Psilocybin for Treatment-Resistant Depression in Autism: a Pilot Trial with Pre-Post Brain and Cognitive Measurement to Understand Mechanisms

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STATEMENT OF COMPLIANCE

A statement confirming the clinical trial will be conducted in compliance with the protocol, ICH GCP, applicable regulatory bodies and institutional requirements must be included here.

For multi-site clinical trials: A statement of compliance should also be included for each site, with the site Principal Investigator's (PI) signature.

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)
- 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
- U.S. Federal Policy for the Protection of Human Subjects (Common Rule)
- U.S. FDA Regulations
- Institutional and REB policies and procedures

_____ _____

Signature of PI Date

LIST OF ABBREVIATIONS

AAQ-II	*Acceptance and Action Questionnaire-II*
ABSI	*Autistic Burnout Survey Items*
ADOS-2	*Autistic Diagnostic Observation Schedule, 2nd edition*
AE	*Adverse Event*
AQ-12	*Autism Quotient-12*
ASA-A	*Anxiety Scale for Autism – Adults*
ATHF	*Antidepressant Treatment History Form*
BDI-II	*Beck Depression Inventory II*
CAT-Q	*Camouflaging Autistic Traits Questionnaire*
CD-RISC 10	*Connor–Davidson Resilience Scale 10 items*
CAMH	*Centre for Addiction and Mental Health*
CFI	*Cognitive Flexibility Inventory*
CGI	*Clinical Global Impression Scale*
CRF	*Case Report Form*
ECG	*Electrocardiography*
11D-ASC	*Eleven Dimensions of Altered States of Consciousness*
EDI	*Equity, diversity, and inclusion*
GAFS-8	*General Alexithymia Factor Score*
GCP	*Good Clinical Practice*
GRID-HAMD-17	*Grid-Hamilton Depression Rating Scale-17*
ICF	*Informed Consent Form*
IP	*Investigational Product*

INQ-15	*Interpersonal Needs Questionnaire*
ISQ-8	*Short Form of Interoception Sensory Questionnaire*
MDD	*Major Depressive Disorder*
MRI	*Magnetic Resonance Imaging*
PAT	*Psilocybin-Assisted Therapy*
PHI	*Personal Health Information*
PHIPA	*Personal Health Information Protection Act*
PI	*Principal Investigator*
QI	*Qualified Investigator*
RBQ-2A	*Adult Repetitive Behaviour Questionnaire-2*
REB	*Research Ethics Board*
RRS-10	*Short Form of Ruminative Response Scale*
RSPM	*Raven's Standardized Progressive Matrices*
SAE	*Serious Adverse Event*
SBQ-ASC	*Suicidal Behaviors Questionnaire – Autism Spectrum Conditions*
SCID-5	*Structured Clinical Interview for DSM-5*
SHAPS	*Snaith-Hamilton Pleasure Scale*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
TCPS 2	*Tri-Council Policy Statement*
TRD	*Treatment-Resistant Depression*
WHOQOL-4	*World Health Organization Quality of Life Short Measure*

CLINICAL TRIAL SUMMARY

Title	Psilocybin for Treatment-Resistant Depression in Autism: a Pilot Trial with Pre-Post Brain and Cognitive Measurement to Understand Mechanisms
Short Title	PAT-DA
Phase	Phase I
Methodology	Open-label clinical trial
Clinical trial Duration	33 months to complete all recruitment, study procedures, and data analysis.
Participating site(s)	Single-Center
Objectives	To assess the feasibility, tolerability, and efficacy of the use psilocybin alongside psilocybin-assisted therapy (PAT) in autistic adults with treatment-resistant depression (TRD). Furthermore, the use of neuroimaging to explore the mechanisms underpinning antidepressant effects of psilocybin.
Number of Participants	Twenty (ten male & ten female) intellectually-able/speech-fluent autistic adults diagnosed with treatment-resistant depression
Study Intervention Reference Therapy/Comparator	2 doses of psilocybin in conjunction with psilocybin-assisted therapy (PAT), 1st safety dose of 10mg, 2nd treatment dose of 25mg
Duration of Intervention	2 dosing sessions 1 week apart, each about 6-8 hours duration
Statistical Methodology	Characteristics of the trial cohort will be summarized by mean (SD), median (minimum, maximum). Summary raw scores will be presented at each assessment time both numerically and graphically. A paired t-test will be used to investigate the pre- to post-treatment brain/cognitive metrics and symptom changes. Exploratory analyses will be performed to determine predictors of response including baseline individual features, using logistic regression. Safety profiles will be described by the percentage of each adverse effect.

1.0 INTRODUCTION

1.1 Background

Both autism and MDD are the leading causes of disability worldwide. Up to 50% of adults with autism ('autistic adults') experience MDD in their lifetime, **with a lifetime prevalence 4-times greater than in the neurotypical (typically developing) population** (Hudson et al., 2019). Meanwhile, half of chronically depressed patients endorse clinically significantly elevated autistic traits (Radtke et al., 2019). Greater functional impairment, longer duration of depression, and heightened suicidality and self-injurious behaviours are noted among people with concurrent MDD and autism than in those with either disorder alone. MDD in autistic adults is considered more challenging to treat, as conventional antidepressants appear to have limited efficacy in autistic adults with co-occurring MDD (K. Williams et al., 2013). Moreover, based on expert opinions and experiences, **at least 50% of autistic adults with MDD have treatment-resistant depression** (TRD), typically defined as failing to respond or not going into remission following two lines of any-class antidepressant of an adequate dose and duration (Carter et al., 2020). This rate of non-response appears higher than that reported in MDD alone (Carter et al., 2020).

1.2 Study Intervention

Psilocybin is a naturally occurring plant alkaloid (Genus: *Psilocybe*) that acts as a classic serotonergic receptor agonist (mainly binding to serotonergic receptor 2A, 5-HT_{2A}). It is a psychedelic drug and is classified as a 'tryptamine', a derivative of the essential amino acid tryptophan (Passie et al., 2002). Psilocybin is primarily a prodrug that is metabolized to the pharmacologically active compound psilocin, which is able to cross the blood-brain barrier. Typical effects of psilocybin include significantly altered states of consciousness, experienced through visual and sometimes auditory effects, changes in perception, distortions of time, and a range of effects including a sense of awe, novel perspectives, existential and personal insight, dramatically heightened empathy and feelings of compassion, strong emotions, and unitive experience. These mystical experiences are correlated with improvements in mood in healthy volunteers and palliative patients with end-of-life distress (Johnson et al., 2019).

Psilocybin-assisted therapy (PAT), is a psychotherapeutic intervention in which the psychological effects of psilocybin play a significant role. PAT procedures typically involve psychological preparation prior to therapist-supported psilocybin dosing sessions. These sessions are used to establish a therapeutic relationship, inform participants about what to expect, and set expectations for the dosing session. During the psilocybin dosing session, trained therapists support the individual through their experience and psychological integration therapy occurs after the dosing experience. PAT has shown impressive antidepressant effects in people with TRD or severe MDD in at least six modern-era clinical trials (Andersen et al., 2021).

1.3 Preclinical Data to Date

Studies in rodents have produced evidence that classic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), psilocin, N,N-dimethyltryptamine (DMT) have therapeutic potential in instilling long-term behavioral changes similar to those observed in traditional antidepressant treatments. These behavioral changes include improvements in coping strategies as well as amelioration of cognitive functions that are commonly compromised in MDD, such as associative learning.

Rodent models of both MDD and autism have suggested a shared characteristic of aberrant neuroplasticity; MDD mainly involves prefrontal and hippocampal hypoplasticity while autism implicates either hyper- or hypoplasticity, depending on the genetic mutation and its brain substrates (Desarkar et al., 2015). Furthermore, preclinical studies in rodents investigating the subacute impact of psilocybin on brain function have indicated that psilocybin can enhance functional and structural neuroplasticity within the prefrontal brain regions as well as prompting hippocampal neurogenesis, both of which are relevant to antidepressant effects (Vollenweider & Preller, 2020). Another study in rodents showed that a dosage of 1mg/kg of psilocybin was sufficient to induce increases in dendritic spine size and density within the medial frontal cortex through modulation of the rate of spinal formation. The changes in dendritic spine formation occurred rapidly, within 24 hours, and about 50% the newly-formed spines remained stable 1 week following treatment, with about 25% of them remaining stable 4 weeks following treatment. The psilocybin-induced spines were not significantly less stable than those formed in control conditions. In addition, following psilocybin dosage, the mice showed a significant reduction in stress-related behaviors and an increase in excitatory (glutamatergic) neurotransmission within layer 5 pyramidal neurons (Shao et al., 2021).

1.4 Clinical Data to Date

Currently, to our knowledge, **there have been no clinical trials conducted or published** investigating the use of psilocybin in autistic people. This neglect is representative of a dire inequity in mental health & research (Markopoulos et al., 2022). Before psilocybin can be administered in a clinical setting, we need a neuroscience-informed clinical trial to better understand and treat TRD/severe MDD in autistic adults.

Based on pooled evidence from clinical trials in neurotypical populations (Andersen et al., 2021), psilocybin shows favorable tolerability profiles and no documented serious adverse events (Andersen et al., 2021). Despite this lack of published studies, anecdotes (from a book (Orsini, 2021) and from PI Dr. Lin's clinic) suggest psilocybin also appears to be well-tolerated and safe in many autistic adults. Given partial mechanistic commonalities shared with psilocybin, a pilot trial shows the initial safety of MDMA in autistic adults (Danforth et al., 2018). Altogether, we anticipate a high safety, minimal risk profile in autistic adults with the standard psilocybin dose, but empirical evidence is needed to support this claim.

Furthermore, several clinical trials have supported the efficacy of PAT as a treatment for MDD in neurotypical populations: One open-label trial of 12 participants with TRD showed a significant decrease in depressive symptoms both 1 week and 3 months following treatment with psilocybin (10mg, then 25mg one week later) and PAT, with 67% of participants achieving remission after week 1 following treatment, and 58% of participants continuing to meet the criteria for a clinically significant reduction in depressive symptoms at 3 months following treatment. 42% of participants were still in complete remission at 3 months following treatment (Carhart-Harris et al., 2016). A second open-label study extending the previous one assessed changes in depressive symptoms in 20 participants, including the original 12 participants for 6 months following treatment, and observed a significant reduction in depressive symptoms at 5 weeks, 3 months, and 6 months following treatment (Carhart-Harris et al., 2018). More recently, a randomized control trial of 24 participants with MDD showed a clinically significant antidepressant response to treatment with psilocybin (20mg/70kg, then 30mg/70kg ~1.6 weeks later), with large effects sizes at week 1 (Cohen *d* = 2.5) and week 4 (Cohen *d* = 2.6) following treatment when compared to the waitlist control group (Davis et al., 2021). A long-term follow-up study of the same participants showed response and remission rates of 75% and 58%, respectively, at 12 months (Gukasyan et al., 2022). Altogether, these results suggest considerable therapeutic potential for psilocybin used in tandem with psychotherapy to induce long-term, clinically significant reductions in depressive symptoms in individuals with TRD.

Studies investigating the effects of psilocybin and PAT on brain function have indicated that PAT decreases brain functional network modularity (i.e., groupings of individual brain regions that share high functional connectivity among each other; as indexed by network segregation into distinct networks, with sparse connections across networks) in neurotypical people with TRD or severe depression. This change in brain network segregation (i.e., relative strengths of within-network connections to between-network connections) is correlated with improvement in depressive symptomatology. This increase in functional network integration (i.e., relative strengths of between-network connections to within-network connections) induced by psilocybin is more marked in 5-HT_{2A} receptor-rich higher-order functional networks (i.e., DMN, salience and frontoparietal networks) (Daws et al., 2022).

Given that only a few studies have examined the effects of psilocybin-assisted therapy on brain function (several of which reuse the same dataset), **we will explore several aspects of brain function which may show mechanistic relationships with depression and treatment changes in autism.** In this way, we can identify candidate mechanisms to inform a larger trial and study design. Specifically, echoing the distinct and shared neuroscience of MDD and autism as reviewed above, we will use functional Magnetic Resonance Imaging (fMRI) to model changes in **(1) brain functional network interactions** and **(2) idiosyncratic brain patterns** following psilocybin-assisted therapy and link these brain metrics to depressive symptom changes.

All contemporary clinical trials have investigated psilocybin in the context of several hours of intensive psychotherapy given its highly potent psychedelic effects and the need for

continuous monitoring. The psychotherapy involves at least 2 hours of preparatory sessions, 6-8 hours of supportive therapy during the dosing sessions in the presence of two trained therapists, and 2 hours of post-dosing integration sessions.

We propose a first-of-its-kind open-label clinical trial to investigate the feasibility, tolerability, and safety of administering psilocybin in autistic adults with TRD. In this study, 20 participants (intellectually able and fluent-speech adults) with autism and co-occurring TRD will receive around 20 hours of manualized psychotherapy that has previously been used with psilocybin (Agin-Liebes et al., 2020). They will also receive psilocybin at 2 different time points, firstly a safety dose of 10mg, followed by a treatment dose of 25mg. This study design is in accordance with previous studies investigating the use of psilocybin with PAT to treat TRD (Carhart-Harris et al., 2016, 2018).

1.5 Optional Dense Sampling Brain Magnetic Resonance Imaging (MRI) Data Collection

In addition to the main clinical trial, we also propose *an **optional** additional sub-study within the main clinical trial of psilocybin-assisted therapy for depression in autism*, i.e., *the optional dense sampling brain MRI data collection*. The classic approach for studying the brain involves collecting data from a number of individuals at a single time point and then group-averaging, thus increasing the ability to generalize findings to a broader population. However, neural heterogeneity in autism, depression, and almost all major psychiatric disorders has, thus far, been a major obstacle to identification of consistent biomarkers using the case-control approach. Furthermore, while functional imaging studies have shown altered activation and connectivity differences in both autism and depression, studies continue to show poor replicability. Biotyping using larger sample sizes is one approach which has attempted to overcome this heterogeneity.

On the other hand, neuroimaging studies that densely sample the individual connectome (i.e., repeatedly scanning a given individual in combination of repeated behavioural /psychological/physiological measures) are beginning to transform our understanding of human brain organization over time. This method is particularly well-suited for examining relationships between brain dynamics and behavioural/psychological variables (states) that vary over relatively short time scales, such as changes in mood and activities levels with time or intervention (Gratton et al., 2018; Poldrack et al., 2015). This dense sampling approach may provide a promising new avenue for brain and psychiatric research for its value in producing a more reliable brain functional network markers linked to dynamical changes in behaviours based on a few participants. This strength may be even more beneficial and pronounced in clinical trials given the nature of trials in repeated measures and behavioural/brain changes following intervention. However, to our knowledge no study has employed this method in psychiatric populations and no studies have applied this approach to clinical trials to date (Gratton et al., 2020). This opens the possibility for CAMH to become a leader in this new field of neuroimaging known as dense sampling and deep phenotyping. This *optional dense sampling brain MRI data collection* (repeated scan) dataset will comprise important feasibility data in order to assess short-term

variability in functional connectivity in autistic people with dynamic changes in depression, anxiety, and emotion regulation, as well as demonstrate the feasibility of the proposed repeated scanning design in autistic people. This optional sub-study represents crucial early work that will be critical to obtain funding for larger studies.

1.6 Risks/Benefits

Possible Benefits

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

Is It safe for autistic adults to try psilocybin?

Psilocybin shows favourable tolerability profiles and no serious adverse events based on pooled evidence from clinical trials in neurotypical people (Andersen et al., 2021). Despite no published studies, anecdotes (from a book (Orsini, 2021) and from PA Dr. Lin's clinic) suggest psilocybin also appears to be well-tolerated and safe in many autistic adults. Given partial mechanistic commonalities shared with psilocybin, a pilot trial shows the initial safety of MDMA in autistic adults (Danforth et al., 2018). Altogether, we anticipate a high safety, minimal risk profile in autistic adults with the standard psilocybin dose, but empirical evidence is needed to support this claim.

Medication Tapering Risks

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

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.

MRI

General Risks: There are four categories of risks to human subjects directly associated with MRI examination, including:

1. Acoustic Noise Levels: The risk associated with acoustic noise levels are related to the noise generated by the pulsing of the gradients. The risk to the participant may be temporary loss of hearing. The easiest and most reliable means of preventing hearing loss is to use disposable earplugs. Disposable earplugs or non-magnetic headphone sets will be used for all participants in this study.
2. Static Magnetic Fields: There are no established risks of exposure to magnetic fields of 3T, other than the incidental risks (listed below). Like other clinical MRI centers, our facilities incorporate a complete range of procedures to assure security of the restricted access area, and careful screening of potential participants, before they enter the restricted access area.
3. Gradient or Time-Varying Magnetic Fields: Risks associated with gradient magnetic fields are related to dB/dt (change in magnetic field over time), which can induce electric fields and currents in conductive media, including biological tissue. The MRI systems will be operated within limits already determined not to pose significant risk to humans.
4. Specific Absorption Rate (SAR): The risks associated with Specific Absorption Rate (SAR) are related to the fact that given a large enough SAR, heating of tissue may occur. Proper and routine monitoring of all RF electronics (e.g. coils, transmitters, system security, etc.) will be performed on a regular basis. There are three categories of incidental risks to all human subjects in a restricted access area. The three categories of concern are related to: (1) malfunctioning or movement of implanted metal objects (i.e., aneurysm clips, pacemakers, etc.); (2) injury from a projectile (i.e., ferromagnetic objects being attracted into the magnet); and (3) asphyxiation due to large amounts of cryogenic gasses generated during a quench (i.e., the event that occurs when a magnet makes the sudden transition from superconducting to resistively conducting). These categories of incidental risk are unlikely given the extensive set of safety checks employed by our facilities prior to scanning.

Psychological distress from MRI: Some participants can experience claustrophobia while in the scanner. To minimize the potential distress from unfamiliarity, the participants will receive instruction using a custom-built social script, which comprises a series of photographs of the research procedures, environments, and files of the sounds emitted by MRI to help participants be acquainted with the scanning environment and learn the procedures at the screening visit (V1). Participants will have the opportunity to examine this space or the mock scanner before the scanning starts. Mild psychological distress must also be considered in these studies. It is not advisable for participants to involve themselves in this study if they show a fearful behaviour to enclosed spaces or if they have a history of not tolerating an MRI scan. It is also possible that the participants may find the scanning procedures stressful. They will be able to discuss any concerns with study staff at any length at any time. On scan days, study staff will be available at all times, including during the scan (via call button and microphone in the scanner room). In addition, medical staff will be on call if participants want to discuss matters with a doctor.

There is no known extra risk associated with multiple repeated MRI scans. In terms of the burdens of repeated MRI scans, there have been multiple studies conducted

applying similar dense-sampling methods in clinical populations, suggesting the feasibility of this design. The dense-sampling method allows for a more complete model of the brain and changes/variance that may be observed in an individual's brain over the course of the study, particularly in response to the intervention (psilocybin dosing & associated therapy session). Given the heterogeneity of the autism spectrum, this data may be quite useful in developing predictive biomarkers for various behavioural phenotypes (i.e. observed behaviours). To acquire the scientific merits of the design while ensuring the tolerable burden associated with repeated MRI scans, the feasibility of the current proposed repeated scan number has been endorsed by four autistic self-advocates.

Risk of Incidental Findings: The possibility of unexpected or incidental findings carries with it some risks. Research scans are not designed to be used for diagnosis. In the unlikely event an atypical finding is seen on these MRI scans, the study team may ask a radiologist or other qualified health professional to look at this participant's MRI data. The participant's identity will not be revealed to the radiologist. Participants must consent for any incidental findings to be shared with any third-party qualified health professionals, including the participant's primary care physician. If the qualified professional recommends further tests to determine the nature and significance of any incidental findings on the specific MRI scan, we will contact the participant to assist in arranging medical follow-up.

Assessment Measures

Assessment measures are designed to address various aspects of psychopathology associated with depression and autism 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 of Main Clinical Trial

To investigate the feasibility, tolerability, and safety of administering psilocybin in autistic adults with TRD.

Hypothesis 1a (feasibility): We will be able to recruit 20 participants within 21 months with retention >90%.

Hypothesis 1b (tolerability and safety): Adverse events (tolerability) and serious adverse events (safety) will be similar to those reported in the literature on classic serotonergic psychedelics in neurotypical populations.

2.2 Secondary Objective of Main Clinical Trial

To use brain network and cognitive modelling to study mechanisms underpinning antidepressant effects of psilocybin for TRD in autism.
Hypothesis 2a: Psilocybin will reduce segregation within major functional brain networks and increase integration between higher-order networks in autistic adults.
Hypothesis 2b: These psilocybin-induced changes in functional network interaction will be idiosyncratic among each participant.
Hypothesis 2c: The post-treatment changes in the brain metrics will be related to improved depressive symptoms.

2.3 Exploratory Objective of Main Clinical Trial

To evaluate a signal of antidepressant and other beneficial effects of psilocybin for TRD in adults with autism.
Hypothesis: While this trial is not powered to determine antidepressant efficacy, we expect an antidepressant effect size to be close to (or comparable to) that reported in neurotypical depression.

2.4 Primary Objective of Optional Dense Sampling Brain MRI Data Collection

To assess the recruitment and retention in the dense sampling (multi-session repeated scanning) design. This will be assessed by evaluating the number of participants offered to enter the study against the number who consent and the number who complete the protocol.
Hypothesis: A moderate proportion (30-50%) of participants in the main clinical trial will agree to consent for this optional dense sampling (repeated scans) design. The attrition (those who withdraw during the repeated scans) will be low (lower than 25%).

2.5 Secondary Objective of Optional Dense Sampling Brain MRI Data Collection

To assess variance in brain functional connectivity across participants and sessions. Session-to-session variance in brain functional connectivity will be linked to day-to-day behavioural measures, including depressive symptoms and autistic burnout.
Hypothesis: Day-to-day behavioural changes will be a predictor of a portion of session-to-session variance in brain functional connectivity.

3.0 CLINICAL TRIAL DESIGN

3.1 Overall Design

This study is a first-of-its-kind open-label study investigating psilocybin-assisted therapy (PAT) in treating treatment-resistant depression (TRD) in autistic adults. The findings of this study will provide preliminary data regarding the feasibility, safety, and efficacy of psilocybin used in tandem with psychotherapy as a treatment option for this underserved population. **All of the following designs have been extensively discussed with four autistic self-advocates in Azrieli Adult Neurodevelopmental Centre. They fully endorse the feasibility of all details of the study designs as follows.**

Overview of Study Design

Main Clinical Trial (Figure 1 and Section 6.1.2.1 and 6.2.1)

All 20 participants (10 males, 10 females, autistic with TRD & intellectually able/speech-fluent) will follow the same *main clinical trial design*. Participants will be pre-screened to determine potential eligibility, and if potentially eligible, the consent discussion process/documentation will begin. Participants must consent to participate in the study before proceeding with study procedures. Each participant will begin with a screening visit (V1), during which eligibility will be determined through clinical and psychiatric assessments of the participant's physical and mental health. Following confirmation of eligibility, the study procedures will begin.

The participant will begin with a 2-4 week tapering period during which they will taper and discontinue any conventional antidepressants. Most conventional antidepressants will require a minimum 2-week tapering period, with the exception of fluoxetine, which will require a 4-week tapering period. Additional time may be added at the discretion of the study investigator. During the tapering period, there will be weekly check-ins with a study psychiatrist by in-person assessment or brief telephone calls to monitor for worsening depression and suicidality. Following the tapering period, participant eligibility will be re-assessed for the eligibility.

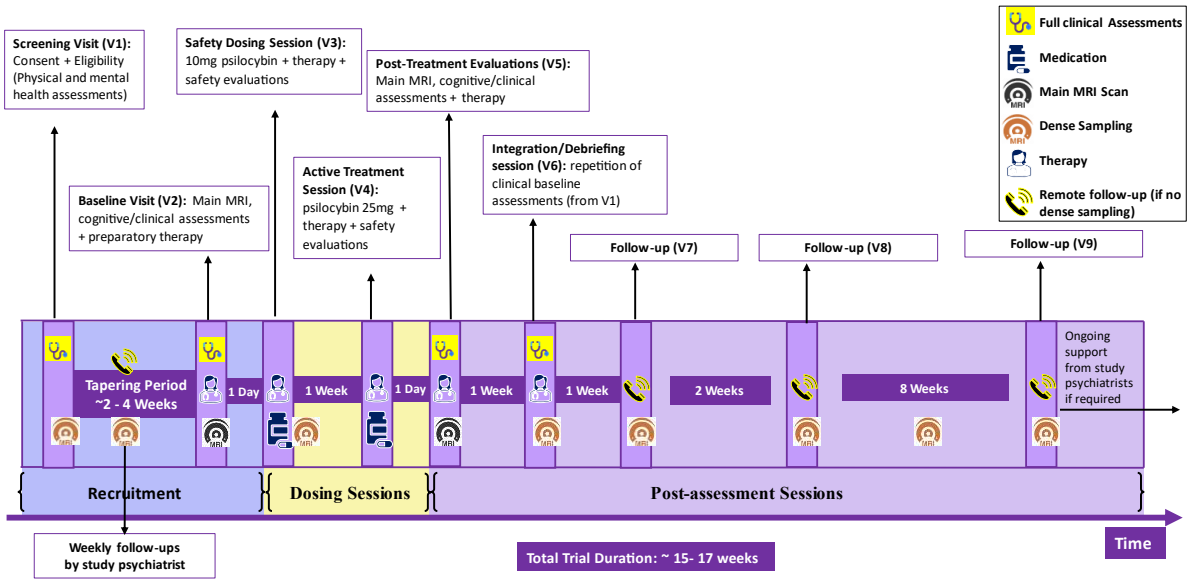
At Study Visit 2 (Baseline, V2), participants will complete a series of questionnaires and assessments (Table 2) and preparatory therapy with trained study therapists. The participant will also receive a brain MRI scan lasting for about 45 minutes. To reduce participant burden, the assessments of the baseline visit can be broken up into multiple days. However, all assessments must be completed within 7 days before the first intervention visit (V3). Ideally, the baseline visit occurs the day before the safety dose is administered (V3).

At Study Visits 3 & 4 (V3/V4), participants will receive oral doses of psilocybin (safety dose of 10 mg at V3, treatment dose of 25 mg at V4), to assess the tolerability and efficacy of psilocybin. These sessions will be held one week apart and will last 6 to 8 hours each. These sessions will take place in a pre-decorated treatment room at CAMH. The sessions will be set up and led by Co-Investigator Dr. Husain. Throughout the entire duration of the dosing sessions, participants will be monitored by a minimum of two trained therapists.

At the end of each session, participants will be evaluated for safety by a study psychiatrist before being discharged. Participants will also rate the 11-Dimension Altered States of Consciousness (11D-ASC) at the end of each dosing day when the subjective effects of psilocybin have subsided to a negligible level.

Visit 5 (V5) will be held one day after administration of the treatment dose (V4). During V5 the participants will complete post-treatment clinical and cognitive assessments, alongside the second and final MRI scans (*of the main clinical trial design*). Participants will also undergo a 1-hour integration therapy session to debrief their experiences the day before. Visit 6 (V6) will be held one week following the treatment dose (V4). During V6 a second 1-hour integration therapy session takes place and all post-treatment clinical assessments will be repeated. Subsequent clinical progress will be evaluated virtually at V7, V8, V9, which will respectively be held 2, 4, and 12 weeks following the treatment session (V4). From V7-V9 the cognitive tasks and MRI will not be done for *the main clinical trial design*. A study psychiatrist will be available to respond to any concerns about changes in mental/physical states throughout the study.

Figure 1. Schematic for the Main Clinical Trial Design



Optional Sub-Study of Dense Sampling Brain MRI Collection (Section 6.1.2.2 and 6.2.2) 10 participants out of 20 participants in the main clinical trial could opt to receive 8 additional brain MRI scans besides the MRI scans at V2 and V5 required in the main clinical trial. These 8 additional scans will be assessed at V1, in the middle of medication washout/tapering period, V3, V6, V7, V8, 8 weeks following the treatment dose (V4), and

V9, respectively. At each optional MRI visit, self-rated Beck Depression Inventory-II (BDI-II) and Autistic Burnout Survey Items (ABSI) will also be collected.

Timeline

In total, there are a minimum of 13 study visits (9 study visits and a maximum of 4 weekly check-in virtual visits during the washout period) for the main clinical trial design. When a participant chooses to participate in the optional dense sampling *brain* MRI data collection, there will be additional 8 MRI scans, which consist of 1 additional study visit because the other 7 visits already exist and overlap with the original visits of the main clinical trial design. There may be more study visits scheduled at the discretion of the study team or the participant. For example, a participant may need to break one session into two separate visits due to the intolerable duration of a single scheduled visit. These study visits will take place over the span of approximately 4 months for each participant. The total expected duration of the clinical trial from the time the study team starts recruiting until data analysis has been completed is 33-months. Following a 9-month startup period (including additional time for acquiring psilocybin and receiving a Section 56 exemption), the study team will recruit approximately 1 participant per month over the period of 21 months. Study interventions and follow-up assessments will be completed by month 27. This leaves approximately 6 months for data analysis which will be completed at month 33.

3.2 Primary Endpoints

The primary safety endpoints of *the main clinical trial design* will be evaluated 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. Blood pressure and heart rate will be examined before (V2) and during the psilocybin dosing sessions (V3/V4). 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. The safety endpoint is the number and severity of adverse events reported throughout the duration of the trial.

Feasibility endpoints of *the main clinical trial design* include the 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 intervention. Throughout all three periods, we will also evaluate adverse events including psychological distress and serious adverse events (e.g., hospitalization, suicide attempt, death).

3.3 Secondary Endpoints

The secondary endpoint *the main clinical trial design* of psychedelics experiences will be evaluated using the 11-Dimension Altered States of Consciousness (11D-ASC), completed following each psilocybin dosing session (V3/V4).

3.4 Exploratory Endpoints

Exploratory endpoints of *the main clinical trial design* include 1) brain changes, 2) changes in cognitive performance, 3) symptoms associated with depression, 4) other behavioural/psychological symptoms/features which are theoretically associated with PAT and depression:

1) Changes in brain network interaction will be evaluated using MRI at V5
2) Cognitive performance associated with hopelessness will be evaluated at V5.
3) Symptoms associated with depression, including core depressive symptoms, rumination, anxiety, suicidality will be evaluated at V6 & V7.
4) Other behavioural/psychological symptoms/features, which theoretically are associated with PAT and depression, including autistic burnout, interoception, alexithymia, psychological inflexibility, resilience, and quality of life, will be evaluated at V6 & V7.

4.0 PARTICIPANT SELECTION AND WITHDRAWAL

4.1 Target Population

The target population for this study is adults aged 18 to 65 years old, who are intellectually-able & speech-fluent with a diagnosis of autism and a concurrent diagnosis of major depressive disorder. They must be experiencing a clinically significant depressive episode that has failed to respond to at least two adequate trials of antidepressants. Participants must meet all inclusionary/exclusionary study criteria as confirmed by the study investigator. In order to be eligible, these criteria must be met at both Screening (V1) and Baseline visits (V2). For participants on concomitant medications, confirmation of eligibility occurs after a successful washout period in which the participant has been tapered off concomitant medications for a period of at least 2-weeks prior to baseline (4-weeks for fluoxetine), as confirmed by a study investigator.

4.2 Participant Recruitment and Screening

The target sample size of *the main clinical trial* is 20 participants (N=20, 10 male, 10 female) diagnosed with autism and treatment-resistant depression. The study will take place at a single site: the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario. The target sample size of *the optional dense sampling brain MRI data collection* is 10 out of the 20 participants that have been enrolled in *the main clinical trial*, regardless of the sex.

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.

CLEARR will be used to recruit participants for this clinical trial. All new referrals will be reviewed by the CLEARR coordinator and CLEARR physician for eligibility to participate using minimal inclusion/exclusion criteria outlined. Once a patient is identified as potentially suitable for the clinical trial, the attending physician will be notified via outlook calendar invite or email that their patient may be eligible for the clinical trial. The attending physician will decide whether research is appropriate for the patient and if so, they will ask the patient for consent to be contacted regarding the clinical trial. If the patient provides verbal consent to be contacted to receive more information about the clinical trial, the physician will connect the patient with the CLEARR coordinator or research team who will further explain the clinical trial. No personal health information (PHI) will be given to the research team prior to obtaining the patient's consent.

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 (Appendix C1 and G1). 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 autism
- Whether they have a clinical diagnosis of major depressive disorder
- Whether they are currently experiencing a major depressive episode
- Treatments taken for major depressive episode (frequency and type of treatment)
- Whether the potential participant has been diagnosed with psychotic disorder, bipolar disorder, paranoid personality disorder, schizoaffective disorder, or borderline personality disorder;
- Diagnosis of a substance use disorder (excluding tobacco) within the previous 6-months;
- If they are currently undergoing therapy and if they are, the date that they started

- Whether the potential participant would be willing to discontinue current antidepressant medications
- Whether they are seeing a doctor on a regular basis for a medical problem
- If they are currently taking medications for the treatment of a physical health problem
- Difficulty with giving blood or needles
- Currently nursing or pregnant
- Willingness to take contraceptives for the duration of the study
- If they have been using contraceptives for at least the previous 3-months
- Currently enrolled in another study involving an investigational product or device
- If they are able to take medication orally
- If they have ever used psychedelic drugs

The information collected during this conversation will be recorded on the pre-screen form (Appendix C1) 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, blood work, and the PAT 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. Participants will also receive reimbursement for TTC travel expenses when taking the TTC to and/or from the study appointments. Reimbursement for traffic expenses is independent from the reimbursement of study visits.

Participants will be reimbursed for the time spent at in-person-only study visits (V1-V5) of *the main clinical trial*. Participants will be reimbursed $40 for three in-person study visits (V1, 3 and 4) that they attend. For Visits 2 and 5, you will be reimbursed $80 for each visit due to extra MRI assessments in addition to the clinical study visits. In total, if participants

complete all in-person study visits of *the main clinical trial design*, they may be reimbursed up to $280 for their time.

For *the optional dense sampling brain MRI data collection*, participants will be reimbursed $60/hour for each additional in-person visit for an MRI scan. When the additional MRI scan visit overlaps with the in-person visit of *the main clinical trial* (i.e., V1-V2 and V5), the compensation for that in-person visit will be covered by the MRI scan compensation. In total, if participants complete all additional MRI scan visits of *the optional dense sampling brain MRI data collection*, they may be reimbursed up to $210 (30 mins per optional MRI visit).

Compensation will be provided at the end of the last study session (for total reimbursement), either in cash or by a gift card. No payment will be provided in advance.

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 be eligible for this clinical trial:

1. Must be aged 18 to 65 years old;
2. Must be deemed to have capacity to provide informed consent;
3. Must sign and date the informed consent form;
4. Stated willingness to comply with all study procedures;
5. Intellectually able: Either 1) the participant has a previous report showing intelligence quotient (IQ) ≥ 70 on the General Abilities Index of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) or any other standardized intelligence scales, or 2) the participant scores >10 percentile on the nine-item form of the Raven's Standard Progressive Matrices Test (RSPM).
6. Ability to read and communicate in English, such that their literacy and comprehension is sufficient for understanding the consent form and study questionnaires, as evaluated by study staff obtaining consent;
7. Primary DSM-5 diagnosis of non-psychotic MDD, single or recurrent, based on the Structured Clinical Interview for DSM-5 (Clinician Version; SCID-5-CV) administered at the first screening visit (V1);
8. Participants diagnosed with treatment-resistant depression defined as individuals with a baseline GRID-HAMD-17 score > 14 and that have not responded to two or more separate trials of antidepressants at an adequate dosage and duration based

on the Antidepressant Treatment History Form (ATHF; Appendix C2); there is no upper limit on the number of treatment failures;
9. Ability to take oral medication;
10. Individuals who are capable of becoming pregnant: use of highly effective contraception for at least 3 months prior to screening and agreement to use such a method during study participation;
11. Individuals who are willing to taper off current antidepressant and antipsychotic medications for a minimum of 2-weeks (or more depending on the medication) prior to Baseline (V2) and whose physician confirms that it is safe for them to do so; and
12. Agreement to adhere to Lifestyle Considerations (section 4.5) throughout study duration.

4.4.2 Exclusion Criteria

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

1. Pregnant as assessed by a urine pregnancy test at Screening (V1) or individual's that intend to become pregnant during the study or are breastfeeding;
2. Treatment with another investigational drug or other intervention within 30 days of Screening (V1);
3. The presence of an unstable seizure disorder as defined by having not been seizure-free for at least 6 months or anticonvulsant treatment has not been stable for at least 4 weeks;
4. The presence of any clinically significant or unstable medical conditions, including cardiovascular, liver, kidney, pulmonary disease, presence of known congenital brain malformation, as per investigator assessment based on medical history and chart review;
5. Moderate or severe DSM-5 diagnosis of an alcohol or substance use disorder in the past 12 months;
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, or neurocognitive disorder as determined by medical history and the SCID-5-CV clinical interview;
7. Any first-degree relative with a diagnosis of schizophrenia-spectrum disorder; psychotic disorder (unless substance-induced or due to a medical condition); or bipolar I or II disorder as determined by the family medical history form and discussions with the participant;
8. Presence of a relative or absolute contraindication to psilocybin, including a drug allergy, recent stroke history, uncontrolled hypertension, low or labile blood pressure, recent myocardial infarction, cardiac arrhythmic, severe coronary artery disease, or moderate to severe renal or hepatic impairment;

9. Substantial lifetime use (>10 years total) or recent use (past 6 months) of ketamine, psychedelics, or MDMA;
10. 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;
11. Have active suicidal ideation with intent and plan as determined by SBQ-ASC.
12. Are currently undergoing psychotherapy or have undergone psychotherapy within 12 weeks prior to Screening.
13. Contraindication to MR imaging: with shrapnel or other metal or electronic implants in their bodies (such as pacemakers, aneurysm clips, surgical devices, metallic tattoos on the head, etc.) or a previous history of claustrophobia.

4.5 Lifestyle Considerations

During this clinical trial, participants are asked to:

- Abstain from alcohol for 24 hours before the intervention or the day of the intervention (V3, V4).
- Abstain from the use of any prescribed opioids, benzodiazepines, or sleep aids (Z-drugs) within 12 hrs prior to the intervention (V3, V4) and for up to 6 hrs after administration.
- Abstain from any illicit drugs (e.g. cocaine, ecstasy/MDMA, hallucinogens) and/or cannabis for the duration of the study.
- Abstain from driving or operating heavy machinery for up to 24 hours after the intervention (V3, V4).

4.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet one or more eligibility criteria required for participation. The screening period for participants in this study occurs before Baseline (V2) and eligibility for the study cannot be confirmed until the participant had tapered off any concomitant medication. In order to be eligible, the participant must meet all eligibility criteria as outlined in Section 4.4. The information collected about the participant during the screening process including demography, screen failure details, eligibility criteria not met, and any AEs/SAEs will be used for the purposes of transparent reporting. Participants who are deemed ineligible will continue with their usual standard of care or may be referred to other research protocols for TRD.

4.7 Participant Withdrawal Criteria

4.7.1 When and How to Withdraw Participants

Participants are free to withdraw from participation in the clinical trial at any time.

An investigator may discontinue or withdraw a participant from the clinical trial for the following reasons:

- Pregnancy or if participants cease effective contraception;
- Significant study intervention non-compliance;
- If any adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the clinical trial would not be in the best interest of the participant; or
- 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.

Notably, even if participants cannot complete a post-treatment brain MRI scan (V5) of *the main clinical trial design* or cannot complete any of brain MRI scans of *the optional dense sampling brain MRI data collection* (either for the personal reasons or for an exclusion criterion for the MRI scan), they will not be discontinued/withdrawn from the trial by an investigator.

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. The aim is to have 20 participants who complete the study.

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 for depression and anxiety in autistic adults 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 will be made to perform an Early Termination Visit.

Participants that withdraw after the first or second 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 & Psilocybin Effects

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a naturally occurring plant alkaloid that belongs to the *Psilocybe* genus. It is classified as a tryptamine, a derivative of the essential amino acid tryptophan. Psilocybin is a prodrug: its pharmacologically active form is psilocin, which is able to readily cross the blood-brain barrier. Psilocybin is metabolized to psilocin through a de-phosphorylation reaction in the liver (Passie et al., 2002).

Psilocybin is primarily administered orally and detectable in the plasma within 20 - 40 minutes at dosages ranging from 8 – 25mg (or 0.06 – 0.2mg/kg). Psilocin is detectable in the plasma after 30 minutes. Psilocybin has an elimination half-life of 50 minutes, while psilocin's elimination half-life is between 2 to 3 hours (Passie et al., 2002).

As a classic serotonergic psychedelic, psilocybin/psilocin acts primarily as an agonist of the 5-HT_{2A} receptor, though it also has a high affinity for other 5-HT receptors such as 5-HT_{2C}. When administered in humans, psilocybin is consistently able to produce several psychological effects within 70 to 90 minutes, including 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 (Passie et al., 2002).

For more information about psilocybin and its effects, please refer to the investigator's brochure.

Psilocybin-Assisted Therapy

The participant will attend 1 preparatory session that occurs within 7-days of the first psilocybin dosing session (V3) to develop a therapeutic alliance, set intentions for the experience, and learn what to expect during the dosing session. In addition, the participant will undergo 2 integrative therapy sessions after the intervention (V5 & V6). Each therapist will undergo training with the study investigator and using the principles outlined in the Yale Manual for Psilocybin-Assisted Therapy of Depression (DOI: 10.31234/osf.io/u6v9y).

These include:

- Preparatory sessions to establish rapport & therapeutic alliances with the participant & study therapist
    - In addition, providing psychoeducation for the participant to set expectations for the dosing sessions
- Providing an appropriate setting for the dosing sessions
- Maintaining a non-intrusive presence
- Responding to invitations to talk
- Responding to intense affective/emotional states
- Responding to agitation or restlessness
- Responding to requests for contact (appropriately & within the participant's boundaries)
- Follow-up sessions, aimed at helping the participant integrate & understand their psychedelic experience

These principles will apply to both dosing sessions (10mg & 25mg). As needed, therapy sessions could be paced more gently with clearer language & instruction (e.g. less open-ended or non-specific questions), from the therapists to be sensitive and responsive to the participant's needs & accommodations.

For a full description of each therapy session and PAT, please refer to the Yale Manual for Psilocybin-Assisted Therapy of Depression. Therapy sessions will not be video recorded. At least one of the therapists will be a clinician and will be available at all times during the dosage session to assess and manage any medical or psychiatric adverse events.

How the study intervention will appear

The psilocybin will be provided by Filament Health (Burnaby, British Columbia, Canada). The doses of psilocybin used in this study will be 10 mg (V3) and 25 mg (V4). The psilocybin will be administered in size 2 hydroxypropyl methyl cellulose (HPMC), white capsules.

5.2 Treatment Regimen

The participant will be administered psilocybin at 2 points during the trial, both following the Baseline Visit (V2) after the participant's eligibility has been confirmed: firstly a safety dose of 10mg during V3 (Day -7), then a treatment dose of 25mg during V4 (Day 0). The procedures are outlined below:

Each participant will be assigned a treatment bottle of 1 capsule of 10mg or 25mg of psilocybin. Under the supervision of a clinician, the capsule of psilocybin will be taken orally with a glass of water. There will be no modifications to the dosage, each participant will receive the same dosage for both medications. However, if adverse effects are experienced, the study clinician may make changes to the intervention, which include therapy after each session. The study clinician may decide that participants may require more therapy sessions. In addition to the psilocybin, two study therapists trained in psilocybin-assisted therapy 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 between 6 to 8 hours when the acute effects of the psilocybin have passed.

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 a licensed physician who will supervise the participant. The participant will receive a capsule containing either 10mg or 25mg of psilocybin, depending on the visit. The capsules will be 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 reflection, a pre-selected music playlist will be played quietly. Two study therapists trained in PAT will be supporting each participant during the dosing session with at least one therapist being present at all times to respond to the emotional and physical needs of the participant. Constant observation by therapists will monitor for adverse events during the dosing sessions. At least one member of the therapist pair will be a clinician. An on-call psychiatrist will be available at all times to further assess as needed for acute concerns.

The effects of psilocybin usually start about 20 to 30 minutes after administration, becoming the most intense in the first 90 to 120 minutes and gradually subsiding in 5 to 6 hours. The participants will be asked to remain in the room for the duration of the session regardless of the intensity of the effects, preferably lying down and mostly silent unless they have a concern or need to communicate a discomfort or seek reassurance from the therapist, or use the restroom. The therapists will 'check-in' with the participant (i.e., ask how the participant is doing) in 30-to-60 minute intervals post-dosing. 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 8 hours post-dosing when the acute effects of psilocybin are resolved (in the opinion of the investigator/therapist/study psychiatrist). The participant must be accompanied home by a caregiver who will remain with the participant for up to 24 hours after the intervention was given. The study team is to be notified that the participant has arrived home safely via phone call. In the absence of receiving a phone call, the study staff will directly contact the participant.

5.5 Participant Compliance Monitoring

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

5.6 Concomitant Therapy

All prescription and non-prescription medications (e.g. over-the-counter drugs and herbal supplements) that participants report taking during the 30 days prior to Screening (V1) will be assessed and recorded at V1. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units, and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use. Where applicable, medication reports should be corroborated with participant medical records. All as-needed (*pro re nata,* PRN) prescriptions should be converted to reflect the actual number of pills or dose taken per day.

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

Permissible Medications

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

For the initial Screening Visit (V1) through to the final study visit (V9), 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 (V3 & V4). Prescription and nonprescription medications with psychoactive properties that are used as needed for non-psychiatric conditions (e.g. pseudoephedrine for allergies or cold, zolpidem/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 3 months prior to screening and for the duration of the study. The following methods of contraception, if used properly and used for the duration of the study, are permissible:

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

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

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

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

Prohibited Medications

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

These medications should not be re-introduced until after Week 12 (V9) when the study is complete. If the medications are re-introduced, the study investigator must be notified and the medications will be documented in the participant's CRF. Participants who require concomitant medication(s) specifically for the treatment of depression at any time through the duration of the study will be assessed for reasons of resuming their medications.

Rescue Medication

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

- Benzodiazepine anxiolytics
    - The preferred pharmacological intervention of choice in case of acute psychological distress (e.g. medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action).
    - The oral route is preferable because IV injection procedures may further exacerbate the participant's anxiety.
- Antipsychotic medications (e.g. risperidone) should be available in the event that an adverse reaction escalates to unmanageable psychosis.
- Management of blood pressure:
    - Asymptomatic with blood pressure (BP) < 180/100
        - Reassure, ensure lights are dim or off, tilt head of bed 15 degrees up and continue to monitor
        - Increase blood pressure measurement frequency to q15min until BP has partly normalized (sBP = 100-159; dBP = 60-99)
    - Asymptomatic with BP <180/100 for >30 minutes
        - Administer captopril* 12.5mg PO/SL x 1 with MD order

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

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

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

5.7 Packaging

The psilocybin will be provided by *Filament Health* (*Burnaby, British Columbia, Canada*). The doses of psilocybin used in this study will be *10 mg and 25 mg*. The entire shipment for this trial will be sent in bulk (i.e. *20 capsules x 10 mg each, 20 capsules x 25 mg each*). Psilocybin capsules will be packaged individually in high-density polyethylene bottles (30cc). The dose for each participant will be stored in individual boxes labelled with the protocol number, trial name, lot number, unique box number, and a statement that the drug is for clinical use only. The IP will only be removed from the safe for one participant at a time on the day of their session. 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 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 the 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 either 10mg or 25mg of psilocybin. The IP will be dispensed and administered to the participants only by a licensed study physician. The study intervention will be administered orally, with water. Capsules should not be opened or chewed.

The investigator must keep an accurate accounting of the number of IP delivered to the site, administered to participants, and destroyed during and at the completion of the study. The IP is to be used in accordance with the protocol by participants. The study team, overseen by the PI, should maintain records that adequately document that the participants were administered the IP dose specified by the protocol.

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

5.9.4 Return or Destruction of Study Intervention

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

6.0 RESEARCH PROCEDURES

6.1 Research Visits

6.1.1 Description of Measures

SCREENING MEASURES

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

GRID Hamilton Depression Rating Scale-17 (GRID-HAMD-17). The GRID-HAMD-17 is a standardized version of the Hamilton Depression Rating Scale, a clinician-rated measure of depression (J. B. W. Williams et al., 2008). In addition to the screening purpose, GRID-HAMD-17 will be used as an objective outcome measure (versus the subjective self-rated questionnaires as described as follows) for depression (Appendix B11).

Autism Diagnostic Observation Schedule-2 (ADOS-2) Module 4. The ADOS-2 is a semi-structured activity-based assessment for evaluation of autistic symptoms. The Module 4 targets intellectually and verbally capable adults with autism. It will be administered by study clinicians (Lord et al., 1989).

Nine-item Form of Raven's Standard Progressive Matrices Test (RSPM). The Raven's Standard Progressive Matrices instrument is a multiple-choice test used to assess mental ability associated with abstract reasoning, termed fluid intelligence. The standard form (RSPM) consists of 60 items, categorized into five sets of twelve matrices presented in black and white, and has been used as an indicator of general intelligence throughout the world. We will use a shortened set of items (nine items) that predicts the total score for the 60-item scale with good accuracy and fares well in clinical populations (Bilker et al., 2012). The reduction from 60 to 9 items represents an 85% reduction in the number of items to be administered. Nine-item Form of RSPM will be used to estimate the general intelligence, especially when a participant does not have a previous record of intelligence quotient derived from any other standardized intelligence scales (Appendix B16 and B17).

For Baseline Autistic Features Associated with Depression:

Autism Quotient-12 (AQ-12). The widely used 50-item AQ tool, originally developed to identify autistic traits in adults of at least average intelligence, uses a 4-point Likert scale, ranging from '1' (definitely agree) to '4' (definitely disagree). Given the critiques of the AQ-50, including its length, factor structure and whether it is suitable to use as an autism severity measure, we will gather the 12 items identified by Lundqvist & Lindne (2017) as having utility to measure autism severity (Appendix B3).

Adult Repetitive Behaviour Questionnaire-2 (RBQ-2A). The RBQ-2A is a 20-item self-administered tool scored on 4- and 3-point frequency or severity scales, with higher scores indicating greater severity. Following previous studies, the 4-point scaled items were collapsed to a 3-point scale, then a total sum score was used giving a possible score range of 20–60 (Barrett et al., 2018) (Appendix B14).

Camouflaging autistic traits questionnaire (CAT-Q) The Camouflaging Autistic Traits Questionnaire (CAT-Q) is a 25-item self-report questionnaire assessing the extent to which a person engages in social camouflaging behaviours, validated in autistic and non-autistic adults with equivalent factor structure between the groups. The CAT-Q captures three domains of social camouflaging: (1) "compensation" (behaviours used to compensate for autism-related difficulties in social situations); (2) "masking" (behaviours used to hide autistic characteristics or present a non-autistic personality to others); and (3) "assimilation" (behaviours used to fit in better with others and not "stand out" from the crowd). Participants rate each of the 25 questions on a seven-point Likert scale between "Strongly Agree" to "Strongly Disagree". Responses are scored between 1 and 7, with higher scores for items which endorse presence of social camouflaging behaviour (Hull et al., 2019) (Appendix B6).

SAFETY MEASURES

Suicidal Behaviors Questionnaire – Autism Spectrum Conditions (SBQ-ASC). The SBQ-ASC is a self-report questionnaire used to measure suicidality in individuals with autism. It consists of 5 scored items: 1) lifetime experience of suicidal thoughts; 2) frequency of intense suicidal thoughts in the last 12 months; 3) perseverative intense suicidal thoughts; 4) likelihood of suicide attempts; 5) communication of future suicide intent & past suicide attempts to others. The SBQ-ASC also includes optional follow-up items which are not scored, based on responses to Item 5: for those who have attempted suicide, the follow-up items address presence of plans, impulsivity, and access to means. For those who have communicated suicide intent to others, the follow-up items address who was told about the participant's suicidality. For those who have never communicated to others their suicidality, these follow-up items address the reason why it was never communicated. Furthermore, these follow-up items assess the lifetime experience of non-suicidal self-injurious behavior (Cassidy et al., 2021) (Appendix B18).

UKU Side Effect Rating Scale. The UKU side effect rating scale is a short and easy-to-use instrument that captures the core dimensions of side effects in patients using psychotropic medications. The UKU side effect rating scale is widely used in both research and in clinical settings (Lingjærde et al., 1987), and is delivered by interviewing and observing the patients and their caregivers. Herein, we will adopt the UKU side effect

rating scale specifically adjusted to adults with IDD, which consists of 35 items out of the original 48 items. This revised checklist seems more feasible to observe items that are concrete and objective than items based on the patients' subjective experiences (Tveter et al., 2014) (Appendix B20).

Outcome Measures

For Secondary Endpoint:

11 Dimensions of Altered State of Consciousness (11D-ASC). The 11D-ASC is a 42-item scale. 11D-ASC consists of eleven dimensions: 1) experience of unity; 2) spiritual experience; 3) blissful state; 4) insightfulness; 5) disembodiment; 6) impaired control & cognition; 7) anxiety; 8) complex imagery; 9) elementary imagery; 10) audio-visual synesthesia; 11) changed meaning. It is well validated and widely used to characterize the subjective effects of psychedelic drugs. This self-rated scale appears as in a visual analogue scale with the upper anchor reading "much more than usual" and the bottom one reading "no more than usual" (Dittrich, 1998) (Studerus et al., 2010) and is scored by measuring the millimeters from the low end of the scale to the subject's mark (integers from 0–100) for each item. Participants will perform the 11D-ASC at the end of each dosing day when the subjective effects of psilocybin have subsided to a negligible level; however, ratings will be done with reference to the period when effects are most intense (Appendix B9).

For Exploratory Endpoint – Depression and Associated Symptoms:

Clinical Global Impression Scale (CGI). The CGI is a well-established research rating tool to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication. The CGI-Severity (CGI-S) asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. This rating is based upon the average severity of observed and reported symptoms, behaviour, and function in the past seven days. The CGI-Improvement (CGI-I) is for the clinician to compare the patient's overall clinical condition to the baseline visit and is rated on a seven-point scale: "Compared to the patient's condition at admission to the project [prior to medication initiation], this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment." (Busner & Targum, 2007) (Appendix B8).

Beck Depression Inventory II (BDI-II). The BDI-II is a brief, self-report measure used to measure the severity of depression and related symptoms. It consists of 21 items, scored on a 4-point Likert scale ranging from 0 ('I do not feel sad') to 3 ('I am extremely sad'). Higher total scores indicate more severe depressive symptoms. It is a well-established tool that is used widely in clinical and research settings (Beck et al., 1996) and shows good psychometric properties in autistic adults (Z. J. Williams et al., 2021) (https://asdmeasures.shinyapps.io/bdi_score/) (Appendix B5).

Snaith Hamilton Anhedonia Pleasure Scale (SHAPS). The SHAPS is a 14-item self-report scale that measures hedonic capacity. Participants are asked to rate themselves on a 4-point Likert scale from 0 ('strongly disagree') to 3 ('strongly agree'). It is both a reliable and valid measure that is frequently used in research and clinical settings (Snaith et al., 1995) (Appendix B19).

Ruminative Responses Scale (RRS)-10. The RRS-10 is a short form of RRS, a self-report rating tool used to describe responses to depressed mood (Treynor et al., 2003). It consists of 10 items and 3 factors (Brooding, Depression, Reflection), with each item being scored on a 4-point Likert scale from 1 ('never') to 4 ('always'), providing total scores ranging from 4 to 40 for ruminative symptoms. The psychometric properties of the RRS have been established in autistic adults (Z. J. Williams & McKenney, 2021) (Appendix B15).

Anxiety Scale for Autism - Adults (ASA-A). The ASA-A is a self-report rating tool used to measure anxiety and related symptoms in autistic adults. It consists of 20 items, and a general anxiety factor alongside 3 group factors (Social Anxiety, Anxious Arousal, and Uncertainty). All items are scored on a 4-point Likert scale from 0 ('never') to 3 ('always), with total scores ranging from 0 to 60. Higher scores indicate higher levels of anxiety (Rodgers et al., 2020) (Appendix B4).

For Exploratory Endpoint – Theoretically Relevant Symptoms and Features:
General Alexithymia Factor Score (GAFS-8). The GAFS-8 is an 8-item scale derived from the Toronto Alexithymia Scale and is a self-report measure used to assess difficulty identifying and describing feelings. Items are scored on a 5-point Likert scale, ranging from 1 ('strongly disagree') to 5 ('strongly agree'). Total scores range from 20 to 100, with higher scores indicating more difficulty interpreting feelings and emotions (Z. J. Williams & Gotham, 2021) (https://asdmeasures.shinyapps.io/TAS8_Score/) (Appendix B10).

Acceptance and Action Questionnaire-II (AAQ-II). AAQ II is a self-rated 7-item instrument to assess experiential avoidance and psychological inflexibility (Bond et al., 2011). Experiential avoidance is an attempt to avoid or neglect unpleasant thoughts, unpleasant feelings, bitter memories, uncomfortable physical sensations, and consequently leads to actions against one's values and causes long-term harm. Psychological inflexibility refers to rigid psychological reaction against one's values to avoid distress, uncomfortable feelings and thoughts and tendency to ignore the present moment. Both experiential avoidance and psychological inflexibility have been suggested as important elements in the etiology and the preservation of depression (Hayes et al., 2006) (Appendix B1).

Autistic Burnout Survey Items (ABSI). ABSI is a 20-item self-rated assessment tool to quantify the experience of autistic burnout, comprising exhaustion, withdrawal, and cognitive overload, driven by stressors amplified in autistic people. The psychometric properties of this measure have been established in autistic adults (Arnold et al., 2023) (Appendix B2).

Connor–Davidson Resilience Scale 10 (CD-RISC 10). The CD-RISC 10 is a 10-item version of the CD-RISC, which is one the most frequently used instruments to measure resilience (Campbell-Sills & Stein, 2007). Resilience describes the ability to 'bounce back' following difficult emotional experiences, and the flexibility to adapt to stressful and demanding situations. Lack of resilience may contribute to the development and maintenance of depression and anxiety in autism. The CD-RISC 10 has been validated as a measure of trait resilience in autistic adults (Hwang et al., 2020) (Appendix B7).

Interoception Sensory Questionnaire-8 (ISQ-8). The original form of the Interoception Sensory Questionnaire (ISQ) was developed to measure autistic adults' perception and interpretation of interoceptive sense (Fiene et al., 2018). Subsequently, a revised 8-item version (ISQ-8) using a condensed 5-point Likert scale was developed with good psychometric properties in autistic adults (https://asdmeasures.shinyapps.io/ISQ_Score/) (Suzman et al., 2021) (Appendix B13).

Quality of Life. We will gather the subjective experience of quality of life (QoL) using a self-rated measure, the WHOQOL-4 (Z. J. Williams & Gotham, 2021). The WHOQOL-4 includes four global QoL items from the content of the World Health Organization Quality of Life–Brief Version (WHOQOL-BREF). Collecting this QoL data could provide a reliable and valid estimate of QoL in autistic people while minimizing their burden given the 4 items in this measures vs. 49 items in the commonly adopted Autism Spectrum Quality of Life (ASQoL) (McConachie et al., 2018) (Appendix B21).

Interpersonal needs questions—15 item (INQ-15). The Interpersonal Needs Questionnaire (INQ-15) is a 15-item self-report questionnaire assessing 'thwarted belongingness' (e.g. 'These days, I often feel like an outsider in social gatherings') and 'perceived burdensomeness' (e.g. 'These days, I think I am a burden on society') (Van Orden et al., 2012). The INQ-15 has been used in previous research with autistic adults and those with high autistic traits (Cassidy et al., 2021) (Appendix B12).

Custom-designed acceptability questionnaire. We design two custom-designed questionnaires inquiring about the acceptability of all components of the main clinical trial and the optional dense sampling of brain MRI data, including recruitment, withdrawal rate, study visit attendance, protocol adherence and the time burden of completing questionnaires (Appendix B22 and B23).

Cognitive Flexibility Inventory (CFI). The CFI is a 20-item self-rated assessment tool to assess the core aspects of cognitive flexibility needed to challenge and replace maladaptive thoughts with more balanced & adaptive thinking. These core aspects include the ability to generate and accept alternative explanations for life occurrences & the agency an individual feels regarding their own life. Items are scored on a 7-point Likert scale with good psychometric properties (Dennis & Vander Wal, 2010). (Appendix B24).

For Exploratory Endpoint – Brain and Cognition

Brain MRI. Participants will receive brain MRI scans conducted on a 3-Tesla MRI system (Siemens Prisma) at Toronto Neuroimaging Facility (ToNI) of University of Toronto, instead of the scanner at CAMH, a MRI GE Discovery 750 scanner. This design is planned because the required fMRI sequence is not available on CAMH's scanner. Specifically, we will collect the functional data using the multi-echo multiband sequence (Cohent et al., 2017), which is not collectable from the MRI scanner of CAMH. Muti-echo multiband fMRI outperforms single-echo multiband fMRI (which is collectable from the MRI scanner of CAMH) in data quality and better denoising (Kovářová et al., 2021; Cohen et al., 2021). At the same time, the multi-echo multiband sequence can still preserve high spatial and temporal resolution. fMRI data quality is grossly impaired by the noises introduced by excessive in-scanner head motion, which is usually more pronounced in autistic and other neurodevelopmental populations. Taken together, the multi-echo multiband sequence available at the TONI should be fitter for the present targeted participants than any available fMRI sequences at the CAMH. Our proposed fMRI acquisition has been rigorously tested and applied safely to autistic populations across the wide age ranges (King et al., 2018; Lin et al., 2022). The acquisition parameters of T1-weighted and diffusion MRI (dMRI) will use Human Connectome Project-like and Adolescent Brain Cognitive Development (ABCD) study-like data acquisition with multiband excitations to reduce scan time, facilitating successful scanning. An additional pulse sequence includes a study-specific implementation of Siemen's ^{1}H-MR spectroscopy (MRS).

These sequences are considered investigational and ToNI has obtained them as a "Work in Progress" (WIP) through a contract with Siemens. To comply with the contract, the consents include language indicating that investigational methods are being used, that there is no additional risk, and that anonymized data may be shared with collaborators. When these sequences become part of the "stock" sequences available on the scanner, we will update the consents. This research project uses investigational MRI research techniques provided by the manufacturer that are not available on clinical MRI scanners. These research scans are performed under strict safety guidelines and do not pose any additional risk to the participant. We will ask each participant for their permission to use these new research MRI methods for this project. MRI data may be shared with Siemens, the manufacturer, for ongoing improvement and quality assurance but participant name and other identifying information will not be included.

For *the main clinical trial:* participants will receive two brain MRI scans, respectively, at V2 and V5. This MRI session for *the main clinical trial* will consist of a T1-weighted image (around 6 mins), fMRI (around 20 mins, divided into two scans), diffusion MRI (around 9 mins), and MRS (around 10 mins), with around 45 mins scanning in total.

For *the optional dense sampling brain MRI data collection:* participants will receive additional eight brain MRI scans consisting of a T1-weighted image (around 6 mins), fMRI (around 14 mins) with around 20 mins scanning in total.

There will be ToNI-specific informed consent forms, ToNI-specific recruitment materials, screening form for MRI scans at ToNI, and ToNI general protocol, as requested by ToNI's policies (https://toni.psych.utoronto.ca/policies/#6). These materials are attached in appendix H (Appendix H1-H4). Participants will read these materials and sign on the ToNI-specific informed consent forms (Appendix H1a and H1b) and screening form (Appendix H2).

Avoid/Escape Go/No-Go task. This Avoid/Escape Go/No-Go task employs a 2 × 2 (Go/No-go x Avoid/Escape) factorial design. On every trial, the agent is presented with one of four cues. Two of the cues are always paired with an aversive sound (Escape condition) while the other two are paired with silence (Avoid condition). The agent's goal is to learn, for each cue, which response (active Go or passive No-go) more frequently results in silence during feedback. For ease of reference, we will refer to the responses that maximize the frequency of silence during the feedback as the "correct" responses throughout the paper. This means that in the Avoid condition, correct responses will prevent the aversive sound from playing, while in the the Escape condition, correct responses will stop the aversive sound that is already being played. The feedback is probabilistic, which means that even "correct" responses will sometimes lead to experiencing the aversive sound. Probabilistic feedback introduces uncertainty and makes it more challenging to learn, which response is correct. We will then use an active inference scheme to model how the proposed perturbations lead to hopelessness, increased Pavlovian control and increased active-escape bias. This task and model have been validated by Co-Investigator Dr. Diaconescu to provide computational hypothesis space for understanding suicidal thoughts and behaviours in neurotypical populations (Karvelis & Diaconescu, 2022).

6.1.2.1 Outline of Study Procedures of Main Clinical Trial

Visit 1 (V1) – Screening Visit

- Administered by trained study staff:
    - Informed consent
    - Review of medical history, family medical history, and demographics
    - ATHF
    - Vital Signs (blood pressure, pulse)
    - Height and weight
    - ADOS-2
    - Nine-item form of RSPM
    - UKU Side Effect Scale
    - Self-rated questionnaires: AQ-12, RBQ-2A, CAT-Q, SBQ-ASC
- Clinician administered:
    - SCID-5-CV
    - GRID-HAMD-17
    - 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 (e.g., fluoxetine) may require a longer tapering period (at least 4 weeks).
- Review of eligibility criteria, medical history, and family medical history
- Review of assessments
- Documentation of contraceptive method to be used by the participant

- Biological specimen collection and laboratory evaluations collected at the Queen Street CAMH laboratory:
  - Clinical laboratory tests:
    - Approximately 20 mL blood will be drawn to conduct the following evaluations:
    - *Haematology:* hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count (with differential), and platelet count.
    - *Chemistry:* albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (direct, indirect, and total), calcium, chloride, creatine kinase, creatinine, gammaGT, glucose, lactate, dehydrogenase, lipase, magnesium, phosphate, potassium, protein-total, sodium, urea (blood urea nitrogen), and uric acid.
  - Urine Samples:
    - *Urinalysis:* a dipstick urinalysis will be performed for blood, glucose, ketone, protein, pH, specific gravity, nitrite, leukocytes, bilirubin, and urobilinogen
    - *Urine drug screen:* for illicit drugs or drugs of abuse. Results of a positive drug screen will be reviewed by the study clinician for pattern of use.
    - *Urine pregnancy test* for all women of childbearing potential
  - ECG: Standard 12-lead ECG to check heart function

Washout Period: Minimum of 2-Weeks

Participants who are on concomitant medications (Section 5.6) must be tapered off at least 2 weeks prior to Baseline (V2). The plan for tapering off medications will be determined at the first screening visit (V1) with the participant and the study physician. 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 SBQ-ASC at each contact/visit.

Any safety assessment visits during the washout period will be called V1a, V1b, etc. During these visits, the SBQ-ASC 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 - Baseline Visit (V2) - Day -15 to Day -8

The Baseline visit (V2) will occur approximately 3-6 weeks after the initial Screening (V2) 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 self-rated questionnaires and clinical assessment (including GRID-HAMD-17 and review of information) can occur in-person or remotely (via telephone/WebEx). When a participant opts to have questionnaires done remotely, they will receive the electronic version of the questionnaires by email or CAMH secure file transfer. The participant could complete the questionnaires electronically or print and fill in the questionnaires, and email (when completed directly electronically or when completed in the paper form then scanned), mail, or fax (when completed in the paper form) the completed questionnaires back to the study team. If participants choose to return the questionnaires by mail, we will provide a pre-paid postage envelope. The following procedures will be performed and recorded at the Baseline visit (V2):

- Administered by trained study staff:
    - Vital Signs (blood pressure, heart rate)
    - Urine drug screening & Pregnancy test
    - CGI
    - Brain MRI (required)
    - Avoid/Escape Go/No-Go task
    - UKU Side Effect Scale
    - Self-rated questionnaires: BDI-II, ASA-A, SHAPS, RRS-10, INQ-15, ISQ-8, GAFS-8, CD-RISC 10, ABSI, AAQ-II, WHOQOLY-4, SBQ-ASC, CFI
- Clinician administered:
    - GRID-HAMD-17
    - Confirmation of eligibility criteria
    - Review of assessments administered
    - Review of medications
- 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 intervention.
    - Note: Therapists will have the option to schedule an additional preparatory session at their discretion.
    - For a more detailed explanation of the preparatory therapy session, please refer to the Yale Manual for Psilocybin-Assisted Therapy of Depression.
    - Prep therapy can occur in-person or via secure videoconferencing software (i.e. WebEx).

Visit 3 (V3) – Safety Dose / Day -7

The intervention will occur the day after Baseline (V2). The participant may have this session ≤7 days following the Baseline visit (V2). If the participant is out of the ≤7 day

window, all baseline assessments are to be repeated. On the day of the intervention the following procedures will take place:

- Study intervention administration (Section 5.0): 1 oral dose of 10 mg of psilocybin administered in conjunction with supportive therapy (PAT).
- Vital signs (blood pressure and pulse) will be taken every 1.5 hours during this session.
- At least one therapist will be present in the room at all times during PAT and be available to respond to participants' physical and emotional needs.
- Participants will be instructed to lie on a bed in a non-clinical environment, and therapists will encourage participants to focus their attention inward and stay with any experience that arises. To enhance inward reflection, a pre-selected music playlist will be played. Administration of questionnaires or other instruments to be completed at the end of the dosing session when the acute effects of psilocybin have resolved:
    - Study team or therapist administered:
        - 11D-ASC to assess the acute drug effects
        - UKU Side Effect Scale
- The participant will be discharged 6-8 hours post-dosing when, in the opinion of the study PI (or delegate), the acute effects of psilocybin are resolved. The participant must be accompanied home by a caregiver who will remain with them for up to 24 hours after the dose was administered.
- Rescue medications are permitted during this visit as outlined in Section 5.6.

Visit 4 (V4) – Treatment Dose / Day 0

This intervention will occur 1 week following the safety dosing session (V3). On the day of the intervention the following procedures will take place:

- Study intervention administration (Section 5.0): 1 oral dose of 25 mg of psilocybin administered in conjunction with supportive therapy (PAT).
- Vital signs (blood pressure and pulse) will be taken every 1.5 hours during this session.
- At least one therapist will be present in the room at all times during PAT and be available to respond to participants' physical and emotional needs
- Participants will be instructed to lie on a bed in a non-clinical environment, and therapists will encourage participants to focus their attention inward and stay with any experience that arises. To enhance inward reflection, a pre-selected music playlist will be played. Administration of questionnaires or other instruments to be completed at the end of the dosing session when the acute effects of psilocybin have resolved:
    - Study team or therapist administered:
        - 11D-ASC to assess the acute drug effects.
        - UKU Side Effect Scale
- The participant will be discharged 6-8 hours post-dosing when, in the opinion of the study PI (or delegate), the acute effects of psilocybin are resolved. The participant must be accompanied home by a caregiver who will remain with them for up to 24 hours after the dose was administered.

- Rescue medications are permitted during this visit as outlined in Section 5.6.

Visit 5 (V5) – Post-Intervention Day 1

- Administered by trained study staff or therapist/clinician:
  - Brain MRI (required)
  - Avoid/Escape Go/No-Go task
  - BDI-II, ABSI, and SBQ-ASC (self-rated questionnaire)
  - UKU Side Effect Scale
- 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 and assessment (except MRI and the cognitive task) 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 therapist's manual (Yale Manual for Psilocybin-Assisted Therapy of Depression).
- The SBQ-ASC and assessment of side effects can occur in-person or remotely (via telephone/WebEx).

Visit 6 (V6) – Post-Intervention Day 7

- Administered by trained study staff or therapist:
  - CGI
  - UKU Side Effect Scale
  - Self-rated questionnaires: BDI-II, ASA-A, SHAPS, RRS-10, INQ-15, ISQ-8, GAFS-8, CD-RISC 10, ABSI, AAQ-II, SBQ-ASC, CFI
- Clinician administered:
  - GRID-HAMD-17
- The self-rated questionnaires and clinical assessment (including GRID-HAMD-17, CGI and side effects) can occur in-person or remotely (via telephone/WebEx). When a participant opts to have questionnaires done remotely, they will receive the electronic version of the questionnaires by email or CAMH secure file transfer. The participant could complete the questionnaires electronically or print and fill in the questionnaires, and email (when completed directly electronically or when completed in the paper form then scanned), mail, or fax (when completed in the paper form) the completed questionnaires back to the study team. If participants choose to return the questionnaires by mail, we will provide a pre-paid postage envelope.
- 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 and assessment 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 therapist's manual (Yale Manual for Psilocybin-Assisted Therapy of Depression).

Visit 7 (V7), Visit 8 (V8) & Visit 9 (V9) – Follow-Up: Week 2, Week 4 & Week 12

Follow-up visits occur at Weeks 2 (V7), 4 (V8), and 12 (V9) after the intervention.

The following assessments will occur at V7:

- Administered by trained study staff:
  - UKU Side Effect Scale
  - Self-rated questionnaires: BDI-II, ABSI and, SBQ-ASC
- Clinician administered:
  - Review of safety assessments

The following assessments will occur at V8 and V9:

- Administered by trained study staff:
  - CGI
  - UKU Side Effect Scale
  - Self-rated questionnaires: BDI-II, ASA-A, SHAPS, RRS-10, INQ-15, ISQ-8, GAFS-8, CD-RISC 10, ABSI, AAQ-II, WHOQOLY-4, SBQ-ASC, CFI
- Clinician administered:
  - GRID-HAMD-17
  - Review of safety assessments

- The self-rated questionnaires and clinical assessments (including GRID-HAMD-17, CGI and side effects) at V7-9 can occur in-person or remotely (via telephone/WebEx). When a participant opts to have questionnaires done remotely, they will receive the electronic version of the questionnaires by email or CAMH secure file transfer. The participant could complete the questionnaires electronically or print and fill in the questionnaires, and email (when completed directly electronically or when completed in the paper form then scanned), mail, or fax (when completed in the paper form) the completed questionnaires back to the study team. If participants choose to return the questionnaires by mail, we will provide a pre-paid postage envelope.

At V9 (or the last study visit if they withdraw from the main clinical trial earlier), participants' acceptability of the main clinical trial protocol using the custom-designed questionnaire will be assessed.

6.1.2.2 Outline of Study Procedures of Optional Dense Sampling Brain MRI Data Collection

In addition to two brain MRI scans at V2 and V5 of *the main clinical trial*, the participants who opts to participate in *the optional dense sampling brain MRI data collection* will also receive brain MRI scans for

- V1 of the main clinical trial (1st scan of the sub-study; 1st scan of the 10 total scans; about 20 minutes)
- In the middle of antidepressant/antipsychotic tapering period (2nd scan of the sub-study; 2nd scan of the 10 total scans; about 20 minutes)
  - Either at the start of the 2nd week for those with 2-week washout
  - Or at the start of the 3rd week for those with 4-week washout

- One day post-V3 of the main clinical trial (3rd scan of the sub-study; 4th scan of the 10 total scans; about 20 minutes)
- V6 of the main clinical trial (4th scan of the sub-study; 6th scan of the 10 total scans; about 20 minutes)
- V7 of the main clinical trial (5th scan of the sub-study; 7th scan of the 10 total scans; about 20 minutes)
- V8 of the main clinical trial (6th scan of the sub-study; 8th scan of the 10 total scans; about 20 minutes)
- Week 8 following V5 of the main clinical trial (7th scan of the sub-study; 9th scan of the 10 total scans; about 20 minutes)
- V9 of the main clinical trial (8th scan of the sub-study; 10th scan of the 10 total scans; about 20 minutes)

At each optional MRI scan visit, the participants will complete the self-rated questionnaires of BDI-II, AAQ-II and ABSI (48 items in total). These measures will be originally collected at V6, V7 and V9 in *the main clinical trial*.

At V9 (or the last study visit if they withdraw from the optional dense sampling earlier), participants' acceptability of the optional dense sampling MRI protocol using the custom-designed questionnaire will be assessed.

6.2 Schedule of Events

6.2.1 Main Clinical Trial

Procedures	Screening Visit (V1)	Tapering Period[1] (2-4 weeks)	Baseline Visit 2(V2, Day -15 to Day -8)	**Safety Dose (V3, Day -7)**	**Treatment Dose (V4, Day 0)**	Study Visit 5 (V5, Day 1)	Study Visit 6 (V6, Week 1)	Study Visit 7 (V7, Week 2)	Study Visit 8 (V8, Week 4)	Study Visit 9 (V9, Week 12)
Location of Visit	Clinic	Remote or Clinic	Clinic	Clinic	Clinic	Clinic	Remote or Clinic	Remote or Clinic	Remote or Clinic	Remote or Clinic
Allowable Window		Weekly		Within 7 days following V2	Within 7-10 days following V3	None	±3 days	±3 days	±3 days	±3 days
Informed consent	X									
Demographics	X									
Medical history	X		X							
Prior/Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria Review	X	X	X							
Vital signs[3]	X		X	X	X					
Height	X									
Weight	X									
Clinical laboratory tests[4]	X									
EKG/ECG	X									
Urinalysis	X									
Urine drug screening	X		X							
Urine Pregnancy test [5]	X		X							
Documentation of birth control	X									
Preparatory/ Integrative therapy & psychoeducation[6]			X	X	X	X	X			

Safety dose (10mg of psilocybin)				X						
Treatment dose (25mg of psilocybin)					X					
Adverse event and serious adverse event review plus UKU Side Effect Scale	X	X	X	X	X	X	X	X	X	X
CRF Completion	X	X	X	X	X	X	X	X	X	X
11D-ASC[6]				X	X					
AAQ-II			X				X		X	X
ABSI			X			X	X	X	X	X
ADOS-2	X									
AQ-12	X									
ASA-A			X				X		X	X
ATHF	X									
BDI-II			X			X	X	X	X	X
CAT-Q	X									
CD-RISC 10			X				X		X	X
CFI			X				X		X	X
CGI			X				X		X	X
GAFS-8			X				X		X	X
GRID-HAMD-17	X		X				X		X	X
INQ-15			X				X		X	X
ISQ-8			X				X		X	X
RBQ-2A	X									
RRS-10			X				X		X	X
RSPM	X									
SBQ-ASC	X	X	X			X	X	X	X	X
SCID-5-CV	X									
SHAPS			X				X		X	X
WHOQOL-4			X						X	X

Acceptability										X
Avoid/Escape Go/No-Go task			X			X				
Brain MRI[7]			X			X				

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 (within 7 days from safety dose) 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/females and people of child-bearing age only.
5. Additional therapy visits may be scheduled at the discretion of the study therapists and/or the study investigator and therapy can occur in-person or via WebEx.
6. To be administered immediately after the acute effects of psilocybin have subsided.
7. Required for the main clinical trial design, around 45 mins

Instruments:
ADOS-2: Autism Diagnostic Observation Schedule; ASA-A: Anxiety Scale for Adults – Autism; ASQoL; Autism Spectrum Quality of Life Form; ATHF: Antidepressant Treatment History Form; BDI-II: Beck Depression Inventory, 2nd edition CGI: Clinical Global Impression; EKG/ECG: Electrocardiogram; GAFS-8: General Alexithymia Factor Score; GRID-HAMD: GRID-Hamilton Depression Rating Scale; MRI: Magnetic Resonance Imaging; RRS: Ruminative Response Scale; SBQ-ASC: Suicidal Behaviors Questionnaire – Autism Spectrum Conditions; SCID-5: Structured Clinical Interview for DSM-5; SHAPS: Snaith Hamilton Pleasure Scale; SRS: Social Responsiveness Scale

6.2.2 Optional Dense Sampling Brain MRI Data Collection

Procedures	Screening Visit (V1)	Tapering Period[1] (2-4 weeks)	Baseline Visit 2(V2, Day -15 to Day -8)	**Additional Visit** (1day post-V3, Day -6)[2]	Treatment Dose (V4, Day 0)	Study Visit 5 (V5, Day 1)	Study Visit 6 (V6, Week 1)	Study Visit 7 (V7, Week 2)	Study Visit 8 (V8, Week 4)	**Additional Visit (Week 8)[2]**	Study Visit 9 (V9, Week 12)
Location of Visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Allowable Window	Within 7 days following Screening Visit	Starting immediately following MRI of V1		Within 1 days following Safety Dose	Within 7-10 days following V3	None	±3 days	±3 days	±3 days	±3 days	±3 days
CRF Completion	X	X	X	X	X	X	X	X	X	X	X
Brain MRI	X[3]	X[3]	X[4]	X[3]		X[4]	X[3]	X[3]	X[3]	X[3]	X[3]
AAQ-II	X	X	X	X		X	X	X	X	X	X
ABSI	X	X	X	X		X	X	X	X	X	X
BDI-II	X	X	X	X		X	X	X	X	X	X
Acceptability											X

Adverse event and serious adverse event review plus the UKU Side Effect Scale	X	X	X	X	X	X	X	X	X	X	X

1. In the middle of either 2-week or 4-week washout period.
2. The additional visit for the optional dense sampling brain MRI data collection.
3. The additional brain MRI scans for the optional dense sampling brain MRI data collection.
4. The original brain MRI scans for the main clinical trial design.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

The proposed sample size of *the main clinical trial* is determined based on the recommendations for pilot trials (Whitehead et al., 2016) and is also a sample size adopted by earlier pilot trials on psilocybin (Carhart-Harris et al., 2016). For the main trial designed with 90% power and two-sided 5% significance, our sample size can detect an effect size (ES) of 0.76 (Cohen's d). We will be able to obtain reasonably reliable estimates on feasibility measures including recruitment (margin of error 15.5%) and retention rate (margin of error 13.1%) and tolerability (margin of error 10.1%). An fMRI study in healthy volunteers reports a very large psilocybin effect size in changes of functional connectivity at Week 1 (ES 1.73) (McCulloch et al., 2022). A meta-analysis of published psilocybin trials reports a large antidepressant effect size in neurotypical populations (ES 0.8) (Galvão-Coelho et al., 2021). Altogether, the proposed sample size of *the main clinical trial* appears to have sufficient power to detect the expected effects.

The proposed sample size of *the optional dense sampling brain MRI data collection* is determined based on a pilot study with the similar dense sampling neuroimaging approach happening at the CAMH (titled "Deriving Everyday Effects of Psychosis - Pilot (DEEP-Pi)"). The Midnight Scan Club dataset, representing the first multi-person deep phenotyping study in healthy individuals, also included a sample of 10 individuals, suggesting that for repeated scanning approaches a sample size of 10 is adequate (Gratton et al., 2018). Nonetheless, we acknowledge this rationale of the sample size decision is arbitrary and recognize this optional dense sampling approach is preliminary and novel.

7.2 Statistical Methods

For Primary Aim (safety/feasibility) of *the main clinical trial*, all participants entering the psilocybin sessions (V3/3) will be included in the analysis of the safety profile and tolerability. Participants completing the two time points of pre- and post-treatment MRI and cognitive tests will be included in the analysis for the neuroscience objective. Participants who at least complete the follow-up at Week 1 (V6) will be included in the final analysis for the exploratory aim of clinical effects, regardless of whether they complete the full protocol. This approach is consistent with the intention-to-treat principle. A paired t-test will be used to investigate the pre- to post-treatment brain/cognitive metrics and symptom changes of *the main clinical trial*. Exploratory analyses will be performed to determine predictors of response including baseline individual features, using logistic regression. Safety profiles will be described by the percentage of each adverse effect.

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 study visit (V1) through the final study visit (V9) will be collected. AEs recorded during this period will be followed through to resolution, or until the event is assessed as chronic or stable.

Preexisting Condition

A preexisting condition is one that is present at the start of the clinical trial. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At the Screening Visit (V1), any clinically

significant abnormality will be recorded as a preexisting condition in the participant's CRF. Where applicable and at the consent of the participant, additional information from the participant's healthcare provider including medical records, may be requested. Throughout the clinical trial, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event

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

Abnormal Laboratory Values

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

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

8.2 Recording of Adverse Events

All adverse events occurring during the study period will be recorded. At each contact with the research participant, the research team will seek information on adverse events by specific questioning. Information on all adverse events will be recorded immediately in the participant's CRF and/or legal health record, and recorded in the adverse event log. All adverse events will be assessed by the PI for relatedness, expectedness, seriousness, and severity in relation to the study intervention. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the CRF and/or legal health record and assessed by the PI in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs (severe unexpected adverse drug reactions) if needed. Adverse events related to the study drug will be reported to Filament Health within 24 hours of the study team becoming aware of the event. These reports should not contain PHI.

8.3 Reporting of Serious Adverse Events

8.3.1 Investigator Reporting: Notifying the Sponsor

There is no sponsor for this study, however Filament Health is the supplier of the psilocybin used in this trial. Filament Health 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 SBQ-ASC to assess and reduce suicide risk. Participants experiencing a serious adverse event will be immediately withdrawn from the study. In the case of increased suicidality, the study physician will conduct an urgent psychiatric assessment with the participant.

The study investigator and study team will meet regularly to review the accrued data, data confidentiality, recruitment, and participants complaints. Participant confidentiality will be maintained through the use of code numbers to identify all participants. All research records will be kept in a locked file and no participants will be identified in any published report.

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

Remote Assessment Safety Procedures

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

8.6 Unblinding Procedures

Not applicable.

8.7 Data and Safety Monitoring Board

According to TCPS 2 (2022) Chapter 11, this study will not have an independent Data and Safety Monitoring Board for the following reasons. First, this study is an open-label and single-site study and does not involve blinded data collection. Second, the possible adverse outcomes of this study are mild to moderate (temporary, non-life-threatening conditions). Third, as noted in Section 4.7.1 and 8.5, this study has clear stopping rules

to ensure the study team can recognize when incidents of harm to participants require a reconsideration of the study design.

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

Please reference this study's Data Management Plan (DMP; Appendix D).

REDCap

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

10.2 Protocol Deviations

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

- Deviations that, in the opinion of the PI, jeopardize the safety of research participants, or that jeopardize the research efficacy or data integrity
- Any change in the approved process for obtaining consent
- Any deviations that lead to a serious adverse event or unanticipated problem

- Any unauthorized collection, use, or disclosure of personal health information (PHI)

10.3 Record Retention

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

10.4 Clinical Trial Registration

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

11.0 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Study Monitoring Plan

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

11.2 Auditing and Inspecting

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

12.0 ETHICAL CONSIDERATIONS

12.1 Research Ethics Board (REB) Approval

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

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

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

12.2 Informed Consent Process & Documentation

12.2.1 Informed Consent

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 ICFs (Appendix A1 and A2) 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 ICFs. Each participant will be provided with a complete (fully signed) copy of the ICFs. The original ICFs and the informed consent process will be documented in the source documents.

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

13.0 PRIVACY AND CONFIDENTIALITY

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

All research activities will be conducted in as private a setting as possible. The study team (including the PI), the study monitor, representatives of the REB, and Health Canada may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records and pharmacy records for the participants in this clinical trial. The participant's contact information will be securely stored at CAMH for internal use during the clinical trial. At the end of the clinical trial, all records will continue to be kept in a secure location in accordance to applicable institutional and regulatory requirements. Safety reports on AEs and SAEs will be reported to Filament Health within 24hrs of the event occurring. In addition, safety data generated from the trial regarding the use of psilocybin and a report on the safety and efficacy of the clinical trial data will be provided to Filament Health. None of these safety reports will contain PHI and all data will be coded.

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Breach of confidentiality will be minimized by the research staff who will maintain research data (identified only by participant code number not related to name, or date of birth). A list of participant names, their ID numbers, and information about how they can be reached will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. To minimize the risk of breach of confidentiality formal training sessions for all research staff emphasizing the importance of confidentiality will be conducted and formal mechanisms limiting access to information that can link data to individual participants will be monitored and established by study personnel. All information obtained from participants will be kept as confidential as possible. Computer-based files/data will be entered into password-secured databases (details below) and paper-based files will be stored in a secure location. These data will only be accessible to personnel involved in the study and they will abide by confidentiality regulations of the REB.

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

Data from this study will be entered into a secure REDCap database. At point-of-entry, data values will undergo consistency edits (e.g., ID validation, range verification, duplicate detection) and personnel will be required to correct errors. Reports will be created via the REDCap program. Data management staff will run logic error programs to check for accuracy and irregularities within and across data structures and within and across sites. Quality assurance checks will be conducted regularly by study personnel. Although

unlikely, instances may occur where REDCap is not available. In the case that this happens, we will follow the CAMH REDCap Downtime Procedures.

14.0 CLINICAL TRIAL FINANCES

14.1 Funding Source

This study is funded through the Labatt Family Innovation Fund in Brain Health from the University of Toronto, Department of Psychiatry.

14.2 Conflict of Interest

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

15.0 PUBLICATION POLICY/DATA SHARING

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

At least three peer-reviewed academic papers (2 on brain imaging and 1 on clinical findings) will be published. The team will also present these findings at national and international conferences. In addition to such conventional knowledge plans, the team will leverage the patient and family engagement resources and the participatory framework within the Azrieli Adult Neurodevelopmental Centre, CAMH, to translate lessons learned from this study and explore how to use the information gleaned to build capacity to carry out these types of studies in an inclusive manner. The key results will also be disseminated to the patients/families from across Canada who are linked to the Azrieli Centre, through websites, newsletters provided to relevant stakeholders, and presentations at community meetings.

15.1 Future Secondary Use of Data

After the study team publishes the main papers of this clinical trial and sub-study (7 articles, including 2 clinical, 1 cognition, 4 brain MRI), de-identified data from this project may be shared and used for future research by internal and/or external project collaborators. De-identified and anonymized data from this clinical trial may be deposited to CAMH's BrainHealth Databank Research Resource (BHDB-RR) for future use by other investigators including those outside the clinical trial. Participant consent to use data collected from this clinical trial for future research will be in accordance with BHDB-RR policies and procedures.

Our research will be conducted using an open-science framework. As such, data may be shared with other investigators or placed anonymized in public repositories. Potentially shared data could include anonymized neuroimaging data, basic demographics (sex and gender, age at the time of scan [though not scan date], diagnosis) as well as behavioral measures and cognitive data collected as part of the main clinical trial and the optional dense sampling brain MRI data. No potentially identifying information will be shared, and T1-weighted anatomical scans will undergo a defacing procedure prior to sharing outside CAMH. Data may be shared with other Canadian or international researchers, and/or placed on public repositories such as openneuro.org. Participants will be informed that data sharing is a part of the study, but if they should withdraw from the study will be offered to have their data remain unshared. If a participant later contacts study investigators to withdraw consent for sharing, all possible steps will be taken to remove data from any platforms or collaborations.

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