Evaluating the feasibility, clinical effects, and safety of psilocybin-assisted psychotherapy for treatment-resistant obsessive-compulsive disorder: An open-label clinical trial.

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STATEMENT OF COMPLIANCE

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

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

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Signature of PI Date

LIST OF ABBREVIATIONS

AE	*Adverse Event*
CAMH	*Center for Addiction and Mental Health*
CGI	*Clinical Global Impression Scale*
CRF	*Case report form(s)*
C-SSRS	*Columbia-Suicide Severity Rating Scale*
DLPFC	*Dorsolateral Prefrontal Cortex*
DMPFC	*Dorsomedial Prefrontal Cortex*
DSMB	*Data Safety & Monitoring Board*
ECG	*Electrocardiography*
EEG	*Electroencephalography*
EMG	*Electromyography*
GAD-7	*Generalized Anxiety Disorder 7-Item Scale*
GCP	*Good Clinical Practice*
ICF	*Informed consent form*
MEP	*Motor Evoked Potential*
MEQ	*Mystical Experiences Questionnaire*
MSI-BPD	*Mclean Screening Instrument for Borderline Personality Disorder*
OCD	*Obsessive Compulsive Disorder*
PAP	*Psilocybin-Assisted Psychotherapy*
PHI	*Personal Health Information*
PHIPA	*Personal Health Information Protection Act*
PHQ-9	*Patient Health Questionnaire*

PI	*Principal Investigator*
QI	*Qualified Investigator*
RMT	*Resting Motor Threshold*
SAE	*Serious Adverse Event*
SCID-5	*Structured Clinical Interview for DSM-5*
SI 1mV	*Stimulus Intensity that evokes MEPs with an average amplitude of 1 mV*
SUSAR	*Suspected unexpected serious adverse reaction*
TASS	*Transcranial Magnetic Stimulation Adult Safety Screen*
TCPS 2	*Tri-Council Policy Statement*
TMS	*Transcranial Magnetic Stimulation*
TR-OCD	*Treatment Resistant Obsessive-Compulsive Disorder*
VAS	*Visual Analog Scale*
WMSWBS	*Warwick-Edinburgh Mental Wellbeing Scale*
WHODAS	*World Health Organization Disability Assessment Schedule*
WHO-QoL-BREF	*World Health Organization Quality of Life Questionnaire – Brief Version*
YBOCS	*Yale-Brown Obsessive Compulsive Scale*
5D-ASC	*Five Dimensions of Altered States of Consciousness*

CLINICAL TRIAL SUMMARY

Title	Evaluating the feasibility, clinical effects, and safety of psilocybin-assisted psychotherapy for treatment-resistant obsessive-compulsive disorder: An open-label clinical trial.
Short Title	Psilocybin-assisted therapy for OCD
Phase	Phase I
Methodology	Open-label clinical trial
Clinical trial Duration	18-months to complete all recruitment, study procedures, and data analysis.
Participating site(s)	Single-Center
Objectives	To assess the safety, feasibility, and clinical effects of psilocybin, administered under supportive conditions to adult participants with treatment-resistant OCD, in improving OCD symptoms as assessed by the frequency of serious adverse events and the change in the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score from Baseline (V2) to Week 3 (Visit 8).
Number of Participants	Ten participants diagnosed with treatment-resistant obsessive compulsive disorder
Study Intervention Reference Therapy/Comparator	Two sessions of orally administered 25mg of psilocybin taken in conjunction with psilocybin-assisted psychotherapy (PAP).
Duration of Intervention	Two days: 5-6 hours each day.
Statistical Methodology	Characteristics of the trial cohort will be summarized by mean (SD), median (minimum, maximum). Conservative nonparametric testing will be used to address the primary and secondary objectives. Exact paired permutation t-tests will be used to determine whether psilocybin-assisted psychotherapy achieves a 50% reduction in YBOCS symptoms.

1.0 INTRODUCTION

1.1 Background

Obsessive-compulsive disorder (OCD) is a highly debilitating illness that has a lifetime prevalence of 2-3% (Ruscio et al., 2010; Weissman et al., 1994). Although the presentation can vary, OCD is characterized by intrusive thoughts, images, or urges which are typically accompanied by repetitive behaviors or mental acts (compulsions). It is a chronic disorder that has significant negative effects on an individual's quality of life particularly impacting social relationships (Stein et al., 2019; Subramaniam et al., 2013).Treatment options for OCD include pharmacological treatment, cognitive behavioural therapy (CBT), and as a last resort, surgery. However, up to 40% of patients diagnosed with OCD do not respond to the available treatment modalities (Bloch et al., 2006; Pallanti & Quercioli, 2006). Although there is some debate in the literature, treatment-resistant OCD is defined as individuals' who have failed to respond to at least 2 therapeutic trials of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (Husted & Shapira, 2004; Pittenger et al., 2005). Given the increased risk of morbidity and mortality associated with treatment-resistant OCD, there is an urgent need for novel interventions (Meier et al., 2016).

1.2 Study Intervention

Recently, 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). It has been suggested that psilocybin has the potential to disrupt an individual's maladaptive habits of cognition, affect, and behavior, alongside well-aligned psychotherapy, can lead to sustained clinical improvements.

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 which is chemically similar to the neurotransmitter, serotonin, and the essential amino acid, tryptophan. It is considered a 5-hydroxytrptamineric (serotonergic) psychedelic along with other similar drugs such as dimethyltryptamine (DMT) and lysergic acid diethylamide (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. With proper screening and preparation, psilocybin has a safe physiological and psychological profile. Psilocybin is currently the preferred compound for use in clinical research involving 5-hydroxytrptaminergic psychedelics because it has

a shorter duration of action and suffers from less notoriety and stigma than other similar drugs (Carter et al., 2005; Gouzoulis-Mayfrank et al., 1999; Hasler et al., 2004).

Psilocybin administered in conjunction with psychotherapy has been used in psychiatry since the 1950s. However, there was a paucity of research until the mid-1990s due to its classification as a Schedule 1 substance in the United Stated (US) (Passie et al., 2002). 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 occur 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).

1.3 Preclinical Data to Date

Preclinical data on the use of psilocybin for the treatment of OCD is limited as it is difficult to for a true animal model to be determined for a condition that is primarily characterized by obsessive thoughts. There is one study published on a rodent model of OCD. Matsushima et al. (2009) studied the effects of psilocybin on marble-burying behavior in mice. Marble-burying behavior has been widely used as a cost-effective model of OCD on the grounds that it is a non-functional and repetitive behavior that may be an outward expression of OCD (Matsushima et al., 2009). Both synthetic psilocybin and the mushroom solution used in the study reduced marble burying behavior without reducing general locomotor activity (Matsushima et al., 2009). Although this study shows interesting results, the generalizability and applicability of these findings in other animal models is yet to be determined (Jacobs, 2020).

1.4 Clinical Data to Date

To date, there are numerous studies supporting the clinical efficacy of PAP for the treatment of depression and end-of-life anxiety (Carhart-Harris et al., 2021; Griffiths et al., 2016; Ross et al., 2016). Currently, there are over 60 studies registered on ClinicalTrials.gov exploring the use of psilocybin to treat various mental health disorders. A recent randomized control trial (RCT) demonstrated large effect sizes sustained for 4.5 years after a single dose of psilocybin administered with psychotherapy in patients with cancer-related existential distress (Agin-Liebes et al., 2020). In addition, several trials have observed rapid and sustained improvements in patients with treatment-resistant depression with one RCT demonstrating similar efficacy between psilocybin compared with an SSRI. Interestingly, secondary outcomes favoured psilocybin (Carhart-Harris et al., 2021).

Although there are several studies demonstrating the efficacy of PAP for the treatment of depression and anxiety, there is limited clinical data available reporting on the use of

psilocybin-assisted psychotherapy to treat OCD. To date, there are several case reports in the literature that indicate psilocybin-mediated relief of OCD symptoms (Leonard & Rapoport, 1987; Lugo-Radillo A Md & Cortes-Lopez, 2021; Moreno & Delgado, 1997; Wilcox, 2014). The most recent report, of a 30-year old male with debilitating OCD symptoms for more than 10 years, described significant reductions in symptoms for up to 6-months after the initial use (Wilcox, 2014). Regrettably, the published case studies do not include precise doses, psychotherapy, or controlled assessment measures.

An open-label study of psilocybin for OCD, Moreno et al. (2006) enrolled nine participants who had an average of 3.4 previous treatment failures. Patients received escalating doses of psilocybin (7mg/70kg – 21mg/70kg), each separated by at least a week. In the 24-hr post-administration monitoring period, all patients experienced a 23-100% reduction from baseline on the Yale-Brown Obsessive-Compulsive Scale (YBOCS), indicating a marked relief from symptoms (Moreno et al., 2006). Two-thirds of patients maintained a greater than 50% decrease in YBOCS score at 24 hours for at least one session. Two patients reported symptomatic relief lasting nearly a week with one patient still in remission at the 6-month follow-up (Jacobs, 2020; Moreno et al., 2006). It is believed that PAP may function as a 'reset button' in individuals with OCD whereby there is an acute disruption in the maladaptive functioning of the default mode network (DMN) (Carhart-Harris et al., 2017; Jacobs, 2020).

There are promising results, but limited studies demonstrating the use of PAP to treat OCD. This study will serve as an important milestone in helping to investigate the feasibility of using PAP as a novel treatment in OCD populations. The goal is to provide preliminary support for the feasibility, clinical effects and safety of psilocybin in treatment-resistant OCD with the hope of motivating further trials, with more rigorous designs, to better examine the therapeutic potential of this approach.

1.5 Risks/Benefits

Possible Benefits

As with any research study, no direct benefit can be promised to research participants. Case reports and one previous study investigating psilocybin-assisted psychotherapy in OCD cohorts have indicated rapid and dramatic reductions in participants' symptoms. Therefore, participants may receive some benefit from the study if PAP is effective in improving OCD symptoms. Participants may also benefit from close monitoring of their clinical conditions.

Psilocybin Risks

Expert consensus indicates that psilocybin is safe in human pre-clinical and clinical trial research (Johnson et al., 2008). 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, altered visual perception, mild paranoid ideas and unusual thoughts. Previous studies indicate that these events are transient, tolerable, and largely resolved within the timeframe of the 8-hour PAP session (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). In addition, these effects are both expected and may be a necessary component of the therapeutic response. Psilocybin can produce sympathetic system activation resulting in physiological effects such as pupillary dilation and detectable, but moderate increases in blood pressure or heart rate, transient nausea, diarrhea, paresthesia, dizziness, fatigue and headache. In rare cases, hallucinogen-induced persistent perceptual disorder (HIPPD) where individuals experience the effects of psilocybin for longer than expected. These have not been any reported cases of this in modern clinical settings, but it has been rarely reported following recreational use. With proper screening and preparation, psilocybin has a safe physiological and psychological profile. As with any investigational product trial, there is a possibility that some participants may experience a worsening of their mental state after the drug experience. Reports of this are very rare.. 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.

Medication Tapering Risks

There will be a washout period of 3-6 weeks for participants taking any concomitant medications. 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 medications used to treat OCD can result in the worsening of a participant's symptoms. During the tapering period, the participant will be seen clinically by the study physician.

fMRI

Minimal risk except for people with metal or magnetic implants (such as metallic clips in the brain or cardiac pacemakers) due to strong magnetic field in scanner. Participants will be screened by the study personnel and by the MR technician at the MR Centre prior to scanning. Some people may feel uncomfortable lying still in the confined space of the MRI scanner. The study physician may prescribe a mild sedative to help relax the participant during the MRI session. In addition, participants may feel tingling sensations during the scan or feel dizzy for a few minutes at the end of the MRI. These are infrequent, but expected sensations. Participants will be able to contact the technologist at any time during the scan.

There are no long term risks caused by the magnetic field strength used in this study. There is a possibility of unexpected or incidental findings. The scan used in this clinical trial is not for diagnostic purposes. If an atypical finding is seen on the scan, a radiologist or other qualified health professional will look at the scan. The participant's identity will not be revealed and if it is recommended that further testing is required, the research team will schedule an appointment to arrange follow-ups with the participant.

Some of the images collected will use new methods or “investigational” protocols that were developed by GE as a Work in Progress (WIP). These do not pose any additional risk to the participants as they images can only be acquired if the images are within the established safety limits.

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.

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

EEG
Scalp irritation from the EEG sensors and preparation gel are possible side effects. OCD symptom provocation during the rest EEG is designed to cause obsessional distress which is expected to cause temporary discomfort that is familiar to the study participant.

TMS
TMS is a non-invasive method to stimulate brain tissue through electromagnetic fields that poses no significant health risk to properly screened study participants. Single pulse TMS is a routine clinical diagnostic tool used in hundreds of neurophysiological laboratories worldwide. Prospective studies designed to systematically evaluate health effects have not found changes in EEG, blood pressure, heart rate, serum cortisol, serum prolactin, cerebral blood flow, memory or cognition. Single pulse TMS of the motor cortex has been used in children and infants as young as 2 weeks of age with no adverse effects reported. The induced electrical current is well below that which is expected to cause harm to nervous tissue. The US FDA has concluded that stimulation at <1 Hz carries virtually no risk seizure and is therefore classified as a non-significant risk device.

TMS of left prefrontal cortex is approved for therapeutic use in OCD. However, the use of TMS in this study is diagnostic. The number of pulses and the minimum pause between pulses is selected such that no significant neuromodulatory effects are induced.

The TMS pulse cause a clicking noise. Study participants will wear earphones and earmuffs to protect their hearing.

Neuronavigation
Neuronavigation uses infrared light reflected by small spheres attached to the head and the TMS stimulation coil to determine the relative positioning and has no known side-effects or health risks.

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

2.1 Primary Objective

To assess the feasibility and clinical effects of psilocybin, administered with psychological support to adult participants with treatment-resistant OCD, in improving OCD symptoms as assessed by the change in the YBOCS total score from baseline. Baseline is defined as the assessment score obtained on Day -1 (V2). The primary time point is Week 3 (V10). We will also analyze changes in YBOCS score from Baseline to Day 1 (V8), and Weeks 3 (V10), 6 (V11), 9 (V12), and 12 (V13) post-dosing.

- To assess feasibility, we will evaluate recruitment and retention rates. Dropout rates during three periods will be evaluated, namely: 1) screening period in which the participant undergoes medication tapering and washout; 2) during the acute course of the study intervention; and 3) during the follow-up after the second dosing session. Throughout all three periods, we will also evaluate adverse events including psychological distress and serious adverse events (e.g., hospitalization, suicide attempt, death).

Hypothesis 1: Two sessions of psilocybin 25mg administered under supportive conditions to participants with treatment-resistant OCD will lead to significant reductions in OCD symptoms from Baseline (V2) compared to Week 3 (V10) as measured by the YBOCS total score, and will be safe and feasible.

2.2 Secondary Objective

The secondary objectives are:

- To assess the clinical effects of psilocybin on:
    - Proportion of participants with response defined as a 35% or more of the YBOCS total score and remission defined as a score of ≤7on the YBOCS from Baseline (V2) to Week 3 (V10).
    - Changes in the Patient Health Questionnaire (PHQ-9), Clinical Global Impression (CGI) scale, World Health Organization Quality of Life Short Version (WHOQOL-BREF), World Health Organization Disability Assessment Schedule (WHODAS 2.0), and Generalized Anxiety Disorder scale (GAD-7) from Baseline (V2) compared to Week 3 (V10).

- Changes in behavioural assessments for well-being (Warick-Edinburgh Mental Wellbeing Scale, WMWS) from Baseline (V2) compared to Week 3 (V10).

To evaluate the safety of psilocybin in participants with TR-OCD by using standardized adverse events monitoring at all-time points. Adverse event monitoring will be prioritized to closely and thoroughly evaluate the acute and sub-acute psychological safety profile. Constant observation by therapists will monitor for adverse events during the dosing sessions. A study psychiatrist or a licensed physician delegated by the qualified investigator will be readily available on site for the entire duration of the psilocybin effect.

2.3 Exploratory Objectives

The exploratory objectives are:

- Five Dimension Altered States of Consciousness Questionnaire (5D-ASC) and the Mystical Experiences Questionnaire (MEQ) will be assessed for correlation with the primary and secondary outcomes as possible predictors of response.
- To assess the effect of psilocybin on neurophysiological measures:
  - Changes in Resting EEG, Task EEG, and TMS-EEG between Visit 3 (V3), taking place before the first Psilocybin administration session, and Visit 9 (V9), taking place after the last Psilocybin administration session.
- To investigate changes in the ongoing EEG recording during the administration of psilocybin, i.e. during Visit 4 (V4) and Visit 7 (V7)
- To investigate correlations between neurophysiological markers and symptom severity
- To investigate changes in the functional connectivity profiles associated with the neurobiological effects of PAP. This will be conducted by examining the changes in functional connections using an EEG and fMRI at Baseline (V2) compared to study Visit 10 (V10).

3.0 CLINICAL TRIAL DESIGN

3.1 Overall Design

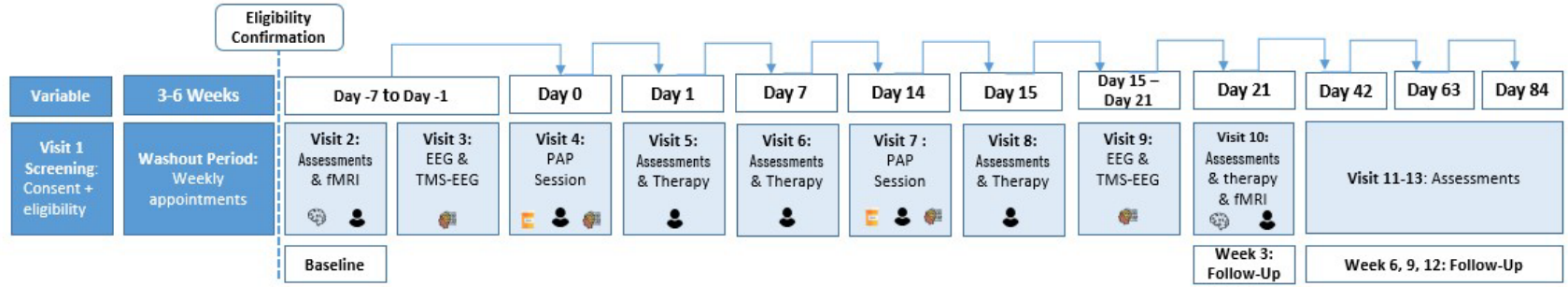
This study is an open-label, proof of concept study investigating the use of psilocybin-assisted psychotherapy (PAP) in treating TR-OCD. The findings of this study will provide preliminary data on the safety and clinical effects of PAP as a treatment option for patients with TR-OCD.

Overview of Study Design:

All 10 participants will follow the same study design. Each participant will undergo a screening assessment where they will complete lab tests, and clinical and psychiatric assessments to determine eligibility. Following the screening visit, participants will undergo a washout period where they will be tapered off concomitant medications over a

period of 3 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. All medications will require a minimum of a 2-week tapering period with the exception of fluoxetine which will require a minimum of 4-weeks. Additional time may be added at the discretion of the study investigator. During this period, there will be weekly check-ins with the study physician. At study Visit 2 (Baseline, V2), participants will complete a series of questionnaires and assessments, preparatory therapy with trained study therapists, and undergo a brain fMRI. To reduce participant burden, baseline can be broken up into multiple days, however all assessments must be completed within 7-days of the first dose. At study Visit 3 (V3), neurophysiological measurements will be performed. Upon completion of V2 and V3, participants will undergo the first psilocybin dosing session at Visit 4 (V4) where they will receive an active dose (25mg) of psilocybin in conjunction with supportive therapy. On the day after the dosing session (Visit 5, V5) and one-week after the dosing session (Visit 6, V6), participants will be asked to complete the same questionnaires that were done at Baseline (V2) and will undergo an integrative therapy session with the trained study therapist. At Visit 7 (V7), 2-weeks after the first psilocybin dose, participants will undergo the second psilocybin dosing session where they will receive an active dose (25mg) of psilocybin in conjunction with supportive therapy. On the day after the second dosing session (Visit 8, V8) and one-week after the second dosing session [3-weeks after dose 1] (Visit 9, V9), participants will be asked to complete the same questionnaires that were done at Baseline (V2) and will undergo an integrative therapy session with the trained study therapist. Between Visit 8 (V8) and Visit 10 (V10), during study Visit 9 (V9), the same neurophysiological measurements will be performed as during Visit 3 (V3). Follow-up assessments will also occur at 6, 9, and 12 weeks (Visit 11, 12, and 13) after the second psilocybin dosing session. The same questionnaires administered at Baseline (V2) will be repeated at each of these study visits.

Figure 1. Study Schematic:
Assessments are defined as questionnaires and clinician administered interviews (Section 6.0) administered at Baseline and repeated throughout the trial.



Timeline

In total, there are a minimum of 16 study visits (13 study visits and a minimum of 3 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 4.0 months. The total expected duration of the clinical trial from the time the study team starts recruiting until data analysis has been complete is 18-months. The study team will recruit approximately 1 participant per month over the period of 10 months. All study interventions and follow-up assessments will be completed by month 14. This leaves approximately 4 months for data analysis which will be completed at month 18.

3.2 Primary Endpoints

The primary endpoint for clinical effects is the change in the YBOCS total score from Baseline (Day -1, V2) to Week 3 (V10). We hypothesize there will be a significant reduction of ≥35% in OCD symptom severity on the YBOCS from Baseline (V2) compared to Week 3 (10).

The co-primary safety endpoint is the number and severity of adverse events reported throughout the duration of the trial. The endpoint for tolerability will be the number of participants that dropped out of the study due to an adverse event.

3.3 Secondary Endpoints

The secondary endpoints are changes from Baseline (V2) to Week 3 (V10) on the YBOCS, PHQ-9, CGI, WHODAS 2.0, WEMWBS, WHOQoL-BREF, and GAD-7.

4.0 PARTICIPANT SELECTION AND WITHDRAWAL

4.1 Target Population

The target population for this study are adults aged 18-65 who are experiencing clinically significant obsessive-compulsive disorder that has been resistant to at least two courses of pharmacological treatment and at least one course of psychotherapy. 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 4-weeks prior to baseline for fluoxetine and 2-weeks prior to baseline for all other medications, as confirmed by the study investigator.

4.2 Participant Recruitment and Screening

The target sample size is 10 participants (N=10) diagnosed with treatment-resistant OCD. 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 units and external healthcare providers. 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.

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.

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 obsessive-compulsive disorder
- Treatments taken for OCD (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;
- 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 medications used to treat OCD
- 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
- Currently enrolled in another study involving an investigational product or device
- If they are able to take medication orally
- If they have used psychedelic drugs in the last 12 months
- Whether they have contraindications to TMS

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 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, fMRI, 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 undergoing the fMRI,the pre- and post-neurophysiology assessments, as well as study visits occurring after the washout period where treatment (therapy or psilocybin) is not administered. The fMRI is an optional part of the study and participants will be in the scanner for roughly 1 hour, however additional time will be needed for preparation (e.g. changing clothes). Participants will be reimbursed $50 per fMRI (maximum of 2), paid in cash on the day the fMRI is completed. The pre- and post-neurophysiology assessments are not an optional portion of the study. Participants will be reimbursed for their time spent completing the neurophysiology sessions. These assessments will take approximately 4hrs each, participants will be reimbursed about $40 per session. Finally, participants will be reimbursed $10 per hour for each study visit that they attend after the washout period where treatment is not administered (Visit 11, Visit 12, Visit 13). In total, if participants complete all study visits, they may be reimbursed up to $240 for their time. Compensation will be provided for all applicable visits and travel reimbursement at the participant's final study visit (V13) in cash if they are attended in-person or e-gift card, if the session is conducted virtually. No payment will be provided in advance.

Study Visit:	Duration:	Compensation:
Neurophysiology before first PAP session [Visit 3]	~4 hours	$40
Neurophysiology after second PAP session [Visit 9]	~4 hours	$40
6-week follow-up [Visit 11, Day 42]	~2 hours	$20
9-week follow-up [Visit 12, Day 63]	~2 hours	$20
12-week follow-up [Visit 13, Day 84]	~2 hours	$20

fMRI (maximum of 2)	~2 hours each	$50 each

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 obsessive compulsive disorder (OCD) based on medical records and assessment using the Structured Clinical Interview for DSM-5 (SCID-5) administered at the first screening visit;
8. Participants diagnosed with treatment-resistant OCD defined as individuals with a score of ≥ 16 on the YBOCS (i.e. moderate symptom severity) and that have not responded to two or more separate pharmacological interventions and one or more trials of cognitive behavioural therapy (CBT); there is no upper limit on the number of treatment failures;
9. Individuals with an eGFR above 40mL/min/1.73m^2 and all blood work within normal limits as assessed by clinical laboratory tests at Screening (V1)
10. Ability to take oral medication;
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 have tapered off current OCD medications for a minimum of 2-weeks prior to Baseline (V2) 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 (use of tobacco and prescribed opioids are permitted) within the preceding 6 months;
5. Have active suicidal ideation as determined by the C-SSRS and/or clinical interview. Significant suicide risk is defined by suicidal ideation as endorsed by items 4 or 5 of the C-SSRS;
6. Any DSM-5 lifetime diagnosis of a schizophrenia-spectrum 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. Have contraindications to TMS as determined by the TASS questionnaire;
9. Have a history of seizures;
10. Are taking anticonvulsants or benzodiazepines (Lorazepam up to 2mg/day is acceptable);
11. Presence of a relative or absolute contraindication to psilocybin, including a drug allergy, history of a stroke in the last year, uncontrolled hypertension, low blood pressure defined as ≤90/60mmHg or labile blood pressure defined as recurrent, sudden, unexplainable BP surges to levels of 140/90mmHg or higher, history of myocardial infarction in the last year, cardiac arrhythmic, severe coronary artery disease, or moderate to severe renal or hepatic impairment, defined by an eGFR ≤40mL/min/1..73m^2 for moderate renal impairment, and a total bilirubin of ≤50μmol/L and serum albumin ≤3.5 for moderate hepatic impairment (please note that participants must have an eGFR above 40mL/min/1.73m^2 and within normal limits on the results in all clinical laboratory tests including liver function tests at Screening [V1] and please refer to the inclusion criterion #9 for details);

12. Use of classic psychedelic drugs such as the serotonergic psychedelics drugs, psilpocybin, ayahausca, and 5-MeO DMT, etc., within the previous 12 months; OR
13. 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 start of each psilocybin treatment session for up to 6 hrs after administration (V4 & V7).
- Abstain from the use of any prescribed opioids, benzodiazepines, or sleep aids (Z-drugs) within 12hrs prior to each psilocybin treatment sessions (V4 & V7) and for up to 6hrs after administration.
- Abstain from any illicit drugs (e.g. cocaine, ecstasy/MDMA, hallucinogens) and 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 each psilocybin administration.

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.

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.

Participants that withdraw after the first dosing session:
If the participant is willing to attend an early termination visit, the following information will be documented:

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

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

4.7.4 Participants who are Lost to Follow-up

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

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

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

5.0 STUDY INTERVENTION

5.1 Description

Pharmacokinetics and Psilocybin Effects

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

As a $5HT_{2A/2C}$ agonist, psilocin is regarded as a "classical" psychedelic; in humans, it commonly elicits significantly altered states of consciousness, experienced through visual and sometimes auditory effects, changes in perception, distortions of time, and a range of effects including a sense of awe, novel perspectives, existential and personal insight, dramatically heightened empathy and feelings of compassion, strong emotions, and non-dual or unitive experience. A number of these 'peak' experiences have been associated with improved quality of life and improvement in mood (Griffiths et al., 2016; McClain et al., 2003; Visser et al., 2010). For a more detailed explanation on the effects of psilocybin and its mechanism of action, please refer to the investigators brochure.

Psilocybin-Assisted Psychotherapy

The participant will attend 1 preparatory session that occurs within 7-days of the first psilocybin dosing session (V4) to develop a therapeutic alliance, set intentions for the experience, and learn what to expect during the dosing session. An additional

preparatory therapy session can be added at the discretion of the study therapists and study investigator. In addition, the participant will undergo 2 integrative therapy sessions after each psilocybin dose (V8 & V10). During dosing, there will be two therapists present. A physician will be available at all times during each dosing session to assess and manage any medical or psychiatric adverse events (either on-call or as a therapist in the room with the patient). Efforts will be made to ensure that the therapists remain the same at every therapy session, however the only days that require two therapists are dosing. Therapy sessions will not be video recorded.

Each therapist will undergo training by the study investigator or delegated investigator using the adapted Yale Manual for Psilocybin-Assisted Therapy of OCD, an evidence informed protocol for PAP . Therapy sessions will not be video recorded. For a full description of each therapy session and PAP, please refer to the Yale Manual for Psilocybin-Assisted Therapy of OCD. This manual will be adapted to meet the needs of the study protocol.

In addition, therapists will undergo protocol-specific training for the study. Therapists involved in the trial must be licensed to provide therapy by a regulatory body. Unlicensed therapists will be directly supervised by a licensed therapist.

Requirements for lead study therapists:

1. Licensed to provide psychotherapy in the province of Ontario:
    a. Social worker
    b. Psychologist
    c. Psychiatrist or physician (M.D or equivalent) with psychotherapy training
    d. Nurse with psychotherapy training (e.g. nurse psychotherapist certificate)
2. Registered with the appropriate regulatory body in Ontario:
    a. College of Registered Psychotherapists of Ontario
    b. College of Psychologists of Ontario
    c. Ontario College of Social Workers and Social Service Workers
    d. The College of Physicians and Surgeons of Ontario
    e. College of Nurses of Ontario
3. Previous experience administering PAP

Unlicensed therapists who are in the process of becoming licensed or therapists who have not had any PAP experience must be supervised under the direct supervision of a lead therapist.

<u>How the study intervention will appear:</u>
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), white capsules.

5.2 Treatment Regimen

There will be 2 dosing sessions. The first dosing session will occur at Visit 4 (V4, Day 0), after the participant has been deemed eligible to participate. The second dosing session will occur 2-weeks after the first dosing session at Visit 7 (V7, Day 14). The participant will follow the same procedures for both dosing sessions. These procedures are outlined below:

Each participant will be assigned 1 treatment bottle containing 1 capsule of 25mg psilocybin. The IP will be given to the participant by the study psychiatrist or a licensed physician delegated by the qualified investigator who will supervise the participant orally take the medication. It will be taken orally with a glass of water provided by the study team. There will be no modifications to the dosage, each participant will receive 1 capsule of 25mg of psilocybin at study Visit 4 and study Visit 7. The effects of psilocybin start about 20 to 30 minutes after administration with peak effects usually occurring in the first 90 to 120 minutes and gradually subsiding in 5 to 6 hours. 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 to 6 hours when the acute effects of the psilocybin have passed.

We chose psilocybin 25 mg dosage for standardization across the study participants, which is the most frequently chosen dose in other psilocybin research studies with almost guaranteed and observed psychedelic effects. A recent study reported no significant differences in weight-adjusted dosing versus fixed dosing (Garcia-Romeu et al., 2021). Furthermore, advantages of fixed dosing outweigh potential minimal advantage of weight-adjusted dosing given that fixed dosing has a lower cost of administering psilocybin and is more convenient to the study team.

We have consulted with our colleagues at Yale University, who are currently conducting a clinical trial comparing one dosing to two dosing schedule (ClinicalTrials.gov ID NCT05370911) and we opted for a two-dosing regimen since OCD symptoms are generally more difficult and rigid to target when compared to anxiety and depressive symptoms; therefore, a second dosing may improve OCD symptoms further due to the ritualistic and ruminating nature of the illness.

5.3 Method for Assigning Participants to Treatment Groups

Not applicable.

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 or a licensed physician delegated by the qualified investigator who will supervise the participant while the medication is taken orally, with water. 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. Participants do not have the option to choose the type of music since the playlist is pre-set specifically for the standardization of psilocybin-assisted psychotherapy sessions across all other psilocybin studies in our institution. 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. An on-call psychiatrist will be available at all times to further assess as needed for acute concerns. Therapy sessions will not be video recorded.

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. A light meal and fruit will be available for the participant for lunch.

About 5 to 6 hours after dosing, the trained therapists will discuss the IP administration experience with the participant. The participant will be discharged 5 to 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 and have a responsible adult present with them for 24hrs after the intervention. 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 data collection forms during each study visit.

Permissible Medications

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

For the initial Screening Visit (V1) through to the final study visit (V13), participants are permitted to use benzodiazepines (up to 2mg of lorazepam equivalent per day for insomnia and anxiety if it is not taken within 12 hours before both of psilocybin doses (V4 & V7). 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 1month prior to screening and for the duration of the study, including up to 12-weeks after the first psilocybin dose (V13). 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

Periodic abstinence (e.g. calendar, symptothermal, or postovulation methods, and tubual ligation/occlusion) 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 3 (V10) until the primary endpoint assessment, or longer if possible. If the medications are re-introduced, the study investigator must be notified and the medications will be documented in the data collection form . Participants who require concomitant medication(s) specifically for the treatment of OCD at any time through the duration of the study will be assessed for reasons of resuming their medications and followed until 12-weeks after the first dose of psilocybin (V13).

Rescue Medication

- The decision to medicate a participant will depend on if the therapists and study investigator determine the safety of the patient and others can be maintained without medical intervention. The final decision will be made by the study investigator. Benzodiazepine anxiolytics
    - The preferred pharmacological intervention of choice in case of acute psychological distress (e.g. medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action).
    - The oral route is preferable because IV injection procedures may further exacerbate the participant's anxiety.
- Antipsychotic medications (e.g. risperidone) should be available in the event that an adverse reaction escalates to unmanageable psychosis.
- Management of blood pressure:
    - Asymptomatic with blood pressure (BP) < 180/100

- Reassure, ensure lights are dim or off, tilt head of bed 15 degrees up and continue to monitor
- Increase blood pressure measurement frequency to q15min until BP has partly normalized (sBP = 100-159; dBP = 60-99)

- Asymptomatic with BP >180/100 for >30 minutes
  - Administer captopril* 12.5mg PO/SL x 1 with MD order
  - Increase blood pressure measurement frequency to q15min until BP has partly normalized (sBP = 100-159; dBP = 60-99)
- Asymptomatic with BP persisting at >180/100 for >60 minutes post-dose, despite administering first captopril dose:
  - Consider potential transfer to ER – decision to be made by study investigator
  - Administer 2nd dose of captopril 12.5mg x 1 with MD order
- Management of severe treatment emergent hypertension:
  - Consider potential transfer to ER – decision to be made by study investigator
  - Administer captopril 25mg PO/SL x 1
  - Call 911 immediately for patients experiencing symptoms of a hypertensive crisis (e.g., chest paint, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficit)
- Note: if there are contraindications to captopril, substitute for hydralazine 10mg PO

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

Information for how to manage subjects during difficult psychological states are detailed in the Yale Manual for Psilocybin-Assisted Therapy of OCD. This manual will be adapted for administration to participants diagnosed with OCD by a clinical psychologist. In addition, the manual will be adapted to this study's REB approved protocol. In addition, each therapist will undergo training by the study investigator or delegated investigator using the adapted Yale Manual for Psilocybin-Assisted Therapy of OCD.

5.7 Packaging

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 entire shipment for this trial will be sent in bulk (i.e. 20 capsules x 25mg each). Psilocybin capsules will be packaged individually in high-density polyethylene bottles. Each of the two 25mg psilocybin doses 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

Not applicable.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Study Intervention Supplies

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

5.9.2 Storage

All IP will be kept in a locked area with limited access. The high-density polyethylene (HDPE) bottles of IP are to be stored as indicated in the investigators brochure. Bottles must be maintained at room temperature (15 to 30 degrees Celsius) 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

All participants will receive the same intervention. Each participant will be assigned 1 treatment bottle containing 1 capsule of 25mg of psilocybin for each dosing session. The IP will be dispensed and administered to the participants by the study psychiatrist or a licensed physician delegated by the qualified investigator. The study intervention will be administered orally, with water. The capsules should be administered in an unaltered state, by mouth, with water. The capsules should not be opened, chewed, or held in the mouth for an extended period without swallowing.

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

McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) 42. The MSI-BPD is a commonly used measure to assess for borderline personality disorder (BPD). The scale consists of 10 items based on the DSM-5 BPD criteria; the first 8 items represent the first eight criteria in the DSM-5 for BPD diagnosis; while the last two questions assess paranoia and dissociation criteria for BPD (Zanarini et al., 2003). Score for the MSI-BPD range from 0 to 10 with each item rated as 1 'if present' and 0 'if absent'. A score of 7 or higher indicates a likelihood for the participant to meet criteria for BPD.

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

TMS Safety Questionnaire. The Transcranial Magnetic Stimulation Adult Safety Screen (TASS) Questionnaire will be used to determine eligibility.

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. The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period. 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, during the washout period, and Baseline determine the patient's study eligibility and potential need for referral to a mental health professional, and

(b) During the study evaluate the patient's need for appropriate medical management such as a referral to a mental health professional.

Primary Outcome Measures:

Yale-Brown Obsessive-Compulsive Scale (YBOCS). The YBOCS is a 10-item scale designed to measure the severity and type of symptoms for OCD. The scale is clinician-rated where the interviewer provides a rating from 0 ('no symptoms') to 4 ('extreme symptoms'). The total score ranges from 0 to 40 with higher scores indicating greater severity of symptoms. It has good psychometric properties and is frequently used to monitor improvement during treatment (Goodman et al., 1989).

Secondary 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).

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a brief measure to screen for the presence and severity of depression. It consists of 9 items rated from 0 ('not at all') to 3

('nearly every day'). It is a reliable and valid measure for depression that is widely used in clinical and research settings.

World Health Organization Disability Assessment Schedule (WHODAS 2.0). The WHODAS 2.0 is a brief measure to assess health status and disability across different cultures and settings. It is a 12-item self-report questionnaire where the participant is asked to rate themselves on a Likert scale from 1 ('none) to 4 ('extreme') across six different domains from functioning: cognition, mobility, self-care, getting along, life activities, and participation.

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').

Exploratory Measures:

Five Dimensions of Altered States of Consciousness (5D-ASC). The 5D-ASC is a 94-item scale 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) (Griffiths et al., 2006; Maclean et al., 2012).The MEQ consists of 30 items of the larger 100-item 'States of Consciousness Questionnaire' (Griffiths et al., 2006; Maclean et al., 2012), and assesses 4 empirically derived factors: mystical experiences (including 'internal unity', 'external unity', 'noetic quality' and 'sacredness'), positive mood (awe, joy, peace and tranquillity); transcendence of time and space (sense of being outside of time, in a realm of no space boundaries, sense of timelessness) and ineffability (e.g. inability to adequately describe experience in words). Responses are rated on a 6-point Likert scale ranging from 0 (none, not at all), through to 5 (extreme, more than ever before in my life).

fMRI: The MRI will be take place at the CAMH College Street location. The participant will be given ear protection provided by the MRI Unit to wear in the scanner. During the scan, the participant will rest and let their mind wander with their eyes open. There will be a mixture of very short scans and some longer scans up to 10 minutes.

The CAMH MRI Unit is a research site, and one of the mandates is to develop and test new MRI pulse sequences that will advance our understanding of brain function and structure. CAMH has established a research agreement with General Electric (GE) to help achieve these goals. This research agreement allows us to modify the stock pulse sequences to generate higher quality data, and to operate the scanner in "research mode", which gives us the ability to alter certain parameters of the stock pulse sequences. MRI machines are designed to operate with patient safety in mind. Our GE MR750 has three operating levels: Normal Level, First Level and Second Level. All GE scanners in Canada can operate in Normal and First Level mode, and ours is operated at First Level mode for all studies. Second Level mode is available only if a research agreement is in place with GE and REB approval is in place for any changes to safety thresholds beyond First Level. No studies at CAMH are operated at Second Level. When a pulse sequence is prescribed and loaded into memory, the scanner determines whether the parameters selected will exceed the safety limits for First Level. If they do, the scanner will not allow the scan to proceed as prescribed, and the technologist must change the parameters so that the First Level limits are not exceeded.

Some of the images we collect use new methods or "investigational" protocols that we have developed by GE as a Work in Progress (WIP). These do not pose any additional risk to the subjects – we can only acquire the images if we are within the established safety limits.

Storage and maintenance of software: Any software associated with GE WIPs will be installed and maintained by the MRI Unit in collaboration with GE engineers.

120 min EEG: A 120 min EEG recording during the Psilocybin session will be recorded. Preparation will take about 20 minutes. The measurement should be started at least 5 minutes before oral administration of Psilocybin and should last until 115 min after oral administration of Psilocybin. A thin EEG cap will be prepared using procedures established in EEG sleep studies that will allow the study participant to lie in a bed. The music played during the session will be recorded as a synchronized track by the EEG amplifier to enable post-hoc synchronization of brain activity to sound.

The following neurophysiological measures will be acquired at the Temerty Centre for Therapeutic Brain Intervention (Queen Street West site), as part of the Pre- and Post-Psilocybin Neurophysiology Sessions. EEG and EMG preparation will require 40 minutes.

Neuronavigation: Anatomical MRI data acquired in the Baseline session will be co-registered with a stereoscopic tracker on the head of the participant. The TMS coil will be calibrated with a similar tracker. The location of the EEG sensors will be pinpointed.

Target coil positions for left DMPFC and left DLPFC will be determined. The duration of this measurement will be 30 minutes. In the event that the fMRI is unavailable, the BEAM F3 method will be used to localize targets.

Rest EEG: In the first phase of the Rest EEG the participant will rest and let their mind wander with their eyes open for 5 minutes. Symptoms of OCD will then be provoked using an individualized external provocation method (Blair Simpson et al., 2000; Tendler et al., 2019), they will for example be asked to touch a surface. Following symptom provocation, another 5 minutes of EEG will be recorded as part of the second phase of the Rest EEG measurement. The provocation will then be removed and (if feasible) the study participant will be able to ritualize (e.g. hand washing). The above two phases will then be repeated. The severity of OCD symptoms will be assessed between phases using a VAS. The duration of this measurement will be 30 minutes.

Task EEG: During the Task EEG, the participant will perform an auditory oddball task consisting of 600 auditory stimuli (sinus tones, intensity of 80 dB, duration 40 ms) delivered binaurally through headphones, with an interstimulus interval (ISI) of 1500 ms (Andreou et al., 2013). The duration of this measurement will be about 20 minutes.

RMT and 1mv SI: The stimulation intensity (measured in units of percentage of maximum stimulator output) will be determined that is required for TMS of the hand area of left primary motor cortex (motor hotspot) to result in a motor evoked potential (MEP) recorded from the right hand muscles with an amplitude above 50 μV 50% of the time (resting motor threshold), and similarly the stimulation intensity required to elicit MEPs with an average peak-to-peak amplitude of 1mV. The motor hotspot will be found manually and an automatic thresholding procedure will be used to determine RMT and SI 1mV. This part of the measurement will take about 20 minutes.

TMS-EEG: TMS-EEG will be applied in blocks consisting of 150 biphasic single pulses of TMS with an inter-pulse interval ≥ 2.5 seconds using masking noise to reduce the auditory evoked EEG potential. There will be six blocks of stimulation with brief pauses between blocks. Target stimulation sites will be left DMPFC and left DLPFC (the order will be counterbalanced between different study participants but remain consistent in any given study participant). The severity of OCD symptoms will be assessed between blocks using a VAS. Before stimulation, participants will be encouraged to relax into a neutral state of mind. Block 1 and 2 stimulates left DMPFC and left DLPFC. OCD symptoms will then be provoked using a similar approach as for the Rest EEG. Block 3 and 4 stimulates left DMPFC and left DLPFC again while OCD symptoms are being experienced. The provocation will then be removed and the study participant will be asked to relax again into a neutral state of mind. Block 5 and 6 stimulates left DMPFC and left DLPFC again. In total, the TMS-EEG procedure will take about 80 minutes.

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
  - SCID-5
  - MRI screening checklist to ensure that it is safe for the participant to partake in the MRI.
    - This will be reviewed by the MRI technologist.
  - TASS
  - Vital Signs (blood pressure, pulse)
  - Height and weight
  - YBOCS
  - MSI-BPD
  - CSSRS
- 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
  - 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:
    - *Hematology:* 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: 3-6 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.

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 3 to 6 weeks after the initial Screening (V1) when the participant has successfully been tapered off any concomitant medication. At the Baseline Visit (V2), the participant's eligibility will be confirmed by the study investigator by reviewing the Inclusion/Exclusion Criteria (Section 4.4) and updating the medical history. The Baseline visit (V2) can occur within 7 days before the anticipated psilocybin session and may be split over multiple days to reduce the burden on the participant (additional study visits will be labelled V2a, V2b etc). The following procedures will be performed and recorded at the Baseline visit (V2):

- Administered by trained study staff:
  - Vital Signs (blood pressure, heart rate)
  - YBOCS
  - C-SSRS
  - CGI
  - Administration of participant completed questionnaires:
    - PHQ-9
    - WHODAS 2.0
    - WHOQOL-BREF
    - GAD-7 to assess symptom severity for common anxiety disorders
    - WEMWBS
- Clinician administered:
  - Confirmation of eligibility criteria

- Laboratory evaluations collected at the Queen Street CAMH laboratory:
    - *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
- Imaging session to be completed at CAMH College Street (Brain Health Imaging Center)
    - fMRI scan
- 2-hour preparatory session with the study therapists which will involve building a therapeutic alliance, psychoeducation about the psychedelic experience, and setting intentions for the psilocybin sessions.
    - Documentation of participant preference and consent for therapeutic touch
    - Note: Therapists will have the option to schedule an additional preparatory session at their discretion.
    - For a more detailed explanation of the preparatory therapy session, please refer to the Yale Manual for Psilocybin-Assisted Therapy of OCD which will be adapted to the protocol and participant population for this study.
    - Prep therapy can occur in-person or via secure videoconferencing software (i.e. WebEx).

Visit 3 (V3) – Pre-Psilocybin Neurophysiology – Day -7 to Day -1

The Pre-Psilocybin Neurophysiology visit (V3) should occur within 7-days of Psilocybin Session Dose 1 (V4). The following procedures will be performed and recorded at the Pre-Psilocybin Neurophysiology visit (V3):

- Administered by trained study staff with a responsible Clinician available on site:
    - Assessment of TMS contraindications
    - EEG, EMG Preparation
    - Neuronavigation
    - Rest EEG (with intermittent symptom provocation)
    - Task EEG
    - RMT and 1mv SI determination
    - Auditory masking noise stimulation
    - TMS-EEG stimulating DMPFC and DLPFC (with intermittent symptom provocation)

Visit 4 (V4) – Psilocybin Session Dose 1 – Day 0

The psilocybin dose 1 visit (V4) should 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. At the Psilocybin Session Dose 1 (V4), the following procedures will take place:

- Review and confirmation of participant preference and consent for therapeutic touch

- Urine dip pregnancy test before dosing begins.
- EEG will be prepared for a 120 min recording. The recording will be started at least 5 minutes before study intervention administration
- Study intervention administration (Section 5.0): 1 oral dose of 25mg of psilocybin administered in conjunction with supportive therapy (PAP).
- Vital signs (body temperature, blood pressure and pulse) will be taken once before dosing, 3 hours post dosing, and at the end of dosing, and documented in the data collection form. Vital signs will also be taken as needed in addition to scheduled times.
- 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:
    - Physician administered
        - C-SSRS
    - Study team or therapist administered:
        - MEQ: measures
        - 5D-ASC to assess the acute drug effects using 5 primary dimensions and respective sub dimensions.
- The participant will be discharged 5 to 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 and have a responsible adult present with them for 24hrs after the intervention.
- Rescue medications are permitted during this visit as outlined in Section 5.6.

Visit 5 & Visit 6 (V5 & V6) – Post-Psilocybin Dose 1 – Day 1 & Day 7

- Administered by trained study staff:
    - Administration of assessments: :
        - PHQ-9
        - WHODAS 2.0
        - WHOQOL-BREF
        - GAD-7
        - YBOCS
        - C-SSRS
        - CGI
- 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 OCD) which will be adapted to fit this study protocol and participant population.

Visit 7 (V7) – Psilocybin Session Dose 2 – Day 14

The psilocybin dose 2 visit (V7) should occur 14 days after the first dosing session. The following procedures will take place:

- Urine dip pregnancy test before dosing begins.
- EEG will be prepared for a 120 min recording. The recording will be started at least 5 minutes before study intervention administration
- Study intervention administration (Section 5.0) 1 oral dose of 25mg of psilocybin administered in conjunction with supportive therapy (PAP).
- Vital signs (body temperature, blood pressure and pulse) will be taken once before dosing, 3 hours post dosing, and at the end of dosing, and documented in the data collection form. Vital signs will also be taken as needed in addition to scheduled times.
- Review and confirmation of participant preference and consent for therapeutic touch
- 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:
    - Physician administered
        - C-SSRS
    - Study team or therapist administered:
        - MEQ
        - 5D-ASC
- The participant will be discharged 5 to 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 and have a responsible adult present with them for 24hrs after the intervention.
- Rescue medications are permitted during this visit as outlined in Section 5.6.

Visit 8 & Visit 10 (V8 & V10) – Post-Psilocybin Dose 2 – Day 15 & Day 21

- Administered by trained study staff:
    - Administration of assessments:
        - GAD-7
        - PHQ-9
        - WHODAS 2.0
        - WHOQOL-BREF
        - WEMWBS

- YBOCS
- C-SSRS
- CGI

- Integrative psychotherapy session will occur with the study therapists. The participant will discuss their experience during the dose session including their thoughts, feelings, and experiences. For more detailed information on the integrative therapy sessions, please refer to the therapists manual (Yale Manual for Psilocybin-Assisted Therapy of OCD which will be adapted to fit this study protocol and participant population.
- fMRI imaging to be completed at Visit 10 (V10 – Day 21) at CAMH College Street (Brain Health Imaging Center). Note: This is only for Visit 10 (V10 – Day 21).

Visit 9 (V9) – Post-Psilocybin Neurophysiology

The Post-Psilocybin Neurophysiology visit (V9) should occur between Visit 8 (Day 15) and Visit 10 (Day 21). The following procedures will be performed and recorded at the Post-Psilocybin Neurophysiology visit (V9):

- Administered by trained study staff with a responsible Clinician available on site:
  - Assessment of TMS contraindications
  - EEG, EMG Preparation
  - Neuronavigation
  - Rest EEG (with symptom provocation)
  - Task EEG
  - RMT and 1mv SI determination
  - Auditory masking noise stimulation
  - TMS-EEG stimulating DMPFC and DLPFC (with intermittent symptom provocation)

Visit 11 - 13 (V1 – V11) – Follow-Up Assessments – Days 42, 63, 84

Follow-up visits occur at Weeks 6 (V11), 9 (V12), and 13 (V13) after the second psilocybin dose. The following assessments will occur at each visit:

- Administered by trained study staff:
  - GAD-7
  - PHQ-9
  - WHODAS 2.0
  - WHO-QoL-BREF
  - Review of prior/concomitant medications
    - Any changes will be reviewed by the study physician
  - YBOCS
  - CSSRS
  - CGI
- The WEMWBS is the only assessment that will not be administered at each study visit. The WEMWBS will only be administered at the Follow-Up at Week 12 (V13).

6.2 Schedule of Events

Procedures	Screening (Visit 1)	Washout period[1] (3-6 , weeks)	Baseline[2] (Visit 2, Day -7 to Day -1)	Pre-Psilocybin Neurophysiology (Visit 3, Day -7 to Day -1)	**Psilocybin Session – Dose 1 (Visit 4, Day 0)**	1-Day post dose 1 (Visit 5, Day 1)	1-week post dose 1 (Visit 6, Day 7)	**Psilocybin Session – Dose 2 (Visit 7, Day 14)**	1-day post dose 2 (Visit 8, Day 15)	Post-Psilocybin Neurophysiology (Visit 9)	3-weeks post-dose 1 (Visit 10, Day 21)	6 weeks post-dose 1 (Visit 11, Day 42)	9 weeks post dose 1 (Visit 12, Day 63)	12 weeks post dose 1(Visit 13, Day 84)
Location of Visit	Clinic	Clinic or remote	Clinic	Temerty Centre	Clinic	Clinic	Clinic	Clinic	Clinic	Temerty Centre	Clinic	Clinic or remote	Clinic or remote	Clinic or remote
Allowable Window		Weekly		≤7 days from V4	≤7 days from Baseline	None	±1 day	None	None	≤7 days	±1 day	±3 days	±3 days	±7 days
Informed Consent	✓													
Demographics	✓													
Medical history	✓		✓											
Prior/concomitant medication review	✓	X----------												----------X
Inclusion/Exclusion Criteria Review	✓	✓	✓											
MRI Screening Form	✓													
TASS	✓													
SCID-5	✓													
Vital signs (blood pressure, pulse)	✓		✓		✓			✓						
Vital signs (body temperature)					✓			✓						
Weight	✓													
Height	✓													
ECG	✓													
Clinical laboratory tests[3]	✓													
Urinalysis	✓													

Urine drug screening	✓		✓											
Urine pregnancy test[4]	✓		✓		✓			✓						
Documentation of birth control	✓													
fMRI			✓								✓			
YBOCS	✓		✓			✓	✓		✓		✓	✓	✓	✓
C-SSRS[5]	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓
CGI[8]			✓			✓	✓		✓		✓	✓	✓	✓
Neuronavigation				✓						✓				
Resting EEG				✓						✓				
Task EEG				✓						✓				
TMS-EEG				✓						✓				
Preparatory/Integrative therapy & psychoeducation[6]			✓		✓	✓	✓	✓	✓		✓			
120 min EEG					✓			✓						
Psilocybin Dose (25mg)					✓			✓						
Adverse event and serious adverse event review and evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Source documentation & CRF completion	✓	X---------- X												
MSI-BDP	✓													
5D-ASC[7]					✓			✓						
MEQ[7]					✓			✓						
GAD-7			✓			✓	✓		✓		✓	✓	✓	✓
PHQ-9			✓			✓	✓		✓		✓	✓	✓	✓
WEMWBS			✓						✓		✓			✓
WHODAS 2.0			✓			✓	✓		✓		✓	✓	✓	✓
WHO-QOL-BREF			✓			✓	✓		✓		✓	✓	✓	✓

1. Additional visits may be needed during the washout period to ensure adequate time for discontinuation of medication. Visits will occur on a weekly basis during this period (V1a, V1b, etc.). Review of medications and assessments for suicidality will occur in addition to other assessments at the discretion of the study investigator.
2. Baseline assessments can occur on separate days (±7 days from the day of the first intervention) to reduce the burden on participants. These visits will be V2a, V2b etc.

3. See Section 6.0: Research Procedures for complete list of required laboratory tests to be performed.
4. For women/people of child-bearing age only
5. The “Last 12 Months” version will be administered at Screening and the “Since Last Visit” version will be administered at all other visits.
6. Additional therapy visits may be scheduled at the discretion of the study therapists and/or the study investigator and pre as well as integration therapy can occur in-person or via WebEx
7. To be administered immediately after PAP when the acute effects of psilocybin have subsided.
8. CGI severity will be used at Baseline and the follow-up version with efficacy index will be administered at all other visits.

Instruments:
CGI: Clinical Global Impression; ECG: Electrocardiogram; fMRI: Functional Magnetic Resonance Imaging; GAD-7: Generalized Anxiety Disorder assessment form; MEQ: Mystical Experience Questionnaire; MSI-BPD: McLean Screening Instrument for Borderline Personality Disorder; PHQ-9: Patient Health Questionnaire; SCID-5: Structured Clinical Interview for DSM-5; TASS: Transcranial Magnetic Stimulation Adult Safety Screen; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale; WHODAS 2.0: World Health Organization Disability Assessment Schedule; WHO-QoL-BREF: World Health Organization Quality of Life abbreviated scale; YBOCS: Yale-Brown Obsessive-Compulsive Scale; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Sample size was based on the primary outcome measure of YBOCS. We based this on the primary outcomes from the study of Moreno et al. (2006), which established marked reductions in YBOCS at 24 hours for different dose groups and presented effect sizes ≥ 1.2 (within group Cohen's d).

Using an effect size of d = 1.2 and 5% significance will require N=10 completers to achieve 90% power. This calculation is for a single-arm design (2-sided) using a paired-sample t-test. This sample size is also sufficient to detect large correlations (r=0.71) between change scores with 5% significance and 80% power.

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. The small sample size means that conservative nonparametric testing is required in order to address the primary and secondary objectives. Exact paired permutation t-tests will be used to determine whether psilocybin-assisted psychotherapy achieves a 50% reduction in YBOCS symptoms.

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 source documentation. 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 <u>any one of the following</u> 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 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 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. the study. These reports should not contain PHI.

8.3 Reporting of Serious Adverse Events

8.3.1 Investigator Reporting: Notifying the Sponsor

There is no sponsor for this study, however Filament Health 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

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

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

8.3.4 Sponsor Reporting of SUADRs: Notifying Sites

Not applicable.

8.4 Reporting of Device Deficiencies

Not applicable.

8.5 Safety Management Plan

Safety of the participants (including data confidentiality) and the scientific integrity of the project will be ensured by the research team led by the PI. Participant safety will be monitored at each study visit by asking the participant about their experience and about any adverse events from the last study visit. All adverse events will be reviewed by the study PI and reported to the REB and/or Health Canada in accordance with the regulatory guidelines as outlined by each entity. Adverse events will be recorded and/or reported as outlined in Section 8.2 and 8.3. Safety reports on 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 a*ssess* 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 8.7.1.

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 OCD. 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

Not applicable.

8.7 Data and Safety Monitoring Board

The trial is a preliminary, open-label, Health Canada regulated clinical trial and therefore, a DSMB is not required.

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 documentation will be recorded in data collection forms.

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.

XNAT Research Data
fMRI imaging for this clinical trial will be managed using XNAT. XNAT is a secure, professionally administered, web-based application for managing research data. This system is maintained on central CAMH servers, with data backed up daily, and is supported by the Research Informatics department.

Rest EEG, Task EEG and TMS-EEG Data
Raw EEG and task data will be maintained on a shared folder on the CAMH IT infrastructure.

10.2 Protocol Deviations

No deviations from or changes to the protocol will be implemented without approval from the REB and/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 if any of the following criteria are met:

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

10.3 Record Retention

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

10.4 Clinical Trial Registration

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

11.0 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Study Monitoring Plan

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

11.2 Auditing and Inspecting

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

12.0 ETHICAL CONSIDERATIONS

12.1 Research Ethics Board (REB) Approval

Research Ethics Board (REB) approval will be obtained prior to beginning any research-specific procedures. Following initial ethics approval, ongoing ethical approval will be maintained and the clinical trial will undergo REB review at least annually, in accordance with regulatory and REB requirements. The clinical trial will be conducted in accordance with the REB-approved study documents and the determinations (including any

limitations) of the REB, and in compliance with REB requirements. Any amendments to the protocol will require review and approval by the REB before the changes are implemented in the clinical trial, unless to eliminate an immediate hazard to the participant.

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

12.2 Informed Consent Process & Documentation

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

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

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

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

13.0 PRIVACY AND CONFIDENTIALITY

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

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

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 Centre for Complex Interventions at the Centre for Addiction and Mental Health (CAMH).

14.2 Conflict of Interest

The research team does not have any conflicts of interest to disclose. However, Dr. Ishrat Husain, provides advisory services to MindSet Pharma Inc, Wake Network Inc, and PsychEd Therapeutics Inc. In addition, Dr. Feusner provides advisory services for NODC Inc. These organizations are not involved in the study and do not impact the design, conduct, or interpretation of results.

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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