effects as assessed by the frequency of serious adverse events and the change in the total score of the MADRS from Baseline (V2) to Week 1 (V5). |
| **Number of Participants** | Sixty participants diagnosed with treatment-resistant depression |
| **Study Intervention Reference Therapy/Comparator** | 1 mg of risperidone in combination with 25 mg of psilocybin taken in conjunction with psilocybin-assisted psychotherapy (PAP) compared to placebo + 25mg of psilocybin or 1 mg of risperidone + placebo. |
| **Duration of Intervention** | One day: 5-6hours |

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| **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. All analyses will be conducted under the ITT approach and run with a blinded grouping variable. Missing data will be handled by using full information maximum likelihood method. Feasibility, safety and tolerability endpoints (primary aim) will be examined by standard frequency analysis. The primary analytic strategy will be mixed-effects generalized linear model to inspect group differences on clinical outcomes at endpoint of the secondary and exploratory aims. Exploratory analysis will be performed on a modified ITT principle, including all participants receiving a study intervention. Dichotomous outcomes (e.g. response, remission, adverse events), serious adverse events and dropouts attributed to adverse events will be compared between groups using a Chi-squared test for assessments at a single time-point, and using generalized estimating equations for repeated assessments.<br>Exact paired permutation t-tests will be used to determine whether psilocybin-assisted psychotherapy with risperidone achieves a 50% reduction in MADRS. |

# 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.

## 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 (Johnson et al., 2019). However, there is no convincing evidence that these psychedelic effects are required for an antidepressant effect in patients with MDD (Johnson et al., 2019). In fact, in a recent study, 24 participants who received PAP for MDD, showed no associations between psychedelic effects and sustained improvement in depressive symptoms, suggesting that psychedelic effects may not be necessary to harness psilocybin's antidepressant effects (Gukasyan et al., 2022).

Recently, 'microdosing' – a way of administering psilocybin that involves taking ~10% of a recreational dose two or three times per week – has gained public popularity as a way to achieve the mental health benefits of the drug without inducing psychedelic effects. However clinical trials in healthy subjects indicate that 'microdosing' psilocybin and other psychedelics confers no mental health benefits over placebo (de Wit et al., 2022; Szigeti et al., 2021). Given the increasing public use of 'microdosing', determining whether psilocybin's psychedelic effects are necessary for its antidepressant effects will inform its acceptability (i.e., in patients apprehensive about the psychedelic "trip" and its associated effects) and its scalability (by reducing the resources required for its safe administration).

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). With proper screening and preparation, psilocybin has a safe physiological and psychological profile.

In its current form, psilocybin is not suitable for wide scale clinical adoption. Despite published safety data, psilocybin-induced alterations in perception and consciousness remain a major barrier to widespread clinical implementation, necessitating an 5-6 hour session of intensive psychological support in a clinical setting during administration, in addition to several lengthy preparation and integration sessions pre- and post-dosing. This complex process could be greatly simplified if the psychedelic effects could be diminished without impairing the antidepressant effects. In humans, the intensity of psilocybin-induced perceptual changes correlates with 5-HT2A activation (Madsen et al., 1995). However, psilocybin's antidepressant effects may be mediated through rapid activation of other critical 5-HT receptors. Two 5-HT2A-receptor antagonists – risperidone (an atypical antipsychotic) and ketanserin (an antihypertensive) – eliminate self-reported psilocybin psychedelic effects in humans (Vollenweider et al., 1998). Thus, this intervention will involve the administration of risperidone followed by PAP to determine if the psychedelic experience of psilocybin is necessary to produce antidepressant effects.

## 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). In vitro studies with rat brain preparations have demonstrated that risperidone has a 10-20 fold greater affinity for the 5-$HT_{2A}$ receptor than for the $D_2$ receptor (Meltzer et al., 1989). Similarly, psilocybin also has a high affinity for the 5-$HT_{2A}$ 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). These results indicate that psilocybin's antidepressant mechanism of action may not be dependent on the psychedelic effects (Hesselgrave et al., 2021).

## 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).

However, all published trials to date are limited by small sample sizes, inadequate control groups, lack of blinding, or highly selected participants. Despite these methodological

limitations, the results of these trials have led to growing enthusiasm for the clinical translation of psilocybin for the treatment of MDD and related disorders. Currently, it is assumed that psilocybin's therapeutic effects in MDD require altered consciousness (i.e. the psychedelic "trip"), which is dependent on serotonin 2A (5-HT2A) receptor activation (Vollenweider et al., 1997). All contemporary clinical trials have investigated psilocybin in the context of several hours of intensive psychotherapy given its highly potent psychedelic effects and the need for continuous monitoring. The psychotherapy involves at least 2 hours of preparatory sessions,5-6hours of supportive therapy during the dosing session in the presence of two trained therapists, and 2 hours of post-dosing integration sessions. This amount of specialized psychotherapy impedes scalability of psilocybin as a pragmatic intervention for MDD and TRD given the limited resources and access to trained therapists in most jurisdictions. However, pre-clinical studies in animal models show that psilocybin's antidepressant effects may not be dependent on 5-HT2A activation (and hence the psychedelic effects) (Hesselgrave et al., 2021). This hypothesis has never been tested in humans. Before psilocybin can be administered in the clinic, we need to understand whether its psychedelic effects are needed for its antidepressant effects.

We propose a proof-of-concept randomized clinical trial to determine whether the psychedelic effects of psilocybin are required to yield antidepressant effects. Using a "double-dummy" design, 60 participants with TRD will receive 10 hours of manualized psychotherapy (which includes 5 to 6 hours of psilocybin dosing session) that has previously been used with psilocybin (Guss et al., 2020) and be randomized to three groups: (1) psilocybin 25 mg plus risperidone 1 mg; (2) psilocybin 25 mg plus placebo; (3) placebo plus risperidone 1 mg. We are only recruiting patients with TRD, as psilocybin has not demonstrated superiority over first-line antidepressants for non-refractory MDD (Carhart-Harris et al., 2021). We are using the atypical antipsychotic risperidone, a potent blocker of the 5-HT2A receptor, due to two reasons: (1) a previous study in healthy volunteers has demonstrated that risperidone 1 mg effectively blocks psilocybin's psychedelic effects (Vollenweider et al., 1998), and (2) risperidone is a readily available, safe, and inexpensive generic drug that is used for the treatment of TRD and other mental disorders. Hence, it would be easily adopted in clinical practice if effective when combined with psilocybin. Although risperidone also has actions on dopaminergic receptors, psilocybin has no direct dopaminergic activity (Creese et al., 1975), and psilocybin's psychedelic effects are not blocked by traditional D2-receptor antagonists like haloperidol (Vollenweider et al., 1998).

In summary, if the proposed proof-of-concept study indicates that psilocybin's psychedelic effects may not be required for its antidepressant effects, and this is confirmed in a future RCT, the use of psilocybin could be standardized and safely expanded without the need for intensive psychotherapy, providing a scalable, novel rapid-acting intervention for TRD. It will also inform the development of further trials studying this combination without psychotherapy and continuous monitoring. This may accelerate clinical translation, social acceptance, and therapeutic development for treatment of TRD, and possibly MDD.

## 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. Therefore, participants may receive some benefit from the study if PAP alone or in combination with risperidone is effective in improving depressive symptoms. Participants may also benefit from close monitoring of their clinical conditions.

Psilocybin & Risperidone 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 5-6 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. In addition, these effects are both expected component of the therapeutic response and it is anticipated that these effects will be diminished when given with risperidone. 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).

On the other hand, in larger RCTs in patients with TRD, risperidone 0.5 – 3.0 mg daily has been safe for use (Cantù et al., 2021). Thus, we expect that a single low dose (1 mg) of risperidone to have minimal adverse effects. Risperidone administered alone has common side effects (>10%) of drowsiness, headache, tremors, twitching or uncontrollable muscle movements, dizziness, nausea, and/or dry mouth. It is possible that participants may experience these side effects but this is unlikely with a single 1 mg dose. Previous studies in healthy volunteers indicate that risperidone, a potent blocker of the 5-HT2A receptor, can effectively blocks psilocybin's psychedelic effects (Vollenweider et al., 1998). This study also demonstrated that the combination of risperidone 1 mg and psilocybin 25 mg is safe to use in healthy volunteers (Vollenweider et al., 1998). Thus, we expect a single low dose (1 mg) of risperidone to have minimal adverse effects.

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 proof-of-concept RCT that will: (1) establish the feasibility and tolerability of combining psilocybin and risperidone in patients with TRD; (2) show that this combination blocks the psychedelic effects of psilocybin; and (3) provide pilot data on the antidepressant effect size of this combination (compared to the antidepressant effect size of psilocybin alone), in preparation of a future larger RCT.

## 2.1 Primary Objective

To evaluate the feasibility and tolerability of administering psilocybin (25mg) with risperidone (1 mg) in adults with TRD by evaluating recruitment, retention, tolerability and safety.

Hypothesis 1a (feasibility): We will be able to recruit 60 participants within 24 months with a retention of >90%.
Hypothesis 1b (safety): There will be no significant difference between the three groups in the frequency of dropouts attributed to adverse effects (tolerability) or serious adverse events (safety).

## 2.2 Secondary Objective

The secondary objectives is to evaluate subjective psychedelic effects as measured by the 5-Dimensional Altered States of Consciousness Rating Scale in the three groups, which will be completed at V3 when the acute effects of psilocybin have worn-off.

- Hypothesis 2: The psychedelic effect size in the psilocybin plus placebo group will be larger than in the psilocybin plus risperidone group and the placebo plus risperidone group (in which it will be close to zero).

## 2.3 Exploratory Objective

To evaluate antidepressant effects in the three groups as measured by the change in the MADRS from Baseline (V2) to 1-week post-treatment (V5). The antidepressant effect sizes are expected to be comparable in the psilocybin plus placebo group and psilocybin plus risperidone group and larger than in the placebo plus risperidone group.

# 3.0 CLINICAL TRIAL DESIGN

## 3.1 Overall Design

This study is a three-arm, 4-week, double blind, proof-of concept RCT for investigating psilocybin-assisted psychotherapy (PAP) administered with risperidone in treating TRD. This three-arm “double dummy” design allows for an assessment of risperidone’s anti-psychedelic effects, while allowing for an assessment of psilocybin’s antidepressant effects alone and combined with risperidone, compared to an “active placebo” (i.e. placebo plus risperidone 1 mg).

Overview of Study Design:

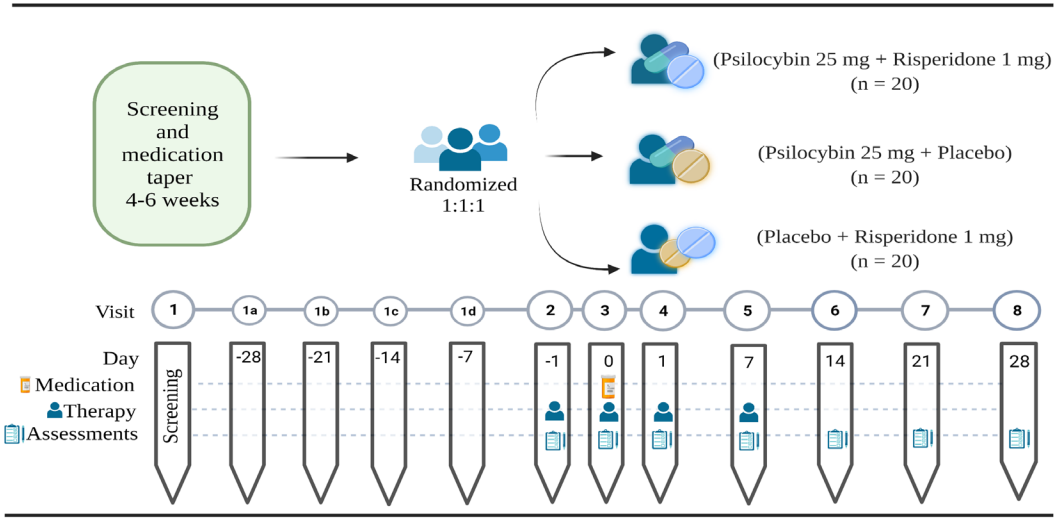
A study team member will obtain informed consent from interested participants prior to study activities being initiated. Following this, participants will undergo a screening assessment where they will complete lab tests, and clinical and psychiatric assessments to determine eligibility. Following the screening visit, eligible participants will undergo a washout period where they will be tapered off concomitant medication over a period of 4 to 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. Participants who are not on prohibited medications will undergo a 2-week monitoring period prior to Baseline (Visit 2). During the tapering period, the study psychiatrist will see participants weekly (V1a, V1b, etc.) for at least 2 weeks to monitor for withdrawal and worsening of depressive 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.

At the Baseline visit (V2), which occurs the day before the dosing session, participants will complete clinical measures, pre-intervention clinical bloodwork 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 to 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 plus risperidone 1 mg, or psilocybin 25 mg plus placebo, or placebo plus risperidone 1 mg. All participants will receive 10 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 in the company of a caregiver or a family member.

After the dosing session, participants will be seen for two 1-hour integration sessions (Day 1 [V4], Week 1 [V5]). At Visit 4, participants will also undergo post-intervention clinical bloodwork. Thereafter, participants will be followed-up after 2 [V6], 3 [V7] and 4 weeks [V8] post-dosing (see Figure 1). A study psychiatrist will be available throughout the duration of the RCT to respond to any concerns or changes in mental/physical state. Participants will not start other interventions for MDD during the study.

*Figure 1. Study Schematic:*




Timeline

In total, there are a minimum of 12 study visits (8 study visits and a minimum of 2 check-in visits during the washout period). There may be more study visits scheduled at the discretion of the study team or the participant. These study visits will take place over the span of approximately 2.5 months. The total expected duration of the clinical trial from the time the study team starts recruiting until data analysis has been complete is 36 months. Following a 6-month startup period including hiring, obtaining psilocybin and receiving a Section 56 exemption, the study team will recruit approximately 2-3 participants per month over the period of 24 months. Study interventions and follow-up assessments will be completed by month 28. This leaves approximately 6 months for data analysis, which will be completed at month 36.

## 3.2 Primary Endpoints

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

Dropouts during three periods will be evaluated: 1) during 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 plus risperidone combination. 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 secondary endpoints for psychedelic effect are the scores on the 5D-ASC visual analogue scale (Dittrich et al., 2010) administered at Visit 3.

## 3.4 Exploratory Endpoints

The antidepressant effects will be assessed by measuring changes from Baseline 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 Weeks 2 (V6), 3 (V7), and 4 (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).

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 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 60 participants (N=60) diagnosed with treatment-resistant depression. 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 external referrals. Participants in this trial must be CAMH patients. External referrals will need to go through the usual referral and admissions processes at CAMH. Clinicians at CAMH 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.

The CAMH Research Registry will also be used to recruit participants for this clinical trial. Upon REB approval to use the Research Registry as a recruitment strategy, authorized research personnel will search and contact potential research participants included within the member database of the Research Registry for study participation. This clinical trial will also be posted on the Research Registry website, as well as the public CAMH website. The recruitment material posted on these websites will be reviewed and approved by Research Communications as well as the REB prior to posting. Once posted, interested participants can use the “Find a CAMH study” feature to explore clinical trials that they are interested in.

Advertisements (Flyers and pamphlets) for the current study will also be posted in patient areas around the CAMH campus (e.g., clinic waiting rooms, main lobbies, etc.).

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
- 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
- History of allergy or adverse reaction to risperidone
- 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, reimbursement will be provided if the participant used public transit for transportation to and/or 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 for all applicable visits and travel reimbursement at the participant's final study visit (Visit 8) via gift card. 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. Ability to take oral medication;
10. 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)
11. 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;
12. Individuals who are willing to and tapered 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;
13. Individuals who are willing to and have tapered off current inhibitors of 5'-diphospho-glucuronosyltransferase (UGT)1A9 and 1A10, aldehyde dehydrogenase inhibitors (ALDHs) and alcohol dehydrogenase inhibitors (ADHs) 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
14. 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) and Baseline (V2) 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. History of allergy or contraindication to risperidone including insulin-dependent diabetes, history of hypoglycemia on oral hypoglycemic agent(s);
11. Lifetime use of serotonergic psychedelic drugs; OR
12. 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 6hrs after administration (V3).
- 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. Presence of these substances will be assessed at a urine drug screening at Visit 1 and Baseline (V2)
- 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.

## 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 may 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.

Pharmacokinetics and Risperidone Effects

Risperidone is an atypical antipsychotic with antagonist binding affinity at serotoninergic, dopaminergic, adrenergic, and histaminergic receptors (Schatzberg & Nemeroff, 2009). It has a very high affinity for the 5-$HT_{2A}$ receptor (Meltzer et al., 1989) and moderately high affinity for the $D_2$ dopamine receptor (Schatzberg & Nemeroff, 2009). Risperidone is taken orally and almost entirely absorbed in the GI tract and metabolized in the liver (Schatzberg & Nemeroff, 2009). The plasma half-life is approximately 3 hours in extensive metabolizers and 20 hours in poor metabolizers (Broder et al., 2012). Clearance values for risperidone and the active metabolite are estimated to be 4.6 and 6L/hr, respectively (Vandenberghe et al., 2015). In general, risperidone is well-tolerated. It does have a broad range of common side effects (>10%) which include somnolence, nausea, dizziness, dry mouth, and tremor (Chopko & Lindsley, 2018). Risperidone has been shown to improve depression in SSRI-resistant patients (Correia & Vicente, 2007). In healthy subjects, risperidone (1 mg) blocked (98-99%) the psychedelic effects of psilocybin including the perceptual disturbances and hallucinatory phenomena (Vollenweider et al., 1998).

Psilocybin-Assisted Psychotherapy

All participants will receive manualized psychotherapy in conjunction to their assigned pharmacological treatment. The participant will attend 1 preparatory session (V2) that occurs within 7-days of the psilocybin dosing session (V3) to develop a therapeutic alliance, set intentions for the experience, and learn what to expect during the dosing session. Ideally, the preparatory therapy session will occur the day before dosing. 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. At least one of the therapists will be a clinician and 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 CORP. (Burnaby, British Columbia, Canada). The dose of psilocybin used in this study will be 25mg. The psilocybin will be administered in size 2 hydroxypropyl methyl cellulose (HPMC). The risperidone will be provided by CAMH pharmacy and will appear as a 1mg oral compounded capsule.

## 5.2 Treatment Regimen

There will be 1 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 2 treatment bottles with 1 capsule in each containing: 1 capsule of 25mg psilocybin or 1 capsule of 1mg of risperidone, or 1 capsule of placebo. Under the supervision of a clinician and based on the group they have been randomized to, the participant will take the intervention in the following order:

1. 1mg capsule of risperidone followed 60 minutes later by a 25 mg capsule of psilocybin
2. Placebo followed 60 minutes later by a 25 mg capsule of psilocybin
3. 1mg capsule of risperidone following 60 minutes later by placebo

Each treatment will be taken orally with a glass of water. There will be no modifications to the dosage, each participant will receive the same dosage for both medications. 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

Participants will be randomized to three groups in a 1:1:1 allocation: 1) psilocybin 25 mg plus risperidone 1 mg; 2) psilocybin 25 mg plus placebo; 3) placebo plus risperidone 1 mg. Randomization will be computer-generated, using a random permuted block method with variable block sizes. The sample will be stratified for severity of depressive symptoms [17-item Hamilton Depression Rating Scale (HamD-17) (Hamilton, 1960) score < 25 vs. > 26]. We have not included additional stratification variables as per best practice in RCTs (Therneau, 1993). We will assess other potential prognostic characteristics (age, self-reported biological sex, gender) in our a priori subgroup analyses. After randomization, 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 the study psychiatrist who will supervise the participant. The participant will receive:

1. 1mg capsule of risperidone followed 60 minutes later by a 25 mg capsule of psilocybin
2. Placebo followed 60 minutes later by a 25 mg capsule of psilocybin
3. 1mg capsule of risperidone following 60 minutes later by placebo

The capsules 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 risperidone will take approximately 60 minutes after administration. 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.

About 5 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. The study team is to be notified that the participant has arrived home safely via phone call. In the absence of receiving a phone call, the study staff will directly contact the participant.

## 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 source document 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.

From 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 of 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, zoplicone 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.

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 1 month 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. In addition, participants must also taper off inhibitors of 5'-diphospho-glucuronosyltransferase (UGT)1A9 and 1A10, aldehyde dehydrogenase inhibitors (ALDHs), and alcohol dehydrogenase inhibitors (ADHs) for a minimum of 2-weeks (or more depending on the medication) prior to Baseline (V2).

These medications should not be re-introduced until after Week 4 (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 data collection form. 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. additional 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 risperidone 1 mg will be provided and packaged by CAMH pharmacy. The psilocybin and placebo will be provided by Filament Health Corp (Burnaby, British Columbia, Canada). The dose of psilocybin used in this study will be 25mg. Filament will provide extra 20% of the capsules needed. The entire shipment for this trial will be sent in bulk (i.e. 48 capsules of psilocybin x 25mg each and 48 capsules of placebo). Psilocybin capsules will be packaged individually in high-density polyethylene bottles with silica desiccant and cotton. 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 Corp will be sent safety reports on adverse events, and suspected unexpected serious adverse reactions. For a description of safety reporting, please see Section 8.3.1 of the protocol.

## 5.8 Blinding of Study Intervention

The randomized allocation will be concealed from all except the research pharmacist, who will have no contact with the study team. Risperidone 1 mg has mild psychoactive effects such as drowsiness and dysphoria. Those receiving risperidone plus psilocybin or risperidone plus placebo may experience these mild psychoactive effects which can help to preserve the blinding.

## 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

The risperidone will be stored with CAMH pharmacy. 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 that meet criteria for reporting will be reported to the REB as a protocol deviation.

### 5.9.3 Dispensing of Study Intervention

Each participant will be assigned 2 treatment bottles with 1 capsule in each containing: 1 capsule of 25mg psilocybin or 1 capsule of 1mg of risperidone, or 1 capsule of placebo. Under the supervision of a clinician and based on the group they have been randomized to, the participant will take the intervention in the following order:

1. 1mg capsule of risperidone followed 60 minutes later by a 25 mg capsule of psilocybin
2. Placebo followed 60 minutes later by a 25 mg capsule of psilocybin
3. 1mg capsule of risperidone following 60 minutes later by placebo

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).

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) At screening (washout period only) and Baseline to 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:

*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
  - ATHFSCID-5
  - HamD-17
  - 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/people 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. 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 at each contact/visit. Participants who are not on any prohibited medications will still undergo a two week period between Screen (V1) and Baseline (V2), where they are assessed for suicidality via the C-SSRS.

Any safety assessment visits during the washout period will be called V1a, V1b, etc. During these visits, the C-SSRS 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, pulse)
  - C-SSRS
  - CGI
  - GAD-7
  - MADRS
  - SETS
  - SHAPS
  - WHOQOL-BREF
  - WEMWBS
- Clinician administered:
  - Confirmation of eligibility criteria
  - Review of assessments administered
- Optional laboratory evaluations collected at the Queen Street CAMH laboratory:

Blood: 20mL of blood will be withdrawn under fasting conditions (minimum 6-hour fast) from participants at Visit 4. The plasma will be separated by centrifuging the blood at 1500 rpm for 10 min at 4°C, and subsequently stored at -80°C for future analysis. This is optional for all participants.

- Mitochondrial biomarkers: (1) circulating cell-free mitochondrial DNA (ccf-mtDNA): We will use the QIAmp 96 DNA Blood kit (Qiagen, Valence, USA) to extract DNA from 200µL of the plasma, according to manufacturer protocols for blood and body fluids. The total DNA will be quantified using spectrophotometric analysis at 260/280 nm in NanoPhotometer ® P-Class (Implen, Westlake Village, CA, US). Quantitative analysis of the ccf-mtDNA will be performed using a real-time polymerase chain reaction (RT-PCR). The PCR reaction will be performed using SYBR Green Technology (Thermo Fisher Scientific, Waltham, MA, USA). Each 20 µL reaction contained 5 µL of template, 1 µL of each primer (10 µM), 10 µL SYBR MIX (2× Sensifast, Bioline,

London, UK), and 3 µL of nuclease-free water. Each reaction will be run in triplicate on CFX96 Touch Real-Time PCR Detection System (Bio-rad, Hercules, California, USA). PCR program: initial denaturation at 95 ◦C for 10 min, followed by 45 cycles consisting of 95 ◦C in 10 s (melting), 65 ◦C for 10 s (annealing), and 72C for 10sec (extension). The program ended with a melting curve analysis measuring fluorescence continuously from 60 to 97 ◦C. We will use primers to amplify the mtDNA genes MT-ND1 and MT-ND4, as well as nuclear β-2 microglobulin.

- (2) mtDNA next-generation sequencing: Genomic DNA will be purified from blood samples (10 ml) (ChemagicTM MSM I DNA extractor; Perkin-Elmer, Waltham, MA) following manufacturer protocol. Briefly, whole mtDNA will be amplified in one large fragment of 16.6kb in length using long-range polymerase chain reaction approach. The mtDNA next generation sequencing (NGS) will be performed on Illumina MiSeq v3 device using 2x300 read length. Libraries will be prepared using standard Illumina DNA Preparation for NGS. The CAMH Biobank team will prepare the samples (pre-sequencing preparation), and send them to the Ontario Institute for Cancer Research facility for DNA sequencing.We will use in-house pipeline for raw data cleaning and variant call. (3) mtDNA-copy number: The mtDNA copy number will be assayed using the relative quantification method using a mtDNA amplicon and a nuclear single copy gene (β-2 microglobulin). The ratio of mtDNA to nuclear DNA will be quantified by 2−ΔCt method using primers for mtDNA and nuclear β-2 microglobulin as well as thermal cycler condition as standard. All qPCR will be performed on the BioRad CFX96 RT-PCR detection system (Bio-Rad Laboratories, Inc.). Each sample will be run in triplicate using 0.6ng of DNA in a 20µl reaction. The PCR reactions will be performed on separate runs with the same samples in the same well positions. Primers will be the same as describe for ccf-mtDNA.
- Neuroinflammation markers: Brain Derived Neurotrophic Factor (BDNF) and Inflammatory Cytokines,
- Plasma levels of Tryptophan, 5-HT and Kynurenine

- *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

- 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 or combine two preparatory visits into a single session, lasting up to four hours.

- Prep therapy can occur in-person or via secure videoconferencing software (i.e. WebEx).
- 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) – one of the following:
  - 1 oral dose of 1mg of risperidone, followed 60-minutes later by 1 oral dose of 25mg of psilocybin administered in conjunction with supportive therapy (PAP).
  - 1 oral dose of 1mg of risperidone, followed 60-minutes later by 1 oral dose of placebo administered in conjunction with supportive therapy (PAP).
  - 1 oral dose of placebo, followed 60-minutes later by 1 oral dose of 25 mg 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 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
    - Treatment Allocation Questionnaire (TAQ): To assess the integrity of blinding procedures, participants, a member of the study team and both therapists will be asked to fill a conventional guess form asking them whether they believe the participant received psilocybin alone, psilocybin with risperidone or risperidone alone, after they have completed all other research

assessments. This will be completed at the end of the dosing session (V3).

- 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:
  - CSSRS
  - CGI
  - MADRS
  - SHAPS

- 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. Integration therapy can occur in-person or via secure videoconferencing software (i.e. WebEx). For more detailed information on the integrative therapy sessions, please refer to the therapists manual (Yale Manual for Psilocybin-Assisted Therapy of Depression).

**On *Visit 4 (V4)* only**

- Biological specimen collection and laboratory evaluations collected at the Queen Street CAMH laboratory:

Optional blood collection: 20mL of blood will be withdrawn under fasting conditions (minimum 6-hour fast) from participants at Visit 4. The plasma will be separated by centrifuging the blood at 1500 rpm for 10 min at 4°C, and subsequently stored at -80°C for future analysis. This is optional for all participants.

- Mitochondrial biomarkers: (1) circulating cell-free mitochondrial DNA (ccf-mtDNA): We will use the QIAmp 96 DNA Blood kit (Qiagen, Valence, USA) to extract DNA from 200µL of the plasma, according to manufacturer protocols for blood and body fluids. The total DNA will be quantified using spectrophotometric analysis at 260/280 nm in NanoPhotometer ® P-Class (Implen, Westlake Village, CA, US). Quantitative analysis of the ccf-mtDNA will be performed using a real-time polymerase chain reaction (RT-PCR). The PCR reaction will be performed using SYBR Green Technology (Thermo Fisher Scientific, Waltham, MA, USA). Each 20 µL reaction contained 5 µL of template, 1 µL of each primer (10 µM), 10 µL SYBR MIX (2× Sensifast, Bioline, London, UK), and 3 µL of nuclease-free water. Each reaction will be run in triplicate on CFX96 Touch Real-Time PCR Detection System (Bio-rad, Hercules, California, USA). PCR program: initial denaturation at 95 ◦C for 10 min, followed by 45 cycles consisting of 95 ◦C in 10 s (melting), 65 ◦C for 10 s (annealing), and 72C for 10sec (extension). The program ended

with a melting curve analysis measuring fluorescence continuously from 60 to 97 ◦C. We will use primers to amplify the mtDNA genes MT-ND1 and MT-ND4, as well as nuclear β-2 microglobulin.

- (2) mtDNA next-generation sequencing: Genomic DNA will be purified from blood samples (10 ml) (ChemagicTM MSM I DNA extractor; Perkin-Elmer, Waltham, MA) following manufacturer protocol. Briefly, whole mtDNA will be amplified in one large fragment of 16.6kb in length using long-range polymerase chain reaction approach. The mtDNA next generation sequencing (NGS) will be performed on Illumina MiSeq v3 device using 2x300 read length. Libraries will be prepared using standard Illumina DNA Preparation for NGS. The CAMH Biobank team will prepare the samples (pre-sequencing preparation), and send them to the Ontario Institute for Cancer Research facility for DNA sequencing.We will use in-house pipeline for raw data cleaning and variant call. (3) mtDNA-copy number: The mtDNA copy number will be assayed using the relative quantification method using a mtDNA amplicon and a nuclear single copy gene (β-2 microglobulin). The ratio of mtDNA to nuclear DNA will be quantified by 2−ΔCt method using primers for mtDNA and nuclear β-2 microglobulin as well as thermal cycler condition as standard. All qPCR will be performed on the BioRad CFX96 RT-PCR detection system (Bio-Rad Laboratories, Inc.). Each sample will be run in triplicate using 0.6ng of DNA in a 20µl reaction. The PCR reactions will be performed on separate runs with the same samples in the same well positions. Primers will be the same as describe for ccf-mtDNA.
- Neuroinflammation markers: Brain Derived Neurotrophic Factor (BDNF) and Inflammatory Cytokines,
- Plasma levels of Tryptophan, 5-HT and Kynurenine

***Visit 6 (V6), Visit 7 (V7) & Visit 8 (V8) – Follow-Up: Week 2, Week 3 & Week 4***

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:
  - CSSRS
  - CGI
  - GAD-7 (except Visit 7)
  - MADRS
  - SHAPS
  - 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.

## 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) | 3-Weeks Post-Intervention (Visit 7, Day 21) | 4-Weeks Post-intervention (Visit 8, Day 28) |
|---|---|---|---|---|---|---|---|---|---|
| Location of Visit | Clinic | Remote | Clinic | Clinic | Clinic | Clinic | Remote | Remote | Remote |
| Allowable Window | | Weekly | | = or < 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[8] | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| CSSRS[3] | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| HamD-17 | ✓ | | | | | | | | |
| MADRS | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| SCID-5 | ✓ | | | | | | | | |
| Vital signs (blood pressure, pulse) | ✓ | | ✓ | ✓ | | | | | |
| Vital signs (body temperature) | | | | ✓ | | | | | |
| Weight | ✓ | | | | | | | | |
| Height | ✓ | | | | | | | | |
| ECG | ✓ | | | | | | | | |
| Clinical laboratory tests[4] | ✓ | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Blood collection for future analysis | | | ✓ | | ✓ | | | | |
| Urinalysis | ✓ | | | | | | | | |
| Urine drug screening | ✓ | | ✓ | | | | | | |
| Urine pregnancy test[5] | ✓ | | ✓ | | | | | | |
| Documentation of birth control | ✓ | | | | | | | | |
| Preparatory/Integrative therapy & psychoeducation[6] | | | ✓ | ✓ | ✓ | ✓ | | | |
| Intervention (1mg of risperidone + 25mg of psilocybin) | | | | ✓ | | | | | |
| Adverse event and serious adverse event review and evaluation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Source documentation & CRF completion | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 5D-ASC[7] | | | | ✓ | | | | | |
| MEQ | | | | ✓ | | | | | |
| GAD-7 | | | ✓ | | | | ✓ | | ✓ |
| SETS | | | ✓ | | | | | | |
| SHAPS | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| WEMWBS | | | ✓ | | | | ✓ | | ✓ |
| WHO-QOL-BREF | | | ✓ | | | | ✓ | | ✓ |
| Treatment Allocation Questionnaire | | | | ✓ | | | | | |

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 (= or <7 days from dosing day) to reduce the burden on participants. These visits will be V2a, V2b etc.
3. The "Last 12 Months" version will be administered at Screening 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 and therapy can occur in-person or via WebEx.
7. To be administered immediately after the acute effects of psilocybin have subsided.
8. The CGI severity index will be used at Baseline and the CGI follow-up (included question #2) will be used at the follow-up visits

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

The proposed sample size will provide informative confidence interval estimates for continuous and binary outcomes. E.g., the margins of error are 8.9% for recruitment rate and 7.6% for retention rate. For continuous outcomes, the margin of error is approximately 0.66SD for between group differences. For the secondary aim, with the planned total sample size of 60 (20 per group) we will have sufficient power (0.80) to detect an effect size (ES) of 0.96 (Cohen's d) for the psychedelic effects measured by 5D-ASC when comparing the psilocybin plus placebo group with the psilocybin plus risperidone and placebo plus risperidone group. Previous RCTs in healthy volunteers, have reported larger effects on the 5D-ASC when comparing psilocybin alone with psilocybin plus a 5HTA receptor antagonist (Vollenweider et al., 1998).

For the exploratory aim, meta-analyses of published trials report very large psilocybin antidepressant ES' (Cohen's $d > 0.8$, CIs $-1.285$ to $-0.367$) (Galvão Coelho et al., 2021) but these are likely inflated due to the small sample sizes in each study and hence it would be unwise to base our sample size calculation on this data. Instead, we based the sample size determination on published recommendations for pilot trials (Julious, 2005). Nonetheless we have sufficient power to detect ES' of 0.96 and 0.91 for the primary clinical endpoint (Week 1) and longitudinal analyses (Day 1, Weeks 1 to 4) respectively, when comparing changes on MADRS between the two psilocybin groups and the placebo plus risperidone group. The power reduces to 0.67 for an ES of 0.8 and 0.33 for an ES of 0.5. The power/sample size calculations assume a 10% dropout rate, two-tailed tests, and significance of 0.05.

## 7.2 Statistical Methods

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.

All analyses will be run with a blinded grouping variable. Analyses will be conducted under the ITT approach and full information maximum likelihood method will be employed to tackle missing data. Diagnostic analysis and sensitivity analysis will be implemented to examine outliers, high influential cases, normality and missing at random assumptions. Standard frequency analysis will be completed for feasibility (recruitment, retention), safety and tolerability outcomes (e.g., frequency and duration of adverse events). Exploratory analysis of clinical outcomes will be performed on the modified ITT principle, including all participants receiving a study intervention.

The primary analytic strategy will be generalized linear model to inspect group differences on clinical outcomes at endpoint. Individual level random effects will be added to the model for longitudinal analysis (thus mixed-effects models). For the secondary aim, we will examine group differences in psychedelic effects measured by 5D-ASC by treating

treatment assignment as the primary predictor in the linear models. For the exploratory aim, treatment difference on antidepressant effects will be examined by comparing changes in MADRS across groups from baseline to one-week post-treatment (i.e. Week 1/V5). Age, self-reported biological sex, and baseline MADRS total scores (to account for potentially larger changes in those with higher baseline symptoms) will be included as covariates. Mixed-effects model will be used to inspect change over time (Day 1, Weeks 1 to 4). Also for the exploratory aim, while not fully powered, non-inferiority test will be conducted to examine if the psilocybin plus risperidone group demonstrate comparable effects on MADRS to the psilocybin plus placebo group. Exact paired permutation t-tests will be used to determine whether psilocybin-assisted psychotherapy with risperidone achieves a 50% reduction in MADRS.

Dichotomous outcomes (e.g., response, remission, adverse effects) will be compared between groups using a Chi-squared test for assessments at a single time, and using generalized estimating equations for repeated assessments. Serious adverse events and dropouts attributed to adverse effects will be compared between groups using a Chi-squared test for assessments at a single time, and using generalized estimating equations for repeated assessments. We will also examine changes in secondary clinical measures using the same general linear model framework. Point and confidence estimates will be the preferred measure to report group differences. These exploratory results will be reported uncorrected as they are provided mainly for descriptive purposes and do not represent primary outcomes. The trial will be conducted and reported as per the CONSORT statement for RCTs.

Subgroup analyses

Subgroup analysis will be completed to compare treatment effects between groups formed by: (1) biological sex (self-reported); and (2) gender, by adding interactions with treatment to the regression models. Results for each sex will be reported separately irrespective of whether self-reported sex is a significant mediator. Exploratory analysis will be conducted to compare responders versus non-responders to identify potential clinical and demographic factors that are associated with clinical benefits.

Final statistical analysis will be completed only at the end of the trial. There will be no interim analysis.

# 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 unfavourable 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 screening visit and until the last follow-up visit. 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 data collection form. 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 Corp. 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 data collection form 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 data collection form 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 Corp within 24hrs of the study team becoming aware of the event. These reports should not contain PHI.

## 8.3 Reporting of Serious Adverse Events

### 8.3.1 Investigator Reporting: Notifying the Sponsor

CAMH is the sponsor for this study and will be notified in accordance reporting guidelines. Filament Health Corp. is the supplier of the psilocybin used in this trial. Filament Health Corp will be sent safety reports on adverse events and serious adverse events within 24hrs of the study team becoming aware of the event. 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

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 AEs and SAEs will be provided to Filament Health within 24hrs of the study team becoming aware of the event. In addition, all safety data related to the psilocybin will be provided to Filament Health.. None of these safety reports will contain PHI and all data will be coded. 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.

Therapeutic Risk Management Measures for Psychological Harm

Psychological well-being will be closely monitored by the study team and study therapists throughout the trial. Study therapists will provide the participant with information about what might be experienced during the dosing session, including physiological, sensory and psychological effects, and the possibility of challenging experiences. The role of the therapists at each of the therapy sessions is to provide support for the participant and create a psychologically safe environment. Therapists will work with the participant to develop grounding exercises according to the participant's preference (e.g., deep breathing, breath-focused awareness, progressive muscle relaxation etc.). These grounding techniques will be re-reviewed on the day of the intervention. Following dosing, integration therapy sessions will be conducted where participants can reflect on their dosing experience with the study therapists. For a full description of therapeutic safety monitoring procedures, refer to the Yale Manual for Psilocybin-Assisted Therapy of Depression. Participants will continue to be followed by the study team for up to 4-weeks after the intervention. Psychological well-being (including suicidality) and adverse event monitoring will be assessed at all time-points.

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

Emergency unblinding will be limited to situations when the PI has determined that appropriate emergency medical care of a study participant requires access to the treatment assignment. The study team will report any intentional or unintentional unblinding to the REB through the protocol deviation reporting process and this will be documented and explained in the final clinical report.

### 8.7 Data and Safety Monitoring Board

The international guidelines for the Data and Safety Monitoring Board will be followed. A DSMB will monitor the conduct of the protocol to ensure the safety of participants and validity and integrity of the data. The DSMB will advise investigators on matters pertaining to participant safety, conduct of the study, and its continuation. Members of the DSMB will create and follow the DSMB charter, which will be agreed upon by all members and submitted to the REB as an amendment for approval. The DSMB will include a chair with expertise in clinical trials, a biostatistician, and one clinician with expertise in safety monitoring. The DSMB will meet prior to initiation of recruitment to review their responsibilities and at least once a year after recruitment begins. The DSMB will have exclusive access to the unblinded data. The study team will be accountable to this independent DSMB, which will make recommendations to the PI and Trial Steering Committee (TSC). The TSC will comprise a patient representative and three external experts in clinical trials, of which at least one who will have expertise in psilocybin. The TSC will meet once prior to initiation of recruitment, and then bi-annually thereafter to ensure that the standards set out in Guidelines for Good Clinical Practice (GCP) are met, monitor and supervise the progress of the study and adherence to the study protocol, and advise on ethical issues. As this is a pilot trial, there are no criteria for early study termination.

## 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 or Health Canada, 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 intentional or unintentional breaking of the blind
- 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)

Note: any intentional or unintentional breaking of the blind will be reported and explained in the final clinical report.

## 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 AEs and SAEs will be reported to Filament Health within 24hrs of the event occurring. In addition, safety data generated from the trial regarding the use of psilocybin and a report on the safety and efficacy of the clinical trial data will be provided to Filament Health Corp. . None of these reports will contain PHI and all data will be coded.

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 Canadian Institutes of Health Research (CIHR).

## 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.

## 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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