Protocol MICRODEP-01

A Double-Blind Randomised Controlled Trial of Microdosing with Psilocybin to treat Moderate Depression

Version 3.4, 19-Jul-2024

PRIVILEGED AND CONFIDENTIAL

Not for distribution beyond intended function

Contents

1. Administrative information

1.1 Trial/Study Registration

This study will be conducted in Australia only. The Therapeutic Goods Administration will be notified of the study via the Clinical Trial Notification (CTN) scheme, and the study will receive human research ethics committee approval before starting. The study will be registered on the following clinical trial registers:

Australian New Zealand Clinical Trials Registry

1.2 Funding

This study will be funded by:

Woke Pharmaceuticals

Suite 301, 10 Bridge St, Sydney 2000

Contact name: Matt Hayne

Position: CEO

Phone: 0417 234 397 Email: matt@wokeph.com

In addition to funding, Woke Pharmaceuticals will provide the study drug but will have no role in the execution of the study, analyses, interpretation, presentation or publication of the data, and may not request undue delays in submission of results.

1.3 Roles and Responsibilities

1.3.1 Study Oversight

The proposed study is an Investigator Initiated Trial sponsored by Macquarie University (Sponsor). The study sponsor will be responsible for convening the Steering Committee, which will be responsible for study design; management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The Steering Committee will have ultimate authority over these activities. The project funders will not have any role in these activities.

The study sponsor will be responsible for developing and maintaining charters for the Steering Committee and the Data Safety Monitoring Board.

The study sponsor will also be responsible for unambiguous allocation of trial-related duties and responsibilities to trial-related staff using a delegation log; and will ensure appropriate training in the protocol and other specific trial related duties is provided, documented and updated throughout the lifetime of the trial.

1.3.2 Study Sponsor

Name	Macquarie University		
Street Address	Balaclava Road North Ryde NSW 2109 Australia	**Postal Address**	Clinical Trials Unit Level 3, 75 Talavera Road Macquarie University NSW 2109 Australia
Contact:	+61 2 9812 3500	**Website:**	www.mq.edu.au

1.3.3 Lead Investigators

The Chief Principal Investigator (CI Polito) will have overall responsibility for the coordination and administration of the study. PI Brett is a clinical pharmacologist and toxicologist, and will have medical responsibility for the project.

Please refer to Appendix 1 for a full list of investigators.

Chief Principal Investigator
Dr Vince Polito
Macquarie University
vince.polito@mq.edu.au

Principal Investigator (Medical)
Dr Jonathan Brett
St Vincents Hospital, Sydney / Macquarie University
jonathan.brett@svha.org.au

Principal Investigator
Dr Adam Bayes
The Black Dog Institute, UNSW
a.bayes@unsw.edu.au

Principal Investigator
Dr Paul Liknaitzky
Monash University
paul.liknaitzky@monash.edu

Principal Investigator

Professor Richard Stevenson

Macquarie University

dick.stevenson@mq.edu.au

Principal Investigator

Professor Anthony Rodgers

The George Institute

arodgers@georgeinstitute.org

Principal Investigator (Psychiatrist)

Dr Joanne Shannon

Macquarie University

joanne.shannon@mq.edu.au

1.3.4 Declaration of Interests

The study is funded by Woke Pharmaceuticals. The PIs are not employed by Woke Pharmaceuticals and will not receive financial benefit from Woke Pharmaceuticals other than for the purposes of conducting this Study.

1.3.5 Committees

1.3.5.1 Study Steering Committee

This study will be overseen by a steering committee, which will be the principal decision-making body for the trials. The steering committee will follow the steering committee charter. See Appendix 1 for a full outline of study collaborators and their roles and responsibilities.

1.3.5.2 Data Safety Monitoring Board

The Study will have a Data Safety Monitoring Board (DSMB) to ensure the safety of trial participants and enhance the integrity of the trial. The DSMB will follow the DSMB charter. See Appendix 1 for a full outline of study collaborators and their roles and responsibilities.

2. Key Abbreviations

Abbreviations	Full Name & Definition
11D-ASC	11 Dimension Altered States of Consciousness Scale
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI	Associate Investigator
AIM	Acceptability of Intervention Measure
AMT	Autobiographical Memory Test
ANZCTR	Australian New Zealand Clinical Trials Registry
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUDIT-C	Alcohol Use Disorder Identification Test (short)
AUT	Alternative Uses Test
BDNF	Brain Derived Neurotrophic Factor
BEAQ	Brief Experiential Avoidance Questionnaire
BFI-2-S	Short Form Big Five Inventory
CFS	Cognitive Flexibility Scale
CMS	Conspiracy Mentality Scale
CPI / CI	Chief Principal Investigator
CRT	Cognitive Reflection Test
C-SSRS	Columbia Suicide Severity Rating Scale
CTSQ	Comprehensive Thinking Style Questionnaire
DASS-21	Short Depression Anxiety Stress Scale
DEQ	Drug Effects Questionnaire
DSMB	Data Safety Monitoring Board
DSST	Digit Symbol Substitution Test
DUDIT-C	Drug Use Disorder Identification Test (short)
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D	EuroQol 5 Dimensions Health Questionnaire

Abbreviations	Full Name & Definition
ERP	Event Related Potential
FIM	Feasibility of Intervention Measure
FSS	Flow State Scale
GDNF	Glial Cell Derived Neurotrophic Factor
GRID-HAMD	Standardised Hamilton Depression Rating Scale
HREC	Human Research Ethics Committee
HU	Change in Healthcare Utilisation
IAM	Intervention Appropriateness Measure
IMP	Investigational Medicinal Product
LC/MS	Liquid Chromatography/Mass Spectrometry
LSD	Lysergic acid diethylamide
LTP	Long-Term Potentiation
LWP	Lost Workplace Productivity
MDD	Major Depressive Disorder
MEG	Magnetoencephalography
MINI	The Mini-International Neuropsychiatric Interview
MODTAS	Modified Tellegen Absorption Scale
MWQ	Mind-Wandering Questionnaire
NAD	Nicotinamide adenine dinucleotide
NAT	Novelty Attention Task
NHMRC	National Health and Medical Research Council
NR-6	Short Form Nature Relatedness Scale
OLE	Open Label Extension
PCS	Phenomenological Control Scale
PI	Principal Investigator

Abbreviations	Full Name & Definition
PICF	Participant Information and Consent Form
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SART	Sustained Attention to Response Test
SAS	Social Assurance Scale
SCS	Social Connectedness Scale
SDS	Sheehan Disability Scale
SETS	Stanford Expectations of Treatment Scale
SMPI	Sydney Melancholia Personal Index
SMS	State Mindfulness Scale
SoA	Schedule of Assessments
TMT	Trail Making Test
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WSAS	Work and Social Adjustment Scale

3. Study Synopsis

Title	A Double-Blind Randomised Controlled Trial of Microdosing with Psilocybin to treat Moderate Depression
Short Title	MicroDep
Protocol Number	MICRODEP-01
Trial Phase	2
Study Design	MicroDep is an investigator-initiated, randomised control trial of low doses of psilocybin as a treatment for moderate depression.
Patient Population	The study will assess participants with major depressive disorder of moderate severity
Number of Participants (Planned)	A total of 266 participants will be enrolled into this study. Vanguard cohort: 25 participants Main cohort: 241 participants
Study Duration	4 years
Study Objectives	Primary Objective: To test whether low doses of psilocybin, administered over a 6 week period, is superior to active placebo in improving clinical outcomes in moderate depression [**efficacy**] Secondary Objectives: To assess whether: 1. the intervention is safe in terms of AEs and SAEs [**safety**] 2. the intervention is tolerable in terms of functional impairment, dose acceptability and retention rates [**tolerability**] 3. general disability improves following treatment [**disability**] 4. quality of life improves following treatment [**quality of life**] 5. comorbid psychopathology (including anxiety, alcohol misuse, drug misuse, tobacco misuse and suicidality) are improved following treatment [**comorbidity**] 6. the treatment is appraised by participants as acceptable, appropriate and feasible [**acceptability, appropriateness and feasibility**] To identify: 7. baseline trait and state characteristics that predict microdosing efficacy, safety and tolerability [**predictors**]

	8. any acute or chronic changes in blood biomarkers that occur during and following treatment [**biomarkers**] 9. any acute changes in neurophysiology that occur during treatment [**neuroimaging**] 10. the impact of microdosing on a range of exploratory cognitive, emotional, social, belief and behavioural measures [**exploratory**]
Inclusion Criteria	Participants may be included in the study if they meet all of the following inclusion criteria. 1. Age ≥ 18 years at the time of screening 2. Self-reported fluency in English 3. Meets the definition of moderate depression, defined as a score of between 15 and 23 on the Hamilton Rating Scale for Depression 4. Diagnosis of major depressive disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI) 5. Able to swallow WP001 or Caffeine capsules 6. Has a body weight between 50kg and 120kg, and BMI above 16. 7. Refrains from the use of any psychoactive medication not approved by the research team from baseline through Study Termination. 8. Agrees to abstain from herbal, complementary or over the counter medications with serotonergic effects including, but not limited to, St John's Wort, S-adenosyl methionine (SAM-e), 5-hydroxytryptophan (5-HTP) and L-tryptophan. 9. Agrees to comply with contraception requirements: a. Women of childbearing potential must have a negative urine or serum pregnancy test at screening and baseline and be non-lactating. During the study, women of childbearing potential must agree to use a highly effective method of birth control up to 7 days after the last dose. b. Male participants must agree to use highly effective method of birth control during the participation in the study up to 7 days after the last dose.

	10. Able and willing to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations and other study procedures 11. Agrees to study investigators communicating directly with all of their External Health Practitioners. 12. Provides a contact (relative, spouse, close friend or other Support Person) who is willing and able to be reached by the investigators in the event of a participant becoming unreachable. 13. Must agree not to operate heavy machinery, any motorised vehicle or perform tasks that might endanger oneself or others, such as those requiring fine motor control, fast response times or real-time planning for three hours following each dosing session.
Exclusion Criteria	Participants will be excluded from the study if they meet any of the following exclusion criteria: 1. Recently started new psychological therapies and/or sessions with health professionals within 30 days of consent (such as counsellor, psychotherapists). Participants with a stable regimen may be included in this study if they agree to continue with the psychological therapies and/or counselling sessions as is (frequency of the therapy and/or sessions should not change) 2. Use of antidepressant or antipsychotic medication in the prior 3 months, or plans to start new antidepressant or antipsychotic medication in the upcoming 2 months 3. Current diagnosis of psychotic disorder, bipolar disorder, personality disorder, post-traumatic stress disorder, or substance use disorders. 4. Identification of a *primary* mental health diagnosis apart from Major Depressive Disorder on the Mini International Neuropsychiatric Interview. 5. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to Columbia Suicide Severity Rating Scale (C-SSRS), and clinical judgment of the investigator will be excluded. Any participant who is likely to require hospitalisation related to suicidal ideation and behaviour, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the screening C-SSRS will be excluded:

	1. Suicidal ideation score of 4 or greater within the last month of the assessment at any frequency. 2. Suicidal ideation score of 4 or greater within the last 12 months of the assessment at a frequency of once a month or more. 3. Any suicidal preparatory acts or preparatory behaviour, within the last 12 months of the assessment. Participants with non-suicidal self-injurious behaviour may be included if approved by the CI. 4. Any suicidal behaviour, including actual, aborted, or interrupted suicide attempts within lifetime. 5. Would present a serious risk to others as established through clinical interview and contact with External Health Practitioners. 6. Require ongoing concomitant therapy with a psychiatric medication for management. 6. Poorly controlled hypertension or other cardiac abnormalities. 7. History of psychosis, bipolar disorder, stroke, epilepsy, brain injury or head trauma. 8. History of serious liver (Child-Pugh B or C), kidney disease (eGFR<60ml/min). 9. First degree relative with psychotic disorder. 10. Pregnant, or trying to get pregnant, or breastfeeding 11. Use of any psychotropic drug (excluding alcohol, nicotine and caffeine) within the last 3 months from date of consent 12. Moderate to severe cannabis or alcohol use disorder in the prior 12 months 13. An illicit or prescription drug use disorder of any severity in the prior 12 months 14. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results 15. Significantly abnormal laboratory blood test defined as outside the normal range and deemed clinically significant by an investigator with expertise in this field 16. Resting blood pressure exceeding 160mmHg systolic and 100mmHg diastolic

	17. Currently taking part in another clinical trial involving interventions such as an investigational drug, device, or psychotherapy 18. Current evidence of, or a history of, any condition, therapy or abnormal laboratory assessment or other events that, in the opinion of the investigator, may affect safety, and/or disrupt their participation for the duration of the study
Name of Investigational Product (s)	WP001 (psilocybin 2 or 4mg) Matching Active Placebo (caffeine 30 or 60mg)
Study Intervention(s) and Methodology	The study will consist of three stages and one sub-study: Study Stages: 1) Vanguard Stage 2) Main Stage 3) Open Label Extension Stage Sub-study: 4) Neuroimaging The Vanguard Stage will test the safety and feasibility of the trial design in a sample of 25 participants. The Main Stage will test efficacy of the intervention in a sample of 241 participants. Both the Vanguard and Main Stages will consist of bi-weekly interventions over a 6 week period. Participants will receive either WP001 or active placebo (caffeine). During the Vanguard and Main Stages, up to 80 participants will be offered the opportunity to participate in the neuro-imaging sub-study. Upon completion of treatment, participants will complete follow up visits at 1 week and 1 month after the final dosing session. Participants will also complete long-term online follow up visits at 3 and 6 months after the final dosing session. Those participants randomised to the Placebo arm in the Vanguard and Main Stages will be offered the opportunity to enter the Open Label Extension Stage after the main cohort has been analysed for safety and efficacy.
Safety Evaluation	This study will have a Data Safety Monitoring Board (DSMB). The DSMB will meet regularly as per the DSMB charter to discuss AEs, AESI's and SAEs.

Statistical Considerations	A modified intention-to-treat (mITT) approach will be used for efficacy analysis. The mITT population is defined as all randomised participants who have received at least one dose of the study drug (active or active placebo). Participants who are randomised but do not receive any study drug will be excluded from analyses. A sample size of 266 will provide 90% power at p=0.05 to detect an effect size of .4.
Data Management	All data will be entered into a secure web-based database, Research Electronic Data Capture (REDCap). Data will be monitored according to the constitution of the DSMB.

4. Study Overview, Design and Intervention

4.1 Background and Rationale

4.1.1 Depression

Major depression is a debilitating psychiatric syndrome comprising pervasive low mood and/or loss of interest (anhedonia) with associated symptoms such as changes in appetite, sleep, psychomotor activity as well as suicidality. It affects 14% of Australians with an estimated annual national cost of $A12.6 billion (Manicavasagar, 2012). It has comorbidity with a variety of other disorders, including anxiety and substance use disorders (Melartin et al., 2002), and is present in roughly 50% of individuals who die by suicide (Bachmann, 2018). Moreover, its incidence continues to rise (Klerman, 1989; Hidaka, 2012; Australian Bureau of Statistics, 2019).

Recent meta-analyses have shown that over 50% of patients on standard pharmacotherapies do not experience marked relief, and many individuals experience unwanted side effects (Cuijpers et al., 2016; Jakobsen et al., 2020). Side effects are a primary reason for discontinuation of treatment and commonly include weight gain, loss of or increase in appetite, sexual dysfunction, insomnia, nausea and drowsiness. Side effects can have severe psychosocial consequences even if they are mild enough to encourage treatment maintenance (e.g., sexual dysfunction can have considerable impact on interpersonal relationships). In instances where side effects are moderate but not severe, adjunctive pharmacotherapeutics may be prescribed to moderate them (e.g., additional medications may be prescribed to address sleep problems). These kinds of prescribing cascades can potentially increase the burden of mild side effects in the patient, impose greater financial strain, and lead to increased risks associated with polypharmacy. Serious side effects can be debilitating and, in some cases, lethal. Moreover, standard antidepressants are toxic in overdose and the safety of their use during pregnancy is unclear in most cases.

4.1.2 Psilocybin – Pharmacology

Emerging evidence is convincingly establishing that psilocybin can be an effective and long lasting treatment for depression (e.g., Davis et al., 2021). In the United States, the potential of this novel treatment has been recognised by the Food and Drug Administraion (FDA), who have granted psilocybin based treatments for depression ‘Breakthrough Status’. This designation, which is reserved for new treatments with preliminary clinical evidence that strongly indicates substantial improvement over existing therapies, results in an expedited drug development process. Psilocybin

may provide a novel treatment option for depression, without some of the side effects associated with current antidepressant medications.

Psilocybin is an indole alkaloid that occurs as a natural prodrug in a variety of psychedelic fungi commonly referred to as “magic mushrooms”. Upon ingestion, it is rapidly dephosphorylated in the stomach, intestine and kidneys to psilocin, which is responsible for the majority of its psychoactive effects (Dinis-Oliveira, 2017). Psilocin is a tryptamine with remarkable structural similarity to the neurotransmitter serotonin. Psilocin crosses the blood-brain barrier where it acts as a partial agonist at several serotonin receptors in the brain, primarily 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1A}. This pharmacological profile establishes it as a classical psychedelic, characterised by compromised modular, but increased global, neural activity. High doses of psilocybin cause subjective alterations in consciousness which may be characterised by changes in sensation, perception and cognition including feelings of ego-dissolution, increased openness, perspective shifting, heightened empathy, euphoria, awe, and time distortion. It has a short half-life of 2-3 hours, with peak concentration and effects occurring at between 45 and 90 minutes (Brown et al., 2017; Madsen et al. 2019). This is followed by a 60 minute plateau, before undergoing hepatic metabolism and renal excretion. Within seven hours, effects have mostly subsided. Despite the short duration of acute drug effects, use of psilocybin can lead to psychological changes that persist for as long as a year (Griffiths et al., 2006). In particular, peak experiences associated with doses in the range of 25-30mg psilocybin have been shown to lead to positive clinical outcomes for sufferers of depression such as improved mood and quality of life and reduced hopelessness, anxiety and suicidal ideation (Edmondson et al., 2008; Griffiths et al., 2016; McClain et al., 2003; Visser et al., 2010). Psilocin has particular affinity for 5-HT_{2A} receptors: pre-administration of the 5-HT_{2A} antagonist ketanserin abolishes almost all induced psychedelic effects. This is particularly relevant to depression research, as patients with depression display increased 5-HT_{2A} density in the prefrontal cortex and pharmacotherapeutic down-regulation of these receptors coincides with onset of clinical efficacy (Van Oekelen et al., 2003). Increased density is also associated with anxiety and difficulty coping with stress (Frokjaer et al., 2008). These mechanisms are broadly implicated in the expression of neurotrophic factor and neurogenesis (Aghajanian, 2009), which appear to be involved in the rapidity of psilocybin’s antidepressant effect. Accordingly, researchers have increasingly advocated for the efficacy of psilocybin in treating mood disorders.

4.1.3 Psilocybin – Therapeutic Value and Risk

Since the re-emergence of psychedelic research in psychiatry, a number of trials have produced evidence for the clinical efficacy of psilocybin, taken at higher doses (e.g., 25mg) as an antidepressant and anxiolytic, with rapid, large and sustained effects (e.g., Carhart-Harris et al., 2021; Carhart-Harris et al., 2016; Davis et al., 2021; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Antidepressant effects have been found in a variety of populations including major depression, end of life, treatment-resistant depression, cancer suffering, generalised anxiety and alcohol use disorder populations (Carhart-Harris et al., 2016; Ross et al., 2021; Ross et al., 2022; Bogenschutz et al., 2015; Goldberg et al., 2020). Results are dramatic, rapid and often also have positive effects on comorbid conditions. Moreover, participants in psychedelic trials report wellbeing improvements in a variety of life domains, suggesting a general augmentation of quality of life, which seems to be tied to cognitive restructuring and personal insight (Griffiths et al., 2006; Carhart-Harris et al., 2014). These quality-of-life improvements may partially explain the resilience and chronicity of the antidepressant effect.

Psilocybin, like most psychedelics, is notable for its low toxicity and excellent safety profile (Gable, 2004). When compared to other recreational drugs, psilocybin containing mushrooms consistently rank as the least, or among the least, harmful to the user and society (Nutt et al., 2007; van Amsterdam, 2010; Bonomo et al., 2019): Bonomo and colleagues found only kava, a kavalactone containing plant, and electronic nicotine delivery systems to be less harmful, and it is arguable that this is premature given the lack of research investigating the long-term effects of inhaling vaporised nicotinic chemicals. A lethal dose of psilocybin is estimated at 6g, indicating a therapeutic index of 1000:1 (Gable, 2004). By comparison, the index for alcohol is 10:1. Psilocybin does not interfere with the mesolimbic pathway to encourage dependency or abuse, and occurs in low enough concentrations naturally that a 60kg individual would have to eat 1.7kg of dried mushrooms or 17kg fresh, to experience fatal consequences (Dinis-Oliveira, 2017). Indeed, there are only two recorded cases of fatal psilocybin overdose (van Amsterdam et al., 2011) and any of the minimal physiological risks associated with its use, primarily cardiovascular effects, can approach negligible with appropriate screening (Ross et al., 2021). Moreover, psilocybin is not associated with any major organ system damage, carcinogenicity, teratogenicity, neuropsychological deficits or neurological damage (Johnson et al., 2008). Physical side effects, such as headaches, nausea, tremors and abdominal pain, have sometimes been reported when psilocybin is taken at larger doses (e.g. 25mg) but are generally not clinically significant and alleviate within a few hours of administration (Ross et al., 2021).

Acute risks generally associated with psilocybin use are psychological namely anxiety, paranoia, dysphoria, confusion and psychotic phenomena. However, these commonly resolve without intervention, and their risk can be mitigated by appropriate screening and the presence of psychological support (dos Santos et al., 2018, Ross et al., 2021). Instances of prolonged adverse psychological effects are rare, estimated to occur at .085% in healthy populations (Cohen, 1960). This appears to be the case for psychedelics even in instances of extreme overdose – reports exist of individuals ingesting up to 2100x the standard dose of LSD without long term psychological impact (Klock et al., 1974; Haden et al., 2020). There is evidence that psychedelics can precipitate psychosis in at risk individuals but no evidence of any dangers in otherwise low-risk individuals (Abraham et al., 1996). Accordingly, individuals with a history of or vulnerability for psychosis are excluded from studies involving psychedelics, as they will be in this instance. When psychotic reactions have been reported in experimental studies, they have been confined to the acute phase of psilocybin when administered at high doses, suggesting the efficacy of screening procedures (Studerus et al., 2011). Population studies have not found associations between long term psychedelic use and negative outcomes but, conversely, have identified positive outcomes from psychedelic use in the general population, including reduced instances of mental health issues (Krebs & Johansen, 2013; Hendricks et al., 2015). Indeed, psilocybin administration to screened and monitored participants since the 1990s has an excellent safety record. Over 800 doses have been administered across the world with no reports of any treatment-related SAEs, medical toxicity, prolonged psychosis or hallucinogen persisting perception disorder (Roscoe & Lozy, 2022). It is important also to note the frequent use of psilocybin containing mushrooms in social and religious contexts across the world for millennia before the advent of prohibition (Arce & Winkelman, 2021). In the current trial, the planned doses are considerably lower than typical recreational doses or doses that have been used in most previous clinical trials (see Table 1), and so present a significantly reduced potential for adverse effects.

4.1.4 Present research

While evidence for psilocybin's capacity to treat depression is compelling, to date, research has focused exclusively on severe, treatment-resistant depression. However, the majority of people with depression experience mild-moderate forms of the disorder (> 81% according to Hägg et al., 2020). This cohort has largely been overlooked in contemporary psychedelic research. Individuals with moderate depression experience impairing symptoms of low mood and anhedonia, which significantly impair quality of life, and contribute to societal burden. These individuals can

sometimes find a degree of relief from existing medications, but the magnitude of treatment effects do not always meet the patient's goals. In addition, side effects of traditional medications often introduce new challenges for patient wellbeing and can make individuals in this group reluctant to persist with treatment (Morilak & Frazer, 2004).

Although considerable attention has been paid to the clinical utility of psychedelics, there have not yet been any clinically focused trials of these substances in the microdose range. A microdose is approximately 0.8 – 5mg of synthetic psilocybin. Microdosing has become a popular phenomenon, with high levels of community use. Individuals who microdose typically report doing so with the specific intentions to increase wellbeing and usually will consume a dose regularly, every 3 or 4 days, over an extended period of time (Kuypers et al., 2019). Large scale survey research indicates that microdosing has become a widespread practice across a broad range of demographic categories, with estimates of 7% - 17% of people who use drugs having used psychedelic substances in this way (Cameron et al., 2020; Petranker et al., 2020). Microdosing does not entail marked perceptual alterations or functional impairments – microdosers deliberately use 'sub-hallucinogenic' doses that are not associated with debilitating changes in conscious experience. Nevertheless, users claim a wide variety of medium- and long-term benefits of microdosing, including improvements in mood, creativity, and productivity, or lessening of mental illness symptoms, addictive behaviour, and pain (Polito & Liknaitzky, 2022).

Microdosing has rapidly become a popular trend over the last seven years, with public interest in the phenomenon notably outpacing scientific evidence on the veracity of microdosers' claims. However, since 2018 there have been more than 30 empirical studies, including at least 8 rigorously controlled lab studies into the effects of microdosing. Together these show compelling evidence that low doses of serotonergic hallucinogens impact cognition in ways that are likely to have clinical benefits (Polito & Liknaitzky, 2022).

In particular, reports of improved mood and reductions in depressive symptoms are extremely common across recent microdosing studies (Kuypers, 2020). Notably, self-report studies of microdosers have shown that low doses of psychedelics are more effective than traditional treatments (Hutten et al., 2019), and that many microdosers cease standard medications after they start microdosing (Lea et al., 2020). Neuroimaging studies have shown that both psilocybin (Cavanna et al., 2022) and LSD (Murray et al., 2022) microdosing leads to reduced activity in the default mode network, and altered patterns of amygdala connectivity that were associated with antidepressant effects (Bershad et al., 2020).

Table 1 lists all previous studies where participants have ingested doses in the microdosing range (defined as studies where participants ingested ≤ 5mg psilocybin or ≤ 20ug of LSD). In two studies, a low dose condition was included as an experimental control in a study that primarily aimed to test the effect of high dose psychedelic assisted psychotherapy (R. Griffiths et al., 2016, 2018). Three other studies have focused on pharmacodynamics and pharmacokinetics across multiple doses (Hasler et al., 2004; Holze et al., 2021; K. E. Madsen, 2016). 12 studies – five with psilocybin (Cavanna et al., 2022; Marschall et al., 2022; Prochazkova et al., 2021; Sanz et al., 2022; van Elk et al., 2022) and seven with LSD (Bershad A. et al., 2019; de Wit et al., 2022; N. Hutten et al., 2020; N. R. Hutten et al., 2021; Murray et al., 2022; Ramaekers et al., 2021; Yanakieva et al., 2019) have specifically investigated the effect of microdosing on mental health or cognition. These studies have investigated the effects of one to 10 doses over a period of up to four weeks. No serious adverse events have been reported in any of these studies. Based on the prior research, both psilocybin and LSD appear to be promising candidates for microdose treatments of mood disorders. Currently, however, there is a greater volume of evidence supporting the efficacy and safety of psilocybin as a clinical treatment in high dose psychedelic research (van Amsterdam & van den Brink, 2022). Therefore, in the current study we propose to investigate microdoses of psilocybin as a treatment for moderate depression.

Table 1 – Previous dose controlled studies investigating low dose psychedelics (i.e, ≤ 5mg psilocybin or ≤ 20ug LSD)

Aim	Doses	Institution	N total (Microdose total)	Design	Reference
Acute psychological and physiological effects	Psilocybin – 3, 8, 15, 22mg / 70kg	Heffter Research Centre	8 (8)	Double-blind, placebo-controlled dose-response study	Hasler et al. (2004)
Safety, tolerability and efficacy for OCD	Psilocybin – 1.8, 7, 14, 21mg / 70kg	University of Arizona, Tuscon	9 (7)	Double-blind, proof of concept study	Moreno et al. (2006)
Effect on time interval reproduction	Psilocybin - .84mg / 70kg	Institute for Frontier Areas of Psychology and Mental Health / Heffter Research Centre	9 (9)	Double-blind, placebo-controlled experimental study	Wackerman et al. (2008)
Efficacy for depression and anxiety in cancer patients	Psilocybin – 1, 3, 22, 30mg / 70kg	Johns Hopkins University	51 (51)	Randomised, double-blind crossover	Griffiths et al. (2016)
Effect on psychological functioning and prosocial attitudes and behaviours	Psilocybin – 1, 20, 30mg / 70kg	Johns Hopkins University	75 (25)	Longitudinal double-blind study	Griffiths et al. (2018)
Acute psychological effects	Psilocybin – 3, 6, 12, 15, 18, 24, 30mg	University of Copenhagen	8 (1)	Randomised, single-dose, double blind dose-effect study	Madsen et al. (2019)

Effects on time perception, mentation and concentration	LSD – 4, 8, 15mg	Goldsmiths, University of London	48 (36)	Randomised, double-blind, placebo-controlled self-report and experimental study	Yanakieva et al. (2019)
Acute subjective and behavioural effects	LSD – 5, 10, 20mg	University of California, Los Angeles	20 (20)	Double-blind, placebo-controlled self-report and experimental study	Bershad et al. (2019)
Safety, tolerability, pharmacokinetics and pharmacodynamics	LSD – 5, 10, 20mg	Eleusis Benefit Corporation / University of London	48 (36)	Randomised, double-blind, placebo-controlled study	Family et al. (2020)
Effect on mood and cognition	LSD – 5, 10, 20mg	Maastricht University	24 (24)	Double-blind, placebo-controlled self-report and experimental study	Hutten et al. (2020)
Effect on circulating BDNF levels	LSD – 5, 10, 20mg	Maastricht University	23 (23)	Placebo-controlled blood analysis	Hutten et al. (2020)
Effect on resting-state amygdala functional connectivity	LSD – 13mg	University of California, Los Angeles	20 (20)	Double-blind, placebo-controlled neuroimage and self-report	Bershad et al. (2020)

Pharmacokinetics and pharmacodynamics	LSD – 5, 10, 20mg	University of Basel	23 (23)	Randomised, double-blind, placebo-controlled study	Holze et al. (2021)
Effect on experienced pain and unpleasantness	LSD – 5, 10, 20mg	University of Basel	24 (24)	Randomised, double-blind, placebo-controlled experimental study	Ramaekers et al. (2021)
Acute neurological effects	LSD – 10, 20mg	University of Chicago	22 (22)	Randomised, double-blind, placebo-controlled neuroimage	Murray et al. (2021)
Cognitive enhancement and creativity	Psilocybin (truffles) - .7, 1.0, 1.7mg	Leiden University & University of Amsterdam	171 (86)	Double-blind, placebo controlled self-report study	Prochazkova et al, (2021)
Acute psychological effects	LSD – 10, 20mg	University of Chicago	56 (38)	Double-blind, placebo-controlled dose-response study	De Wit et al., (2022)
Effect on affect and affective processing	Psilocybin (truffles) - 1.5mg	Leiden University	52 (52)	Randomised, double-blind, placebo-controlled self-report study	Marschall et al. (2022)
Effect on awe and aesthetic experiences	Psilocybin (truffles) - 1.5mg	Leiden University	30 (30)	Randomised, double-blind, placebo-controlled study	van Elk et al. (2022)

Subjective effects and effects on behaviour, creativity, perception, cognition and brain activity	Pilocybin (.5g truffles = .8mg)	University of Buenos Aires	34 (34)	Randomised, double-blind, placebo-controlled mixed design study	Cavanna et al. (2022)
Effect on speech signatures	Pilocybin (.5g truffles = .8mg)	University of Buenos Aires	34 (34)	Randomised, double-blind, placebo-controlled experimental study	Sanz et al. (2022)

4.2 Objectives and Outcomes

This study will be assessing the safety, feasibility and efficacy of low-dose psilocybin as a treatment for depression (of moderate severity).

4.2.1 Primary Objective:

To test whether low doses of psilocybin administered over a 6 week period is superior to active placebo in improving clinical outcomes in moderate depression [**efficacy**]

4.2.2 Secondary Objectives:

To assess whether:

1. the intervention is safe in terms of AEs, SAEs and suicidality [**safety**]
2. the intervention is tolerable in terms of functional impairment, dose acceptability and retention rates [**tolerability**]
3. general disability improves following treatment [**disability**]
4. quality of life improves following treatment [**quality of life**]
5. comorbid psychopathology (including anxiety, alcohol misuse, drug misuse, tobacco misuse and suicidality) are improved following treatment [**comorbidity**]
6. the treatment is appraised by participants as acceptable, appropriate and feasible [**acceptability, appropriateness and feasibility**]

To identify:

7. baseline trait and state characteristics that predict microdosing efficacy, safety and tolerability [**predictors**]
8. any acute or chronic changes in blood biomarkers that occur during and following treatment [**biomarkers**]
9. any acute changes in neurophysiology that occur during treatment [**neuroimaging**]
10. the impact of microdosing on a range of exploratory cognitive, emotional, social, belief and behavioural measures [**exploratory**]

4.2.3 Primary Endpoint:

Change in Hamilton Ratings Scale for Depression (GRID-HAMD) from baseline to week 6 [**efficacy**].

4.2.4 Secondary Outcomes:

1. Change in GRID-HAMD from baseline to week 10 (1M FollowUp) [**efficacy**]
2. Rates of clinical response (50% reduction on GRID-HAMD from baseline score) at week 6 (primary endpoint) and week 10 (1M FollowUp) [**efficacy**]
3. Rates of remission (score <8 on GRID-HAMD) at week 6 (primary endpoint) and week 10 (1M FollowUp) [**efficacy**]
4. Proportion of participants with Severe Adverse Events or Adverse Events associated with participation in the trial from week 1 through to week 6 [**safety**]
5. Proportion of participants with suicidality (CSSRS-Brief scores >1) during the study [**safety**]
6. Proportion of participants who down-titrate dose [**tolerability**]
7. Proportion of participants who remain in study until study week 6 (study endpoint) and week 10 (1M FollowUp) [**retention**]
8. Change in Sheehan Disability Scale (SDS) from baseline to week 6 and week 10 [**disability**].
9. Change from baseline to acute timepoints on driving simulator test / trailmaking [**Impairment**]
10. Change in EQ-5D from baseline to week 6 and week 10 [**quality of life**]
11. Changes in anxiety, alcohol misuse, drug misuse, tobacco misuse from baseline to week 6 and week 10 [**comorbidity**]
12. Ratings of the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) at week 6 [**acceptability / feasibility**]

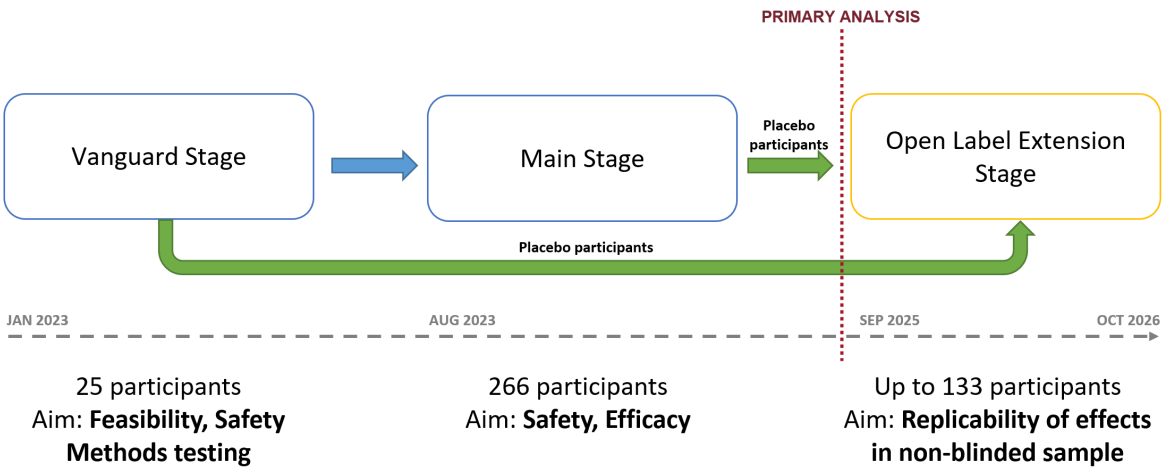
13. Change in blood-based biomarkers from baseline to week 1 and week 3 [**acute biomarkers**]
14. Change in blood biomarkers from baseline to week 6, week 7 and week 10 [**sustained biomarkers**].
15. Changes in resting state, visual longterm potentiation, and auditory oddball response from baseline to first dosing day [**neuroimaging**].

4.3 Study Design

The study is a double-blind randomised controlled trial of 266 participants who are diagnosed with moderate MDD and are not receiving antidepressants.

Participants will complete a study period of six weeks, followed by visits at week 7 (i.e., one week follow up) and 10 (i.e., one month followup). There will be additional online follow up visits at week 19 (i.e., 3 month follow up) and week 32 (i.e., 6 month follow up). Participants will attend two dosing sessions per week during the first five weeks and one in the sixth. During this period, they will complete a variety of psychological and biomarker measures, and some will also participate in an MEG sub-study.

If we find evidence of efficacy at the completion of the Main Stage, participants randomised to the control condition in either the Vanguard or Main Stages will have the option to undertake the intervention with the active drug in an Open Label Extension Stage.



4.3.1 Stages

This Study will be conducted across 3 stages:

1) Vanguard Stage
2) Main Stage
3) Open Label Extension Stage (for participants randomised to the placebo arms)

These stages will progress sequentially. The Main Stage will only commence if safety and feasibility of the Vanguard Stage is acceptable. The Open-label Extension Stage will only commence if there is evidence of efficacy in the Main Stage. The Open-label Extension stage will commence as soon as analysis of the primary outcome in the Main Stage has been conducted.

There will also be a neuroimaging substudy during the main stage, which will recruit up to 80 participants to investigate acute changes in brain activity associated with the Investigational Medicinal Products.

4.3.1.1 - Stage 1 – Vanguard Stage

The first stage of the project will consist of a Vanguard Stage , enrolling 25 participants. The primary aim of this stage is to assess the safety of the drug and feasibility of the study. In this stage we will evaluate the feasibility of our methods, procedures, and protocols related to safety and adverse events in a rigorous way, with real world patients. This will provide an extra level of assurance that all aspects of the project are ready for the subsequent larger safety and efficacy trial. Research to date indicates that participants report mood benefits with a range of very low doses of psilocybin (Polito & Liknaitzky, 2021), however there is evidence that doses less than 3mg are unlikely to be effective (Cavanna et al., 2022; K. E. Madsen, 2016; van Elk et al., 2021). In the Vanguard Stage, participants will be randomised 1:1 (balanced for age, sex at birth and time since first episode) to receive 4mg synthetic psilocybin or 60mg caffeine capsules. An active placebo is being utilised to control for expectancy effects, which are prevalent in studies with inadequate placebo control (Polito & Liknaitzky, 2022). Caffeine was selected as the active placebo due to its indistinct stimulant psychopharmacological effects, which may be hard to distinguish from low doses of psilocybin. Subjective reports from individuals who microdose indicate that the effects of low doses of psilocybin are often compared to caffeine (Santos, 2022). Dosing will occur bi-weekly for 6 weeks. Participants will complete assessments as per the Schedule of Assessments (Table 3). Antidepressant effects from traditional pharmacotherapeutic treatments are generally noticeable after a six-week period. Accordingly, this timeframe will provide a clinically meaningful comparison. Additionally, if there are distinct acute and sustained effects of psilocybin on mood, these will be captured by the

proposed design. Participants will be dosed in the presence of a study delegate. The first dosing session will take place in the clinic rooms at 2 Technology Place, and participants will be monitored by study staff with oversight by the study psychiatrist (AI Shannon) for a period of four hours following dosing. Our clinical monitoring and escalation procedures are outlined in Section 10.5. If any participant shows signs of discomfort during the initial dosing session, the study psychiatrist may specify additional monitoring on subsequent dosing sessions. The study psychiatrist will regularly monitor participants' responses to the study drug throughout the trial and may titrate down to a lower dose if this is judged appropriate (see section 10.5.3).

Participants will have follow up visits at week 7 (i.e., 1 week follow up) and week 10 (i.e., 1 month follow up). Upon the last participant's completion of the 1 month follow up visit in the Vanguard Stage, blinded safety data will be reviewed by the investigators, study team and the DSMB. The DSMB will provide a recommendation on whether to:

a) initiate the Main Stage without any design changes; or
b) initiate the Main Trial stage with design modifications; or
c) if there are significant feasibility or safety findings, terminate the entire study.

The Main Stage will only be initiated after full review and approval to proceed.
There will be additional follow up visits at week 19 (i.e., 3 month follow up) and week 32 (i.e., 6 month followup). Participants will complete these final two visits online and/or via telehealth.
The schedule of assessments in the Vanguard Stage is identical to the Main Stage with two exceptions: First, during the first visit, participants will provide blood samples at eight timepoints for pharmacokinetic and biomarker analyses (see section 6.1.12). Second, participants in the Vanguard Stage will complete qualitative interviews about their subjective experiences following their first and tenth dosing session. There will be no qualitative interviews in the Main Stage. The aims of the Vanguard Stage only concern safety and feasibility. No analyses related to efficacy will be conducted at the conclusion of the Vanguard Stage. If the DSMB recommends progression without any protocol modifications, Vanguard stage participants will be pooled with participants in the Main Stage for analyses related to efficacy of the main intervention.

4.3.1.2 Stage 2 – Main Stage

The Main Stage of the study and will enrol 241 participants (or 266 participants if protocol modifications have been made following the Vanguard Stage). The design and assessments in the Main Stage are identical to that of the Vanguard Stage (described in the previous section). Every third

participant will be invited to participate in the neuroimaging sub-study, to a study maximum of 80 participants. Should a targeted participant decline participation, the next screened participant will be invited. Participants will be randomised 1:1 ratio (balanced for age, sex at birth and time since first episode of depression) to either the active or active placebo arms. Participants will be randomised by a study coordinator using an automated stratification system implemented in REDCap. Participants will be dosed bi-weekly and will follow the schedule of assessments (Table 3). Participants will complete online long-term follow up visits at week 19 (3 month follow up) and week 32 (6 month follow up).

4.3.1.3 Stage 3 – Open Label Extension Stage

The third stage of the project will consist of an Open Label Extension for participants randomised to the active placebo arm in either of the previous Stages. There are three reasons for including the Open Label Extension stage in this project:

1. Beneficence – Inclusion of this stage allows all participants in the study access to the treatment if it is found to be effective.
2. Retention – We expect that participants who believe they are in the placebo condition during the Vanguard and Main stages will be more likely to remain in the study if they know they will be offered the chance to try the active intervention (if it is effective).
3. Replication – The Open Label Extension stage will allow us to test the replicability of any efficacy findings from the earlier stages in a sample of non-blinded participants.

Upon completion of the last participant's dosing visit in the Main Stage, if there are no significant safety findings and the primary endpoint is met, participants previously randomised to a placebo arm will be contacted and offered the opportunity to repeat the intervention with the active treatment. There will be a reduced set of study measures for these participants, as outlined in the Schedule of Assessments (Table 3). Participants will be dosed with the same drug regime and with the same level of clinical and safety monitoring as the Main Stage, however there will be a reduced number of blood draws. Participants will provide blood samples only at baseline, 3B, and and 6B visits.

Participants will complete online long-term follow up visits at week 19 (3 month follow up) and week 32 (6 month followup).

4.3.2 Study Setting

This will be a single site study based at Macquarie University, New South Wales, Australia. All dosing sessions will occur in-person at the study site.

4.4 Study Intervention

4.4.1 Investigational Medicinal Products

4.4.1.1 WP001 Capsules

WP001 capsules will be provided in containers by Woke Pharmaceuticals. The labelling on the containers will clearly indicate that the capsules contain Psilocybin. Each capsule will contain 1mg Psilocybin. Participants in the active condition will be administered 4mg psilocybin and so will consume 4 capsules during each dosing session. Participants who have been titrated down to 2mg, will consume 2 capsules. WP001 is classified as a Schedule 9 drug in Australia, and therefore is required to be stored according to local regulations. The containers will be fitted with child resistant caps and must be stored in a lockable steel safe in Macquarie University Hospital Pharmacy, with the drug preparation area having restricted access measures in place. A drug register must be maintained by the unblinded Pharmacist. Only the Pharmacy staff shall have access to the container.

4.4.1.2 Caffeine Capsules

Caffeine capsules will be provided in containers by Woke Pharmaceuticals. Each capsule will contain 15mg caffeine. Participants in the placebo condition will be administered 60mg caffeine and so will consume 4 capsules during each dosing session. Participants who have been titrated down to 30mg, will consume 2 capsules The caffeine capsules have been manufactured to look identical to the WP001 capsules, however the container will clearly indicate that the capsules are caffeine. Only the Pharmacy staff shall have access to the container. Caffeine is not a restricted drug, and therefore will not need to be stored with the same restrictions as WP001 capsules. However, the drug preparation and storage area should still have restricted access measures in place.

4.4.2 Labelling, packaging, Storage, Preparation and Return of Investigational Product

The Principal Investigator, or Study Delegate shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Due to the packaging of the investigational product, the delegated Pharmacist will be unblinded to the study treatments. The Study Pharmacy Manual will provide detailed information on the handling, storage, destruction and administration of the investigational product.

4.4.3 Preparation of Investigational Product

Upon randomisation within REDCap, the unblinded Pharmacist will be sent the participant's randomisation assignment. This randomisation assignment will not be shared with any blinded study team members. The standard dose for all participants will be either WP001 4mg or Caffeine 60mg. In the event the study psychiatrist wishes to reduce the dose during the participant's participation in the study, this will be communicated to the unblinded Pharmacist who will adjust the dose as appropriate. To prepare for dosing visits, the unblinded Pharmacist will dispense the appropriate dose and product for the participant and place the capsules in a bag labelled with the participant's study number. Once in the bag, the capsules will not be identifiable as caffeine or WP001, however all bags must be labelled as per local regulations as if they contained WP001. A study delegate will collect the blinded drug from the Pharmacy, administer to the participant and observe for the time frame as required per protocol.

5. Participants and outcomes

A total of 25 participants will be enrolled to the Vanguard Stage and 241 participants enrolled to the Main Stage. In total 266 unique participants will be enrolled overall. Up to 133 individuals randomised to placebo conditions in the Vanguard or Main Stages will be invited to also take part in the Open Label Extension Stage.

Recruitment into the Main and Open Label Extension Stages will only be initiated after data analysis of the prior Stage has been completed, and it is considered safe to open the next cohort.

5.1 Participant Recruitment

We have a five-step screening protocol to ensure that only eligible, low risk participants can enrol in the study:

1. Prospective participants who contact the trial staff requesting participation in the trial will be invited to take a pre-screening questionnaire with self-rated symptom measures, plus detailed information on medication. Participants will also be required to provide the details of their regular treating clinician. This must be a GP or psychiatrist.
2. Applications will be reviewed and participants excluded if appropriate.
3. If the prospective participant is considered preliminarily eligible, their nominated clinician will be contacted to inform them of their patient's application and to ask if they have any concerns.

4. Prospective participants will complete a formal screening with the study psychiatrist in person to identify the patients' developmental history, comorbidities, general suitability for the trial, and depression severity ratings.
5. Participants will complete an ECG and blood test (including measures of sodium, potassium, chloride, bicarbonate, urea, creatine, eGFR, urate, calcium, corrected calcium, phosphate, total bilirubin, ALP, GGT, AST, ALT, protein, albumin, cholesterol, triglycerides, magnesium, TSH and INR).

Potential participants who are referred to the study and provide suitable responses to the online pre-screening questionnaire (i.e., steps 1-3 above) will be added to a database of screenable participants. These participants will be invited to a formal screening session as soon as trial staff have capacity to process new enrolments. We will provide regular email updates to screenable participants every two months, informing them about the overall progress of recruitment and giving an estimate of when they may be invited to the next stage (i.e., formal screening).

5.2 Eligibility Criteria

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular participant is suitable for this study. Participants must meet all inclusion criteria and none of the exclusion criteria. The Principal Investigator, or qualified study delegate shall document the participant's eligibility clearly in the medical and/or study records.

5.2.1 Inclusion criteria

Participants may be included in the study if they meet all of the following inclusion criteria.

1. Age ≥ 18 years at the time of screening
2. Self-reported fluency in English
3. Meets the definition of moderate depression, defined as a score of between 15 and 23 on the Hamilton Rating Scale for Depression
4. Diagnosis of major depressive disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI)
5. Able to swallow WP001 or Caffeine capsules

6. Has a body weight between 50kg and 120kg, and BMI above 16.
7. Refrains from the use of any psychoactive medication not approved by the research team from baseline through Study Termination.
8. Agrees to abstain from herbal, complementary or over the counter medications with serotonergic effects including, but not limited to, St John's Wort, S-adenosyl methionine (SAM-e), 5-hydroxytryptophan (5-HTP) and L-tryptophan.
9. Agrees to comply with contraception requirements:
    a. Women of childbearing potential must have a negative urine or serum pregnancy test at screening and baseline and be non-lactating. During the study, women of childbearing potential must agree to use a highly effective method of birth control up to 7 days after the last dose.
    b. Male participants must agree to use highly effective method of birth control during the participation in the study up to 7 days after the last dose.
10. Able and willing to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations and other study procedures.
11. Agrees to study investigators communicating directly with all of their External Health Practitioners.
12. Provides a contact (relative, spouse, close friend or other Support Person) who is willing and able to be reached by the investigators in the event of a participant becoming unreachable.
13. Must agree not to operate heavy machinery, any motorised vehicle or perform tasks that might endanger oneself or others, such as those requiring fine motor control, fast response times or real-time planning for three hours following each dosing session.
14. Participants cannot drive to study visits and must either live within the catchment area of the study site (defined as anywhere that is accessible by a rideshare service during business hours costing less than $80) or must have someone who can drive them to every study visit. If participants are driven by another person, they will be reimbursed a flat rate of $100 per visit.

5.2.2 Exclusion criteria

Participants will be excluded from the study if they meet any of the following exclusion criteria:

1. Recently started new psychological therapies and/or sessions with health professionals within 30 days of consent (such as counsellor, psychotherapists). Participants with a stable regimen

may be included in this study if they agree to continue with the psychological therapies and/or counselling sessions as is (frequency of the therapy and/or sessions should not change)

2. Use of antidepressant or antipsychotic medication in the prior 3 months or plans to start new antidepressant or antipsychotic medication in the upcoming 2 months.
3. Current diagnosis of psychotic disorder, bipolar disorder, personality disorder, post-traumatic stress disorder, or substance use disorders.
4. Identification of a *primary* mental health diagnosis apart from Major Depressive Disorder on the Mini International Neuropsychiatric Interview or during a general psychiatric interview.
5. Any participant presenting current serious suicide risk, as determined through psychiatric interview, responses to Columbia Suicide Severity Rating Scale (C-SSRS), and clinical judgment of the investigator will be excluded. Any participant who is likely to require hospitalisation related to suicidal ideation and behaviour, in the judgment of the investigator, will not be enrolled. Any participant presenting with the following on the screening C-SSRS will be excluded:
    a) Suicidal ideation score of 4 or greater within the last 12 months of the assessment at any frequency.
    b) Any suicidal preparatory acts or preparatory behaviour, within the last 12 months of the assessment. Participants with non-suicidal self-injurious behaviour may be included if approved by the CI.
    c) Any suicidal behaviour, including actual, aborted, or interrupted suicide attempts within 10 years.
    d) Would present a serious risk to others as established through clinical interview and contact with External Health Practitioners.
    e) Require ongoing concomitant therapy with a psychiatric medication for management.
6. Poorly controlled hypertension or other cardiac abnormalities.
7. History of psychosis, bipolar disorder, stroke, epilepsy, brain injury or head trauma.
8. History of serious liver (Child-Pugh B or C), kidney disease (eGFR<60ml/min).
9. First degree relative with psychotic disorder.
10. Pregnant, or trying to get pregnant, or breastfeeding.
11. Use of any other psychotropic drug (excluding alcohol, nicotine and caffeine) within the last month from date of Baseline visit.
12. Moderate to severe cannabis or alcohol use disorder in the prior 12 months.
13. An illicit or prescription drug use disorder of any severity in the prior 12 months.

14. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.
15. Significantly abnormal laboratory blood test defined as outside the normal range and deemed clinically significant by an investigator with expertise in this field.
16. Resting blood pressure exceeding 160mmHg systolic and 100mmHg diastolic.
17. Currently taking part in another clinical trial involving interventions such as an investigational drug, device, or psychotherapy.
18. Current evidence of, or a history of, any condition, therapy or abnormal laboratory assessment or other events that, in the opinion of the investigator, may affect safety, and/or disrupt their participation for the duration of the study.

5.2.3 Neuroimaging eligibility criteria

In addition to meeting the main eligibility criteria, participants in the neuroimaging substudy must meet the following additional inclusion criteria.

1. Provide consent to take part in the sub-study.
2. Does not have any non-removable magnetic or metal material attached to body (e.g., metal implants, dental work or pacemaker).
3. Does not have claustrophobia.
4. Able to walk a total distance of 1km.

5.2.4 Open Label Extension Criteria

Before being enrolled into the Open Label Extension stage participants will be rescreened and must again meet all of the eligibility criteria listed in 5.2.1 and 5.2.2.

6 Study Procedures

6.1 Study Assessments and Measures

Study assessments will be self-report measures that participants will complete directly, electronically via REDCap or Gorilla or on paper, unless otherwise stated.

6.1.1 Administrative

6.1.1.1 Informed Consent

Participation in this research study is entirely voluntary. The Investigator, or qualified study delegate must obtain documented consent from each potential participant and/or participant's legally acceptable representative prior to participating in this study. The Investigator, or study delegate will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study. The participant or his/her legally authorised representative should be given sufficient time and opportunity to ask questions and decide whether or not to participate in the study. No study procedures shall be completed prior to the completion of the consenting process. Participants will only be provided the ethics committee approved informed consent forms (ICF).

Participants selected to participate in the Neuroimaging Sub-study will be required to sign an additional ICF.

Should an ICF amendment be approved by the Ethics Committee whilst a participant is still receiving treatment (active or active placebo (caffeine)), they must be re-consented with the updated consent form at their next scheduled study visit. Participants in follow up will only be re-consented if the amendment addresses significant safety concerns or updates.

Participants who are re-screened must sign a new consent form.

We will be seeking participants' unspecified consent for the use of the data and samples for this research study and potential further research which may or may not be related to depression.

6.1.1.1.1 Pre-Screening

Following receipt of a participant referral, participant pre-screening consent will be sought electronically prior to undergoing pre-screening.

6.1.1.1.2 Vanguard/Main Stage

Participants that are fulfil the pre-screening eligibility criteria will be invited to take part in the vanguard or main stage of the study. The participant's written consent will be obtained and documented. The consent process may be in person, face to face between the participant and investigator(s). However consent may also be obtained via telehealth or remotely over the phone.

6.1.1.1.3 Neuroimaging Component/sub-study

This study has an optional neuroimaging sub-study. Approximately one participant each week will be invited to this sub-study (based on laboratory capacity). Should a participant decline, the next enrolled participant will be invited to take part in the neuroimaging sub-study. The participant's decision (whether or not), to take part in the neuroimaging sub-study will not affect their participation in the vanguard or main stage of the study.

6.1.1.1.4 Considerations.

Participant's electronic or written consent will be obtained prior to any assessments or measures being taken. Consent will be obtained electronically for the prescreening and through a written consent for the other stages where the consent process may be conducted in person or via telehealth or remotely.

A member of the research team will provide the consent form, either the investigator or clinical research coordinator/assistant. The consent form(s) may be provided electronically via email or as a physical copy given directly to the potential participants or as a mailout.

Participants may take as much time as they need before deciding to take part or decline. Only medically qualified investigators will be responsible for taking consent.

6.1.1.2 Eligibility Criteria

Participants that fulfil all of the inclusion criteria and none of the exclusion criteria will be eligible and enrolled in the study.

6.1.1.3 Randomisation

Participants will be randomised via REDCap following the baseline visit.

6.1.1.4 Medical and Mental Health History

The participants medical and mental health history will collected to establish their background information and to assess their suitability.

6.1.1.5 Medication History

The participants use of medication history will collected to establish their health and background information and to assess their suitability.

6.1.1.6 Adverse Event Reports

Participants will be asked to describe any adverse events/serious adverse events that they have experienced. Adverse events information will be collected and recorded from the time of first dose. Serious adverse events will be collected and recorded from the time of informed consent.

6.1.2 Medical

6.1.2.1 Blood laboratory tests

Table 2. Safety Blood Sample Laboratory tests			
Biochemistry			Other
Alkaline phosphatase (ALP)	Creatinine	(Total) Protein	International Normalised Ratio (INR)
Gamma-glutamyl transferase (GGT)	eGFR	Albumin	Thyroid Stimulating Hormone (TSH)
Aspartate transaminase (AST)	Sodium	Globulin	Full blood count
Alanine transaminase (ALT)	Potassium	Urate	
Total Bilirubin	Chloride	Urea	
Calcium	Bicarbonate	Magnesium	
Corrected Calcium	Cholesterol		

Medical safety blood sample at week 3B visit is to be collected pre dose. Results to be reviewed prior to the administration of next dose.

6.1.2.2 Electrocardiograms

A standard 12-lead ECG will be obtained from participants and reviewed by an investigator or medically qualified delegates. Clinically significant abnormal findings at screening will be recorded in the participant's medical history. Additional ECGs should be performed when clinically necessary. Participants should be in a resting position at least 10minutes prior to having an ECG taken. If ECG is conducted at the same timepoint as blood samples, ECG should be performed before blood collection.

6.1.3 Psychopathology

6.1.3.1 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al., 2011b) is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviour. Four constructs related to suicidality are measured. Firstly, severity of ideation is rated on a 5-point scale ranging from 1 (*wish to be dead*) to 5 (*suicidal intent with plan*). Secondly, the intensity of ideation is assessed through five items; two of which (frequency and duration) are rated on a 5 scale, and three of which (controllability, deterrents, and reason for ideation) are rated on a 6-point scale. Thirdly, suicidal behaviour is assessed, including attempts, preparatory acts, and non-suicidal self-injurious behaviour. Finally, the lethality of suicidal behaviour is assessed on a 6-point scale (from 0 = *no physical damage*, to 5 = *death*) rating the level of actual medical damage of any suicide attempts. The C–SSRS is considered the "gold standard" for measuring suicidal ideation and behaviour in clinical trials with the FDA labelling it the preferred instrument is such settings (Giddens et al., 2014).
See Appendix 2.1 and 2.2.

6.1.3.2 Columbia Suicide Severity Rating Scale – Brief

This measure consists of the first five items of the C-SSRS and will be utilised to quickly assess suicidality on dosing days without imparting unnecessary participant burden.
See Appendix 2.3.

6.1.3.3 The Mini-International Neuropsychiatric Interview (MINI)

The MINI (Sheehan et al., 1998) is a short structured diagnostic interview was developed for use in clinical trials. The MINI assesses the 17 most common mental health disorders. These clinical interviews will be conducted by one of the one of the investigators or trial staff trained in clinical and diagnostic assessment to determine eligibility. They will be used to determine clinical diagnosis (past and present), as well as whether or not the patient is psychologically stable enough to safely participate in the psilocybin-assisted psychotherapy (i.e. does not have current or past psychotic illness, significant personality disorder, etc.). The interview will also contain questions regarding prior drug use, including use of psilocybin.
See Appendix 2.4.

6.1.3.4 Standardised Hamilton Depression Ratings Scale (GRID-HAMD)

The GRID-HAMD (Williams et al., 2008) is an improved standardised version of the original HAM-D (Hamilton, 1960), which is considered the gold standard clinician-rated instrument measuring depressive symptomology and has been favoured in psilocybin trials investigating depression. It is intended as an assessment of the severity of depression in individuals already diagnosed with the condition. The GRID-HAMD was developed through an international consensus process and improves on the original measure by separating symptom frequency and intensity, refining problematic anchors and integrating clinician and convention driven assessment for each item. It comprises of 17 items assessing psychological and somatic aspects of depression, each scored by an administering clinician during a semi-structured interview. The GRID-HAMD has high interrater reliability, which is important for assessor-rated scales and appears to have greater validity than the HAMD (Williams et al., 2008). See Appendix 2.5.

6.1.4 Safety Measures

6.1.4.1 Pre-Screening Questionnaire

A set of questions ascertaining whether potential participants do not meet eligibility criteria to the best of their knowledge before they are screened by the psychiatrist and investigators aimed at reducing participant and investigator burden. See Appendix 2.6.

6.1.4.4 Qualitative Interview

Participants in the Vanguard Stage will complete a qualitative interview during weeks 1 and 6. They will retrospectively report about the acute effects of their previous dosing session. The aim of this interview will be to identify the specific phenomenology of the pharmacological effects of the study drug (and active placebo). The interview will focus on affect, sensations, thoughts and metacognition. The interview will follow the principles of a microphenomenological investigation (Petitmengin et al., 2007, 2019). In this qualitative framework the interviewer begins the interview with a broad general invitation for the participant to describe their experience. The interviewer deliberately avoids introducing any new content to the interview and instead continuously follows up on anything that the participant introduces asking for greater levels of specificity. The results of microphenomenological analyses can reveal new links between first person phenomenology and neurological or psychometric data.

6.1.5 Tolerability Measures

6.1.5.1 Trail Making Test (TMT)

The TMT is a neurophysiological test of visual attention, mental flexibility and visuomotor integration originally developed by Ralph Reitan in 1944, now commonly used as a diagnostic tool for assessing neuropsychological impairment. The task involves two different tracking conditions: one involving the connecting of numbers from 1 to 25 in sequence and one connecting numbers and letters in alternating ascending order, each in the shortest time possible without lifting one's pen from the paper (Reitan & Wolfson, 1993). See Appendix 2.7.

6.1.5.2 Driving Simulator

Driving performance will be assessed using a Forum 8 driving simulator. The simulator consists of a car unit with adjustable car seats and a dashboard and includes a steering wheel, turn sign indicators, gear lever, brake and accelerator pedals for vehicle control. The system generates realistic roadway scenery which is presented on three integrated TV screens 1.90 m in front of the centre of the steering wheel . The speed and gear number are displayed on the dashboard and screen. Auditory feedback is provided by speakers and included the sound of the engine, braking, speeding in curves, and driving off-road. A highway driving test scenario was developed by Forum 8, tailored to Australian traffic situations (e.g., common traffic signs, vehicles, buildings, and scenery). The test will run for approximately 15 min. Participants will complete a 5 min practice test drive prior to the commencement of the first test. The test scenario aims to resemble the on-the-road driving test in normal traffic. Participants are instructed to drive with a steady lateral position in the left traffic lane while maintaining a steady speed of 100 km/h. Overtaking manoeuvres are allowed whenever the car approaches a slower-moving car. These events will be removed prior to analysis. Weaving of the car, expressed as standard deviation of the lateral position (SDLP), is the primary outcome measure of the test. Secondary outcome measures include the standard deviation of speed (SDS, km/h) and lapses. A lapse is defined as a change in mean lateral position of greater than 100 cm, lasting for at least 8s. The data will therefore be analysed for (1) the number of lapses, (2) the duration of each lapse, and (3) the changes in lateral position during each lapse.

6.1.5.3 11-Dimension Altered States of Consciousness Scale (11D-ASC)

The 11D-ASC is a 42-item scale, developed by Studerus and colleagues (2010), measures altered states of consciousness (ASCs) based on the original 94-item 5-Dimensional Altered States of Consciousness Rating Scale (Dittrich, 1998). The 11 dimensions ASCs are experience of unity,

spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synaesthesia, and changed meaning of percepts. Responses are made by marking a horizontal visual analogue scales (VAS) of 100 millimetres length, anchored by 'no, not more than usual' on the left and as 'yes, very much more than usual' on the right. This measure has been widely used to measure the acute effects of psychedelic drugs. See Appendix 2.8.

6.1.5.4 Drug Effects Questionnaire (DEQ)

The DEQ is a VAS scale that measures overall subjective drug effects. Various version of the measure were reviewed by Morean et al. (2013). We will use a tailored version of the scale that includes items indexing drug intensity. See and Appendix 2.9.

6.1.5.5 Microdosing Effects Rating Scale

The Microdosing Effects Rating Scale is a 12 item, self-report measure designed for the purposes of this study. The measure investigates the valence, intensity and potency of psychoactive effects associated with microdosing. Respondents answer using a visual analogue scale and a 7-point Likert scale. Appendix 2.10.

6.1.5.6 Psychotomimetic States Questionnaire (PSI)

The PSI is a measure specifically aimed at targeting the psychotic-like acute effects of recreational drugs (Mason et al., 2008). Its 48 items cover different aspects of psychotic states, namely delusory thinking, perceptual distortions, cognitive disorganisation, anhedonia, mania and paranoia. Items consist of statements that respondents indicate their agreement with during acute drug effects.

See Appendix 2.11.

6.1.5.7 Antidepressant Side-Effect Checklist (ASEC)

The ASEC (Uher et al., 2009) measures 21 adverse reactions to antidepressants. For each item, participants rate the severity of the symptom on a four-point scale. In addition, respondents indicate whether they believe it was a side-effect of the given drug. See Appendix 2.12.

6.1.6 Disability Measures

6.1.6.1 Sheehan Disability Scale (SDS)

The SDS (Sheehan, 1986) is a five-item measure of functional impairment. Three items, rated on a 10-point Likert scale, assess how a person's symptoms over the past week interfered with their ability to participate in work, social, and family life. The final two items assess the number of days that symptoms have led to absenteeism (missed days from school/work) and reduced productivity over the past week. The SDS has generally shown good internal consistency across several populations of psychiatric diagnosis (Arbuckle et al., 2009; DeMuro et al., 2014; Hodgins, 2013) and has been used to discriminate levels of impairment in diverse psychiatric populations (Olfson et al., 1997). The averaged total score on the first three items of the SDS will be measured at baseline and compared to both post-intervention (14 days post Dose 2) and long term follow up (26 weeks post Baseline) as a secondary outcome of disability. Scores on the remaining two items will contribute to the measure of 'Lost Productivity' (see below). See Appendix 2.13.

6.1.6.2 Lost Workplace Productivity (LWP)

Following the definition of lost productivity used by Cremonini et al. (), which includes lost time and reduced effectiveness in the measurement of lost productivity, lost productivity will be calculated for all participants engaged in paid work during the study from baseline to long term follow up. Lost productivity is calculated as follows:

$$LWP = A + [B * (1 - C)]$$

Where A = Hours Missed from paid job(s) because of symptoms, B = Hours working at paid job(s) despite interference of symptoms, C = Percent effectiveness while working at paid job(s). Variables A and B are collected in the Sheehan Disability Scale, outlined above. Variable C will be collected through an additional question asking participants to estimate "On days that you went to school or work in the last week despite feeling impaired by your symptoms, how effective do you feel that you were?" This is scored as a percentage where 0% = completely impaired; no work was achieved and 100% completely unimpaired; achieved the same amount of work as without symptoms. See Appendix 2.14.

6.1.6.3 Short Form Profile of Mood States (POMS-SF)

The POMS-SF (Shacham, 1983) is a 37 item short form the 65 item Profile of Mood States (POMS; McNair et al., 1981), which was developed as a measure of the type and severity of current or recent

psychological distress. The measure consists of a list of 37 adjectives to which respondents indicate the degree to which each describes themselves during the last week using a 5-point Likert scale. As with the POMS, completing the POMS-SF yields a global distress score, Total Mood Disturbance, as well as scores for six subscales (Fatigue–Inertia, Vigour–Activity, Tension–Anxiety, Depression–Dejection, Anger–Hostility, and Confusion–Bewilderment), without sacrificing internal consistency. Estimates of Cronbach's alpha range from .80 to .91, higher than for the POMS (.74-.91; Curran et al., 1995). Analyses suggest omitted items from the POMS were marked by significant conceptual overlap, suggesting it is an excellent alternative to the POMS. See Appendix 2.15.

6.1.6.4 Change in Healthcare Utilisation (HU)

Frequency data will be collected on previous 3-month utilisation of various healthcare services including primary care (visits to GPs, health clinics, psychologists, psychiatrists, dentists, physiotherapists, counsellors, mental health clinic or other primary care providers), hospitalisations, and emergency department (ED) visits. Visits across all domains will be summed for a total HU score, and visits to psychologists, psychiatrists, counsellors or mental health clinics will be summed for a total mental healthcare utilisation score. Previous 3-month HU will be collected and compared from baseline to long term follow up. See Appendix 2.16.

6.1.6.5 Work and Social Adjustment Scale (WSAS)

The WSAS (Marks, 1986) is a self-report measure of general impairment attributable to an identified problem. The 5-item scale has been used to study a variety of psychopathologies, including depression. Participants indicate the degree to which the preidentified problem affects their life and functioning. In depression samples, Cronbach's alpha scores range from .81 to .94 and the test-retest correlation over the course of treatment is .73 (Mundt et al., 2002). Scores correlate with disorder severity and perceived clinical improvement. See Appendix 2.17.

6.1.6.6 The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

The ASSIST (WHO, 2002) measures degree of involvement with alcohol, tobacco and other drug. It is not an assessment of use disorder. Respondents indicate how frequently they have used various substances, urges to use and effects on functioning in a 3-month timeframe. The scale has been modified to assess nicotine use rather than tobacco use. An item has also been added to assess the substance quantity that is consumed alongside frequency. Appendix 2.18.

6.1.7 Quality of Life Measures

6.1.7.1 EQ-5D

The EQ-5D (Brooks, 1996) is a measure of health-related quality of life used to assess patients' health status and evaluate the effectiveness of health care interventions consisting of three parts: the descriptive system or self-classifier, a VAS for the measurement of overall self-rated health and the EQ Index. The descriptive system measures health across five dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients indicate the severity to which each dimension is experienced on a three point scale (level 1 = no problems, level 2 = some/moderate problems, level 3 = severe/extreme problems). The VAS component consists of a hashed vertical scale on which respondents are asked to indicate their overall health between 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D is sensitive to changes over time and different diagnostic categories (Badia et al., 2001). See Appendix 2.19.

6.1.7.2 Warwick-Edinburgh Mental Wellbeing Scale (WEBWBS)

The WEMWBS (Tennant et al., 2007) is a quality of life measure that aims to assess psychological wellbeing covering concepts associated with positive mental health, such as positive affect, satisfying interpersonal relationships, positive functioning, and hedonic and eudaimonic life aspects. It builds on previous affect and wellbeing scales used to assess similar constructs, such as the PANAS and WHO-5, by combining and shortening them to form a concise but encompassing measure. The scale has 14 items in response to which participants indicate the frequency with which they experience them on a 5-point Likert scale from 'none of the time' to 'all of the time'. It has excellent internal consistency (0.9) and shows high correlations with other mental health and well-being scales and lower correlations with scales measuring overall health. Its distribution is near normal, and the scale does not show ceiling effect and discriminates between population groups in a way that is largely consistent with the results of other population surveys. One week test-retest reliability is high (0.83). See Appendix 2.20.

6.1.8 Comorbidity Measures

6.1.8.1 Alcohol Use Disorder Identification Test (AUDIT-C)

The AUDIT is a ten-item self-report assessment of alcohol consumption, drinking behaviours, and related problems (Saunders et al., 1993). Here we use a shortened version for the purpose of preliminary screening (AUDIT-C). Respondents answer the three items on a 5-point scale (0 = *Never*

or *none*, 4 = *Daily* or *greatest number*). The measure can be used to detect alcohol use disorders in both clinical and general populations (Allen et al., 1997). See Appendix 2.21.

6.1.8.2 Drug Use Disorder Identification Test (DUDIT-C)

The DUDIT is an 11-item measure designed to assess presence of substance use disorders (Berman et al., 2005). Here we use a shortened version for the purpose of screening participants preliminarily (DUDIT-C). Responses to the four items are made on a 5-point scale (0 = *Never* or *none*, 4 = *Daily* or *greatest number*). The DUDIT has strong psychometric properties with clinical and non-clinical populations, including high convergent validity, discriminant validity, and internal consistency (Berman et al., 2005; Voluse et al., 2012). When compared with an interview based on ICD 10, the DUDIT had a sensitivity to detecting substance use disorders of 90% and a specificity of 80% (Berman et al., 2005). See Appendix 2.22.

6.1.8.3 Sydney Melancholia Prototype Index (SMPI)

The SMPI (Parker et al., 2010) is a 24-item measure used to classify melancholic vs non-melancholic subtypes of depression. Melancholic depression is generally characterised by psychomotor disturbance, appetite and weight loss, diurnal mood variation, less likely to be triggered and often with a family history. This compares with non-melancholic depression which often lacks these typical neurovegetative features, is more likely triggered by external events and is associated with personality vulnerabilities.. The measure is made up by two scales of 12 items, each measuring melancholic and non-melancholic prototypic features. Each item reads as a statement with which raters indicate their level of agreement on a 5-point Likert scale (1 = *Completely disagree*, 5 = *Completely agree*). There is evidence that melancholic depression is qualitatively different from other forms of depression (e.g. Parker et al., 2013), is less likely to be reactive (Parker et al., 2012) and produces differences in clinically relevant variables (e.g. Parker et al., 2015). While the SMPI has good predictive validity and internal consistency, factor analyses suggest it might not measure a single construct (Lorenzo-Luaces et al., 2020). See Appendix 2.23.

6.1.8.4 The Short Depression Anxiety Stress Scale (DASS-21)

The DASS-21 (Lovibond & Lovibond, 1995) is a short version of the DASS (Lovibond et al., 1995), which is aimed at measuring the magnitude of 3 emotional states, depression, anxiety and stress, each with their own subscale. It is a preferred tool amongst clinicians for assessing severity of

depression and anxiety. It demonstrates robust correlations with other measures of depression and anxiety. See Appendix 2.24.

6.1.9 Predictor Measures

6.1.9.1 Phenomenological Control Scale (PCS)

The PCS (Lush et al., 2021) measures individual ability to generate felt experiences to meet expectancies, that is, an individual's propensity to alter subjective experience in a manner that is consistent with particular goals. Those high in phenomenological control are more susceptible to extrapersonal suggestion. As the psychedelic experience can be influenced by internal or external suggestion, the PCS is a potential predictor of an individual's reaction to psychedelic drugs. It has 10 items that take the form of experimenter suggestions. A self-report scale records objective evaluations of response (did a participant's hands move together) as a binary score, and subjective ratings of the experience (how much an individual reports feeling the sense of a magnetic force on their hands), scored on a 5-point Likert scale. Preliminary evidence suggests the PCS is a reliable tool for measuring trait response to imaginative suggestion outside the context of hypnosis. See Appendix 2.25.

6.1.9.2 Modified Tellegen Absorption Scale (MODTAS)

The MODTAS (Jamieson, 2005) measures trait absorption, which has been defined as the tendency to recruit "total attention involving a full commitment of available perceptual, motoric, imaginative and ideational resources to a unified representation of the attentional object" (Tellegen & Atkinson, 1974, pg. 274). The scale consists of 34 items of various experiences of absorption, which are rated on a five-point Likert scale (0 = *never* to 4 = *very often*). These items result in five primary factors (Synaesthesia, Altered States of Consciousness, Aesthetic Involvement, Imaginative Involvement, and Extrasensory Perception) and a single higher order factor representing trait absorption. The MODTAS has excellent internal consistency (Cronbach's alpha = .94; Cardeña & Terhune, 2014). See Appendix 2.26.

6.1.9.3 Short Form Big Five Inventory (BFI-2-S)

The 30-item BFI-2-S (Soto & John, 2017) is an abbreviated version of the BFI-2 that measures personality at the factor-level of the BFI-2. Big Five models conceptualise personality as being best summarised by the factors of Extraversion, Agreeableness, Conscientiousness, Negative Emotionality (or Neuroticism), and Open-Mindedness (or Openness to Experience). The BFI-2-S was created by

selecting two items from each of the 15 lower-order facets of the original BFI-2. It has been validated in both university and internet samples and shows adequate internal consistency for a short scale (Cronbach's alpha 0.73–0.83). The BFI-2-S shows similar correlations to self- and peer-reported personal criteria as the original BFI-2, capturing 93% of the variance of the original scale, higher than the 84% captured by the BFI-2-XS. See Appendix 2.27.

6.1.9.4 Mind-Wandering Questionnaire (MWQ)

The MWQ (Mrazek et al. 2013) measures trait levels of mind-wandering, that is, thought unrelated to a given task. The scale employs five examples of mind-wandering and respondents indicate the frequency with which they engage in such behaviours on a 6-point Likert scale (1 = *Almost never* to 6 = *Almost always*). The scale shows high internal consistency (α = .85) and convergent validity with existing measures of mind-wandering and related constructs. Score on the MWQ is correlated with worse reading comprehension, greater stress and lower life satisfaction. See Appendix 2.28.

6.1.9.5 Comprehensive Thinking Style Questionnaire (CTSQ)

The CTSQ (Newton et al., 2021) is a 24-item questionnaire that measures a thinking styles across four factors: Actively Open-minded Thinking, Close-Minded Thinking, Preference for Intuitive Thinking, and Preference for Effortful Thinking. The items were derived by testing numerous thinking styles measures in a large sample and retaining items that correlated highly (r = 0.21 or above) with the CRT. Items are rated on a 6-point Likert scale (1 = *strongly disagree* to 6 = *strongly agree*), yielding a score for each of the four factors. CTSQ factors scores were predictive of a number of outcomes including religious, paranormal and conspiratorial beliefs (Newton et al., 2021). See Appendix 2.29.

6.1.9.6 Brief Experiential Avoidance Questionnaire (BEAQ)

The BEAQ (Gámez et al., 2014) is a measure of experiential avoidance assesses unwillingness to remain in contact with distressing thoughts, emotions and physical sensations, even when such avoidance leads to adverse outcomes in the long-term. The BEAQ consists of 15 items rated on a five-point Likert scale (1 = *strongly disagree* to 6 = *strongly agree*) and covers six dimensions: behavioural avoidance, distress aversion, procrastination, distraction/suppression, repression/denial, distress endurance. Higher summed scores (reflecting higher experiential avoidance) have been linked to increased psychopathology (Gámez et al., 2014). It has good internal

consistency (Cronbach's alpha = .80-.89) and test-retest reliability has been demonstrated in several translations of the scale (Schaeuffele et al., 2021; Vázquez-Morejón et al., 2019). See Appendix 2.30.

6.1.9.7 Cognitive Flexibility Scale (CFS)

The CFS (Martin & Rubin, 1995) measures an individual's awareness of alternative options, willingness to be flexible and self-efficacy in doing so. The scale has 12 items with which respondents indicate agreement on a 6-point Likert scale. See Appendix 2.31.

6.1.9.8 Conspiracy Mentality Scale (CMS)

The CMS (Stojanov & Halberstadt, 2019) is a new measure of conspiratorial thinking that differentiates between conspiracy theory ideation (7 item subscale) and rational scepticism (4 item subscale). These subscales were constructed using exploratory and confirmatory factor analysis and item response theory analysis. The subscales showed excellent reliability (Cronbach's alpha .93 and .94 for conspiracy theory ideation and rational scepticism, respectively) and satisfactory test-retest reliability over a two-week period (r = 0.71, p < 0.001 for both subscales). Participants respond to the items on a seven-point scale (1 = *strongly disagree* to 7 = *strongly agree*). See Appendix 2.32.

6.1.9.9 Cognitive Reflection Test (CRT)

The CRT (Frederick, 2005; Primi et al., 2016; Sirota et al., 2021; Thomson & Oppenheimer, 2016; Toplak et al., 2014) measures the ability to override an intuitive, incorrect response with a more reflective, rational, correct response (Frederick, 2005). Multiple alternate forms of the CRT exist, allowing for repeat testing without introducing familiarity-based noise to results (Sirota et al., 2021; Tamas, 2020; Thomson & Oppenheimer, 2016; Toplak et al., 2014). Each comprises three to seven simple, multiple-choice mathematical problems, each designed with an intuitive but incorrect answer. Two scores are derived: a reflective score (the sum of correct answers), an intuitive score (sum of intuitive errors). Non-intuitive errors do not contribute to either score. The CRT has construct equivalence across alternate forms and good internal consistency considering the small number of items (Cronbach's alpha = 0.60 – 0.73 for reflective scores; 0.58-0.67 for intuitive scores; Sirota & Juanchich, 2018). Scores on the CRT have validity in predicting a wide array of outcomes including decision-making characteristics (Frederick, 2005), religious and paranormal beliefs (Pennycook et al., 2012), and political ideology (Deppe et al., 2015). See Appendix 2.33.

6.1.10 Acceptability, Appropriateness and Feasibility Measures

6.1.10.1 Stanford Expectations of Treatment Scale (SETS)

The SETS (Younger et al., 2012) aims to measure positive and negative aspects of pre-treatment expectancy and determinants of placebo and 'nocebo' responses. This is particularly important in psychedelics studies where it is difficult to utilise a comparable placebo and participants have expectations for how a psychedelic experience will manifest. The six items are responded to on a 7-point Likert scale indicating agreement with statements pertaining to the upcoming treatment. Expectancy as measured by the SETS is predictive of treatment outcome and the scale has good discriminant validity from relevant personality traits (Younger et al., 2012). See Appendix 2.34.

6.1.10.2 Acceptability of Intervention Measure (AIM)

The AIM (Weiner et al., 2017) is a 4-item scale that measures the degree to which an intervention is perceived as agreeable, palatable, or satisfactory. The AIM will be presented with reference to "low dose psilocybin for moderate depression". Responses are made on a five-point scale (1 = *completely disagree* to 5 = *completely agree*). See Appendix 2.35.

6.1.10.3 Intervention Appropriateness Measure (IAM)

The IAM (Weiner et al., 2017) is a 4-item scale that measures the perceived fit, relevance, or compatibility of an intervention. The AIM will be presented with reference to "low dose psilocybin for moderate depression". Responses are made on a five-point scale (1 = *completely disagree* to 5 = *completely agree*). See Appendix 2.36.

6.1.10.4 Feasibility of Intervention Measure (FIM)

The FIM (Weiner et al., 2017) is a 4-item scale that measures the extent to which an intervention can be successfully used or carried out within. The AIM will be presented with reference to "low dose psilocybin for moderate depression". Responses are made on a five-point scale (1 = *completely disagree* to 5 = *completely agree*). See Appendix 2.37.

6.1.11 Neuroimaging Measures

6.1.11.1 Visual Long-term Potentiation

This paradigm (Teyler et al., 2005) acts as a non-invasive measure of long-term potentiation (LTP), a form of neural plasticity thought to be the principal mechanism underling long-term memory and

learning in the brain (Sumner et al., 2020). Specifically, the paradigm investigates activity dependent increases in synaptic activation following repeated neuronal co-activation. This process is measured by presenting participants with a series of vertical and horizontal sine gratings to the left and right visual fields at a low temporal frequency (~1Hz) both preceding and proceeding a high frequency (~9Hz) presentation of one of these two counterbalanced stimuli. After several blocks of this and a 30 minute break, participants are presented with a final block that reveals enduring changes in visual response (LTP).

6.1.11.2 Auditory Oddball

In this paradigm, participants are presented with sequences of repetitive auditory stimuli that are infrequently interrupted by a deviant stimulus. The reaction of the participant to this "oddball" stimulus is recorded. Detection of the oddball is recorded as an ERP (Squires et al., 1975), the amplitude and latency of which vary with the improbability of the oddball and the difficulty of discriminating the oddball respectively. This recording is indicative of the participant's attention and reaction to novelty.

6.1.11.3 Resting State Measurements

Resting state measurements are taken over 10 minutes, five of which the participant has their eyes open and five of which they have them closed. In doing so, we assess patterns of connectivity and power whilst the participant is not actively engaged in a task.

6.1.11.4 Novelty Attention Task (NAT)

The NAT (Vivanti et al., 2018) measures the fixation duration to a repeating and a novel stimulus presented side by side on a computer screen. In each trial, two strimuli appear simultaneously, one on the left and one on the right side of the computer screen. One stimulus is different on each trial (the novel stimulus), while the other remains unchanged across trials (the repeating stimulus). The stimuli comprise blocks of a) gemotetic shapes, b) clock faces, and c) human faces. No explicit direction is given. During observation, participants' eye-movements are recorded using an eye-tracking system and analysed using frame-by-frame predefined areas of interest: novel stimulus and repeating stimulus. The dependent variable is the rate of change (slope) of attention duration to the Novel and to the Repeating stimuli over trials (i.e., rate of habituation).

6.1.12 Biomarker Measures

Although there has been increasing scientific interest in the cognitive and psychological effects of microdosing psychedelics in recent years, we still do not know very much about the physiological effects of microdosing. Preliminary research indicates that a range of blood based biomarkers (i.e., proteins, enzymes and metabolites) may be sensitive indicators of the neurogenerative effects of serotonergic psychedelics. Blood samples collected will also be used to investigate the pharmacokinetics of psilocybin using liquid chromatography-mass spectrometry (LC/MS).
Blood samples will be collected from participants for the purposes of testing for a range of biomarkers of interest.

We will conduct the following tests:

- Typtophan metabolite analysis (Tryptophan, kynurenine, kynureninc acid, 3OH -Kynurenine, Anthranilic acid, Quinolonic acid, picolinic acid, neopterin, serotonin, melatonin) and NAD metabolites.
- Multiplex cytokine array – testing the following proteins: GM-CSF, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12(p70), IL-13, MCP-1, TNFα).
- Enzyme-Linked Immunosorbent Assay (ELISA) analysis of BDNF, GDNF, cortisol and c-reactive protein
- Genetic analyses of BDNF and kynurenine pathways.
- Analysis of psilocin, psilocybin, and psilocin-glucuronide levels in blood plasma.

The samples will be collected at the timepoints indicated in the schedule of assessments and will be stored in the Macquarie Neurogenerative Disease Biobank.

All the biomarker, genetic and pharmacokinetic tests above will be performed at Macquarie University with the exception of the multiplex cytokine array, which will be tested overseas at Eve Technologies in Calgary, Canada.

These samples will be stored indefinitely and will only be used for the purposes outlined in the study protocol.

Week 3B Biomarker blood samples to be collected 45min (+/- 10mins) post dose
In Week 1A of the Vanguard Phase, participants will provide samples at 8 timepoints: at 0, 15min, 30min, 45min, 60min, 120min, 180min, 240min post dosing (+/- 5mins). During this visit only, an IV canula will be inserted at the first blood draw timepoint. Analysis of Pharmacokinetics markers will be performed at Macquarie University by an unblinded scientist (AI

Heng). The results of this analysis will be kept securely until the end of the Vanguard phase of the project, and will be then provided to the study team in a blinded and anonymous format.

Throughout the study, Clinical Trial Coordinators will conduct vital measures (blood pressure, heart rate) each time a blood draw is taken for biomarker and pharmacokinetic samples.

6.1.13 Exploratory Measures

6.1.13.1 Core Flow State Scale (C-FSS)

The C-FSS (Martin & Jackson, 2008) is a measure developed from the Flow State Scale, a scale designed to measure the positive experiential state whereby a performer is totally connected to their performance (Jackson & Marsh, 1996). The C-FSS, by contrast, is a brief measure of flow that assesses the phenomenology of the experience itself. Thus, it captures the subjective expereince of flow rather than the factors that comprise or precipitate it. It is made up of 10items, to which respondents indicate their level of agreement on a 5-point Likert scale. The C-FSS displays good internal consistency (samples range from α = .83 to .9) and correlates strongly with the short FSS (r = .72) but with 48% of the variance unexplained, clearly measures a separate latent construct. See Appendix 2.38.

6.1.13.2 State Mindfulness Scale (SMS)

The SMS (Tanay & Bernstein, 2013) operationalises and measures state levels of mindfulness. It contains 21 items relating to mindfulness of mind and body with which participants indicate their agreement on a 5-point Likert scale. The authors report excellent internal consistency, construct validity and predictive validity. See Appendix 2.39.

6.1.13.3 Digit Symbol Substitution Test (DSST)

The DSST (Weschler, 1955) is a two-minute test to assess processing speed and working memory, often used as an indication of dementia, brain damage and depression. Participants match digits with corresponding symbols as fast as possible during the allotted time. The number of symbols matched correctly provides an individual's score on the test. It has previously been utilised to explore potential psychedelic-induced cognitive enhancement (de Wit et al., 2022). See Appendix 2.40.

6.1.13.4 Sustained Attention to Response Test (SART)

The SART (Robertson et al., 1997) is a go/no-go behavioural task designed as a replicable measure of lapses between automatic response production and executive control used to assess dysexecutive deficits. Participants view a random series of digits at a regular rate and must press a response key following each presentation with the exception of a previously nominated no-go digit. As 89% of presentations represent go digits lulls the respondent into a state of absentmindedness. The test indicates their ability to resist this state and retain attention by the number of correct no-go responses. 225 digits are presented in a continuous sequence over 4.3 minutes. Manly and Robertson (2005) maintain that while it may be better conceived as a test of inhibition control, the test has ecological and clinical validity and is reliable over retest in the short (one week) and long term (two years).

6.1.13.5 Autobiographical Memory Test (AMT)

The AMT (Williams & Broadbent, 2000) was developed following evidence that depressed individuals displayed reduced capacity for encoding and recall of autobiographical memory (OGM) specificities, termed overgeneral memory. The test assesses autobiographical memory specificity by providing cues designed to elicit memory recall. The participant generates a memory that fits the cue within an allotted time, generally 30 seconds, and it is assessed by the experimenter for specificity. Failure to replicate OGM in depressed patients is rare and possibly linked to hippocampal atrophy following chronic HPA axis activation. See Appendix 2.41.

6.1.13.6 Social Connectedness Scale (SCS)

The SCS (Lee & Robbins, 1995) measures the felt sense of belongingness, a unique construct constituted by companionship, affiliation and connectedness, distinct from related concepts such as attachment and social support. The SCS is composed of 8 items from all three aspects of belongingness, with which respondents indicate their level of agreement on a 6-point Likert scale. It has excellent internal consistency (α = .91) and 2-week test-retest reliability (.96). It has a small, but marginally significant correlation with the SAS. See Appendix 2.42.

6.1.13.7 Social Assurance Scale (SAS)

The SAS (Lee et al., 1995) is a companion scale to the SCS and measures the need for reassurance to maintain a sense of belongingness. It is also 8 items, consisting of 4 items each from companionship

and affiliation, with which respondents indicate agreement in the same manner as with the SCS. It has good internal consistency (α = .77) and 2-week test-retest reliability (.84). See Appendix 2.43.

6.1.13.8 Short Form Nature Relatedness Scale (NR-6)

The NR-6 (Nisbet & Zelenski, 2013) is a 6-item short form of the Nature Relatedness Scale (NRS; Nisbet et al., 2009), which measures *relatedness* to nature, a concept similar to the notion of ecological identity but broader in that it "encompasses emotions, experiences and understanding of human interconnectedness with all living things" (Nisbet et al., 2013). Thus is an assessment of nature connectedness rather than merely environmental attitudes. There are six items with which participants indicate agreement on a 5-point Likert scale. The NR-6 performs similarly to the 21-item NRS in terms of predictive validity, internal consistency, temporal stability and predicted happiness, environmental concern and nature contact. See Appendix 2.44.

6.1.13.9 Alternative Uses Test (AUT)

The AUT (Guildford, 1967) assesses divergent thinking and creativity. Participants are instructed to think of as many uses for a simple item as possible in two minutes. Responses are measured in four ways – fluency (number of alternative uses), originality (difference between uses), flexibility (assortment of uses) and elaboration (level of detail and development of uses).

6.1.13.10 Sense of Self Scale (SSS)

The Sense of Self Scale (Polito, 2021) assesses multiple domains of self representation (sense of agency, embodiment, and sense of presence) across various multisensory modalities (self experiences related to the body, self experiences related to thoughts, and self experiences related to events in the environment). The measure contains 33 items that load onto seven factors: Agency for Actions and Events, Agency for Thoughts, Expected Outcomes, Body Ownership, Thought Ownership, Interactional Fidelity, and Environmental Fidelity. Items are scored on a seven point Likert scale. See Appendix 2.45.

6.1.13.11 Expectancy Belief Questionnaire (EBQ)

These are investigator generated items describing various traits and states that align with the constructs tested by the measures employed by this trial. Participants will be asked at baseline whether they expect microdosing will influence their expression of a trait and then again at endpoint whether they believe it did influence their expression of that trait. Each item is rated on a VAS from -

50 to +50, where -50 indicates full confidence in a negative change, +50 indicates full confidence in a positive change and 0 indicates no effect. See Appendix 2.46.

7. Study Visits and Schedule

7.1 Study Visit Requirements

7.1.1 Participant Screening

7.1.1.1 Pre-Screening Period:

Participants may be referred to this study via a letter or email from their GP. Referrals should contain basic information such as patient name, date of birth, contact details, demographic information, substance use history and medical history. Upon receipt of information, the study delegate will distribute a link to REDCap, which will contain a pre-screening consent and questionnaire. Upon receipt of the completed pre-screening questionnaire, the study delegate will contact the participant to have preliminary discussions regarding their eligibility in this study.

7.1.1.2 Screening Period:

Participants passing the pre-screening stage will be invited to attend a tele-health or on-site screening visit. Informed Consent will be obtained using an Ethics Committee approved ICF as outlined in Section 11.2. The screening period is designed to obtain patient consent and determine patient eligibility for the study. The screening visit procedures will occur as per the schedule of assessments (Table 3) and all assessments completed within the 30 days prior to the baseline visit. All patients that sign an informed consent form will be entered into the electronic database (REDCap) and be assigned a subject ID. All assessments performed will be entered into the database.

A participant is considered enrolled in the study after meeting all eligibility criteria and being randomised.

Participants that have signed the informed consent form and do not meet the inclusion/exclusion criteria will be considered a screen failure. All assessments performed and the inclusion or exclusion criteria that was not met will be entered into the database. These participants will be directed to support services, where appropriate, including (but not limited to):

- Their GP or psychiatrist
- Their psychologist
- Local community mental health services
- The Suicide Call Back Service (https://www.suicidecallbackservice.org.au/; 1300 659 467)

- Local emergency mental health services such as:
    - Mental Health Line: 1800 011 511
- General mental health services such as:
    - Beyond Blue (https://www.beyondblue.org.au/; 1300 22 46 36);
    - Black Dog Institute (https://www.blackdoginstitute.org.au/);
    - Head to Health (https://headtohealth.gov.au/);
    - Lifeline (https://www.lifeline.org.au/; 131 114);
    - Mental Health Online (https://www.mentalhealthonline.org.au/);
    - MindSpot (https://mindspot.org.au/; 1800 61 44 34);
    - PANDA (Perinatal Anxiety & Depression Australia) (www.panda.org.au)

Recruitment and Screening for the Vanguard Stage and the Main Stage will not occur simultaneously. Recruitment will be paused upon enrolling the 25th participant into the Vanguard Study. The DSMB will review the results from the Vanguard Stage and provide advice on whether to proceed with the Main Stage.

The screening visit assessments may be conducted across a telehealth (psychiatric) and an in-person visit to provide flexibility and options for the participant and study team.

7.1.2 Re-Screening

Participants failing to meet inclusion criteria or meeting exclusion criteria may be re-screened after 6 months of their screen failure date. Participants may only be re-screened if the Principal Investigator, or qualified Study Delegate documents their justification as to why the participant may now meet the eligibility criteria. Participants may only be re-screened once.

7.1.3 Randomisation and Blinding to allocation

During the Vanguard and Main Stages, allocation of participants to active placebo or active cohorts will be performed in a separate REDCap database that is only accessible by the unblinded pharmacist, after participants have given their written informed consent, have completed the necessary screening assessments and confirmed to meet the eligibility criteria.

The eCRF REDCap database will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient. This identification number will then be provided to the unblinded pharmacist via email, to be used in the randomisation database.

Randomisation will occur after baseline measures are completed and participant is confirmed eligible. Study treatment in randomised cohorts must be initiated no later than 14 days after randomisation.

All other trial personnel, including the psychiatrist, physician, investigators, outcome assessors, clinical trials staff and statistician, will remain blinded throughout the participant's involvement in the trial. An unblinded pharmacist will dispense substances to a study delegate to maintain investigator blinding. Moreover, substances will be prepared in such a way as to be indistinguishable from each other to maintain double blinding.

To reduce the likelihood of unmasking, participants will be informed before receiving their first dose that the effects of microdosing can be subtle and are experienced differently and to different degrees by different people. Masking will be monitored by asking participants at each dose day to guess whether they have taken an active or active placebo dose.

Participants will receive a Participant Identification Card on or after the baseline visit if eligible. The Participants will be educated by the Principal Investigator or Study Delegate to carry this card with them at all times and present it to medical practitioners.

7.1.3.1 Sequence generation

Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer-generated randomisation schedule. Randomisation will be stratified by age and sex at birth. Upon enrolment and randomisation, the external health practitioners associated with the participant's involvement in the trial will be informed of their enrolment.

7.1.4 Study Treatment

Randomised participants will enter the study treatment phase. Participants will attend bi-weekly visits for 6 weeks. Visit requirements are outlined in the Schedule of Assessments (Table 3) and in Section [7.2].

7.1.4.1. WP001 and Caffeine Capsule Preparation, Administration and Compliance

Participants will be dosed on-site twice weekly for six weeks under observation by the Principal Investigator or study delegate. Refer to section 4.4 for more detail regarding labelling, packaging, storage, administration and return of investigational product. Participants will be required to undergo on-site observation for four hours after the first dose to observe any adverse drug reactions. Participants will be provided with meal vouchers for this session. The first dose shall be administered

in the Macquarie University Clinic Building, with easy access to the hospital in the event a significant adverse drug reaction occurs. If no significant adverse drug reaction occurs, subsequent doses will be administered in a designated non-clinic room. Doses will be administered at least 2 days, but no more than 5 days apart. A missed dose will need to be reported if this regime is not followed.

7.1.5 Follow Up

Upon completion of the end of treatment visit, participants will participate in two follow up visits. The follow up visits will be completed one week and one month after the participant's last dosing visit. Participants will also complete two online follow ups at three and six months after their last dosing visit. Follow up visit requirements are outlined in the Schedule of Assessments (Table 3) and in Section 7.2.

7.1.6 Retention

Once a participant is enrolled, investigators will make every reasonable effort to monitor the participant for the duration of the study. Research staff will take on the responsibility to respond to participant correspondence in a timely manner to ensure a sense of support and promote retention. Retention strategies include:

- Keeping the number of visits a participant must make to the study site to a minimum and utilising online data collection where possible to reduce participant burden.
- Providing a convenient and accessible study site and reimbursing participants for travel costs.
- Providing meal vouchers to participants on days where visitation is longer than 3 hours.
- Scheduling all appointments in advance with input from the participant following their screening and enrolment to facilitate planning ahead and incorporating the treatment schedule into weekly routines.
- Providing a comfortable and accepting atmosphere.
- Identification and tracking of AEs.

Participants will not be reimbursed for their time to avoid imposing financial pressure to participate in an experimental pharmacotherapeutic paradigm.

7.1.7 Exit Plan

At the conclusion of their involvement with the trial (either at completion or discontinuation), participants will be provided with an exit plan. This will summarise their participation in the clinical

trial, inform them of potential involvement in the open-label extension, and provide contact information for more information on the trial.

7.1.8 Neuroimaging Sub-Study

Participants that are enrolled in the vanguard or main stages and that meet the neuro-imaging sub-study eligibility criteria will be invited to take part in the sub-study. It's expected that 1 participant will be recruited per week into this sub-study however actual enrolment rate may differ. A maximum of 80 participants will take part in this sub-study. Should a participant decline, the next enrolled participant will be invited to take part.

Participants consenting to the sub-study will undergo a MEG scanning session at the timepoints indicated in the Schedule of Assessments. The MEG scans will identify neurophysiological changes related to state based effects of micro-dosing. Participant's brain activity will be measured during a resting state, after viewing a series of simple visual stimuli (visual LTP component) and after listening to a series of divergent auditory tones (novelty oddball component). The Sub-Study investigates multiple aspects of experience dependent and independent neuroplasticity. Specifically, the resting state measures identify broad changes in neural networks, the visual long-term potentiation component investigates activity dependant increases in synaptic activation following repeated neuronal co-activation; and the oddball component investigates changes in the mismatch negativity event related field to deviant stimuli.

7.1.9 Withdrawal and Discontinuation

A participant will be withdrawn from the study if they withdraw their consent to continue in the study. Participants who withdraw will no longer receive treatment from the study and will be asked to confirm whether they agree to continue with remaining study visits - in particular primary endpoint and followup vistits - or if they are withdrawing entirely.

Treatment discontinuation is considered as when participants stop receiving treatment for any reason and will be considered separate from withdrawal. Should participants discontinue from treatment they will proceed to the end of treatment visit and then the follow up visits.

Treatment discontinuation may occur if any of the following are met:

- Requested by the participant,
- by the investigator on behalf of the participant

- Decided by the investigator in the best interests of the participant or if the participant's safety is compromised
- one of the exclusion criteria above is identified or violated,
- any other condition emerges which is judged by the study team as likely to impact on the ability of the participant to complete the trial
- trial termination.

Decisions about withdrawing participants will be made with the advice of study clinicians.

If a participant withdraws from the study, the study team will write to the referring GP to inform them of the reasons for withdrawal. Participants withdrawing from the study will be referred to the support services listed in section 7.1.1

Any ongoing adverse events known at the time of withdrawal or discontinuation, will be managed as clinically appropriate and if the participant agrees, they will be followed up until the event has been resolved.

In the case where a participant is unable to be contacted and/or repeatedly does not attend visits, the study team will attempt to contact participant, at least 3 times, through all known contact details and each attempt will be documented.

7.1.10 Dose Modification

Participants will initially receive 4 capsules either 4 x 1mg psilocybin or 4 x 15mg caffeine. Following each dosing session, participants will complete a questionnaire rating their level of perceived drug effects and any perceived impairment across multiple domains (see *Microdosing Effects Rating Scale* in section 6.1.5.5). This questionnaire will be emailed to participants at the end of each dosing day and must be completed before the next study visit can commence. Any participant who a) nominates a preference for changing their dose, b) average score of >70 out 100 on the subjective effects subscale, or c) any score ≤ 3 out of 7 on the impairment subscale must be assessed by the study psychiatrist before any additional doses are administered. The psychiatrist will take in to account these reports of subjective experience and an objective measure of neurocognitive performance (the Trail Making Test, see section 6.1.5.1) when assessing each participant's dosing. Based on this assessment and the psychiatrist's clinical judgement, the psychiatrist may recommend titrating the dose down for the remainder of the study. For participants randomised to the active arm, the dose will be reduced to 2mg psilocybin for all subsequent doses, and for those randomised to the placebo arm, the dose will be reduced to 30mg caffeine.

7.2 Study Visit Assessments

Assessments at each visit are listed below.

Assessments marked with an asterisk are to be completed by the participant at home on the day of dosing. This will allow us to obtain retrospective reports of participant's' experiences during the period immediately following dosing. Participants who do not complete emailed assessments will be asked to retrospectively complete these at the start of their subsequent site visit.

Assessments marked with ^ may be administered by telehealth consultation. Telehealth sessions should be scheduled as close as possible to the corresponding study visit, however we allow ± 3 days flexibility.

7.2.1 Prescreening

1. History of antidepressant / antipsychotic medication
2. Pre-screening Questions
3. Patient Health Questionnaire (PHQ-15)
4. Alcohol Use Disorders Identification Test (short) (AUDIT-C)
5. Drug Use Disorders Identification Test (short) (DUDIT-C)
6. Questions about previous diagnoses

7.2.2 Screening

1. Formal consent
2. Medical and Mental Health History
3. Mini International Neuropsychiatric Interview (MINI)
4. Columbia Suicide Severity Rating Scale (C-SSRS)
5. GRID-HAMD
6. Short Profile of Mood States (POMS-SF)
7. ECG
8. Blood draw (safety / biomarkers)
9. Note: Screening may be separated into different visits to provide flexibility. 7.2.2 items 1 to 6 may be conducted via telehealth.

7.2.3 Baseline

1. Blood draw (safety / biomarkers)
2. Columbia Suicide Severity Rating Scale (C-SSRS) ^
3. GRID-HAMD ^
4. Short Depression Anxiety Stress Scale (DASS-21)
5. Sydney Melancholia Prototypic Index (SMPI)
6. The Alcohol Smoking and Substance Involvement Screening Test (ASSIST)
7. Sheehan Disability Scale (SDS)
8. Lost Workplace Productivity
9. Change in Healthcare Utilisation (HU)
10. Work and Social Adjustment Scale (WSAS)
11. EQ-5D
12. Edinburgh Mental Wellbeing Scale (WEMWBS)
13. Stanford Expectations of Treatment Scale (SETS)
14. Short Form Profile of Mood States (POMS-SF)
15. Brief Experiential Avoidance Questionnaire (BEAQ)
16. Modified Tellegen Absorption Scale (MODTAS)
17. Short Big Five Inventory (BFI-2-S)
18. Mind Wandering Questionnaire
19. Comprehensive Thinking Style Questionnaire (CTSQ)
20. Cognitive Flexibility Scale (CFS)
21. Conspiracy Mentality Scale
22. Cognitive Reflection Test (CRT)
23. Digit Symbol Substitution Test
24. Sustained Attention to Response Test
25. Social Connectedness Scale (SCS)
26. Social Assurance Scale (SAS)
27. Short Form Nature Relatedness Scale (NR-6)
28. Alternative Uses Test (AUT)
29. Sense of Self Scale (SSS)
30. Expectancy and Belief Questionnaire
31. Driving simulator
32. Phenomenological Control Scale (PCS)
33. Visual Longterm Potentiation [Neuroimaging sub-study only]

34. Auditory Oddball [Neuroimaging sub-study only]
35. Resting State[Neuroimaging sub-study only]
36. Novelty Attention Task [Neuroimaging sub-study only]

7.2.4 Week 1a (First dosing day)

1. Receive microdose/placebo
2. Columbia Suicide Severity Rating Scale – Brief
3. Microdosing Effects Rating Scale*
4. Drug Effects Questionnaire*
5. Psychotomimetic States Inventory (PSI)
6. Digit Symbol Substitution Test
7. Sustained Attention to Response Test
8. Autobiographical Memory Test
9. Social Connectedness Scale (SCS)*
10. Social Assurance Scale (SAS)*
11. Alternative Uses Test (AUT)
12. Sense of Self Scale (SSS)*
13. Pharmacokinetic blood draws at eight timepoints [Vanguard Stage only]
14. Drug Effects Questionnaire at eight timepoints [Vanguard Stage only]
15. Visual Longterm Potentiation [Neuroimaging sub-study only]
16. Auditory Oddball [Neuroimaging sub-study only]
17. Resting State [Neuroimaging sub-study only]
18. Novelty Attention Task [Neuroimaging sub-study only]

Note: Participants will undergo medical observation for a period of four hours following their first dose (see Section 10.5.2)

7.2.5 Week 1b

1. Report Adverse Events
2. Receive microdose/placebo
3. GRID-HAMD ^
4. Columbia Suicide Severity Rating Scale – Brief

5. Driving simulator
6. Trail Making Task
7. Microdosing Effects Rating Scale*
8. Drug Effects Questionnaire*
9. 11D-ASC*
10. Short Form Profile of Mood States (POMS-SF)*
11. Qualitative interview [Vanguard Stage only]

7.2.6 Week 2a, 3a, 4a and 5a

1. Report Adverse Events
2. Receive microdose/placebo,
3. Columbia Suicide Severity Rating Scale – Brief
4. Microdosing Effects Rating Scale*
5. Drug Effects Questionnaire*

7.2.7 Week 2b and 4b

1. Report Adverse Events
2. Receive microdose/placebo
3. GRID-HAMD ^
4. Columbia Suicide Severity Rating Scale – Brief
5. Trail Making Task
6. Microdosing Effects Rating Scale*
7. Drug Effects Questionnaire*
8. Core Flow State Scale*
9. State Mindfulness Scale (SMS)*
10. Short Form Profile of Mood States (POMS-SF)*

7.2.8 Week 3b

1. Report Adverse Events
2. Blood draw (safety / biomarkers)
3. Receive microdose/placebo

4. GRID-HAMD ^
5. Columbia Suicide Severity Rating Scale – Brief
6. Trail Making Task
7. Microdosing Effects Rating Scale*
8. Drug Effects Questionnaire*
9. Short Form Profile of Mood States (POMS-SF)*

7.2.9 Week 5b

1. Report Adverse Events
2. Receive microdose/placebo
3. GRID-HAMD ^
4. Columbia Suicide Severity Rating Scale – Brief
5. Driving simulator
6. Trail Making Task
7. Microdosing Effects Rating Scale*
8. Drug Effects Questionnaire*
9. 11D-ASC*
10. Short Form Profile of Mood States (POMS-SF)*

7.2.10 Week 6a

1. Report Adverse Events
2. Receive microdose/placebo
3. Columbia Suicide Severity Rating Scale – Brief
4. Microdosing Effects Rating Scale*
5. Drug Effects Questionnaire*
6. Psychotomimetic States Inventory (PSI)
7. Digit Symbol Substitution Test
8. Sustained Attention to Response Test
9. Autobiographical Memory Test
10. Sense of Self Scale (SSS)
11. Qualitative interview [Vanguard Stage only]

7.2.11 Week 6b (EoT)

1. Report Adverse Events of Special Interest
2. Blood draw (safety / biomarkers)
3. Columbia Suicide Severity Rating Scale (C-SSRS)
4. GRID-HAMD
5. Short Depression Anxiety Stress Scale
6. Sheehan Disability Scale (SDS)
7. The Alcohol Smoking and Substance Involvement Screening Test (ASSIST)
8. Lost Workplace Productivity
9. Change in Healthcare Utilisation (HU)
10. Work and Social Adjustment Scale (WSAS)
11. EQ-5D
12. Edinburgh Mental Wellbeing Scale (WEMWBS)
13. Acceptability of Intervention Measure (AIM)
14. Intervention Appropriateness Measure (IAM)
15. Feasibility of Intervention Measure (FIM)
16. Short Form Profile of Mood States (POMS-SF)
17. Brief Experiential Avoidance Questionnaire (BEAQ)
18. Phenomenological Control Scale (PCS)
19. Modified Tellegen Absorption Scale (MODTAS)
20. Short Big Five Inventory (BFI-2-S)
21. Mind Wandering Questionnaire
22. Comprehensive Thinking Style Questionnaire (CTSQ)
23. Cognitive Flexibility Scale (CFS)
24. Conspiracy Mentality Scale
25. Digit Symbol Substitution Test
26. Sustained Attention to Response Test
27. Social Connectedness Scale (SCS)
28. Social Assurance Scale (SAS)
29. Short Form Nature Relatedness Scale (NR-6)
30. Alternative Uses Test (AUT)
31. Sense of Self Scale (SSS)

32. Expectancy and Belief Questionnaire
33. Antidepressant Side Effect Checklist (ASEC)

7.2.12 1 week and 1 month follow up

1. Blood draw (safety / biomarkers)
2. Columbia Suicide Severity Rating Scale (C-SSRS) ^
3. GRID-HAMD ^
4. Short Depression Anxiety Stress Scale
5. The Alcohol Smoking and Substance Involvement Screening Test (ASSIST) (1M follow up only)
6. Sheehan Disability Scale (SDS)
7. Lost Workplace Productivity
8. Change in Healthcare Utilisation (HU) (1M follow up only)
9. Work and Social Adjustment Scale (WSAS)
10. EQ-5D
11. Edinburgh Mental Wellbeing Scale (WEMWBS)
12. Short Form Profile of Mood States (POMS-SF)
13. Brief Experiential Avoidance Questionnaire (BEAQ)
14. Modified Tellegen Absorption Scale (MODTAS)
15. Short Big Five Inventory (BFI-2-S)
16. Mind Wandering Questionnaire
17. Comprehensive Thinking Style Questionnaire (CTSQ)
18. Cognitive Flexibility Scale (CFS)
19. Conspiracy Mentality Scale
20. Digit Symbol Substitution Test
21. Sustained Attention to Response Test
22. Social Connectedness Scale (SCS)
23. Social Assurance Scale (SAS)
24. Short Form Nature Relatedness Scale (NR-6)
25. Alternative Uses Test (AUT)
26. Sense of Self Scale (SSS)

7.2.13 3 month and 6 month Follow up

1. Columbia Suicide Severity Rating Scale – Brief
2. Short Depression Anxiety Stress Scale
3. The Alcohol Smoking and Substance Involvement Screening Test (ASSIST)
4. Sheehan Disability Scale (SDS)
5. Lost Workplace Productivity
6. Change in Healthcare Utilisation (HU)
7. Work and Social Adjustment Scale (WSAS)
8. EQ-5D
9. Edinburgh Mental Wellbeing Scale (WEMWBS)
10. Modified Tellegen Absorption Scale (MODTAS)
11. Short Big Five Inventory (BFI-2-S)
12. Mind Wandering Questionnaire
13. Comprehensive Thinking Style Questionnaire (CTSQ)
14. Conspiracy Mentality Scale
15. Social Connectedness Scale (SCS)
16. Social Assurance Scale (SAS)
17. Short Form Nature Relatedness Scale (NR-6)
18. Sense of Self Scale (SSS)

7.3 Schedule of Assessments (SoA)

	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
Assessment / Measure Name	**PreScreening (SelfReport Questionnaire)**	**Screening (Psychiatric)** [2]	**Screening (Safety)** [2]	**Baseline**	**Wk 1A**	**Wk 1B**	**Wk 2A**	**Wk 2B**	**Wk 3A**	**Wk 3B**	**Wk 4A**	**Wk 4B**	**Wk 5A**	**Wk 5B**	**Wk 6A**	**Wk 6B**	**1Wk Follow Up**	**1M Follow Up**	**3M Follow Up**	**6M Follow Up**
Consent																				
Formal consent	X[1]	X																		
Medical History																				
Medical and Mental Health History		X																		
Medication History	X																			
Medical Assessments																				
Report AEs and SAEs / [5]					X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Report AESIs																X				
ECG			X																	
Blood Sample – Safety			X							X										
Blood Sample - Biomarkers				X	X[6]					X						X	X	X		
Pre-screening Questions	X																			

Assessment / Measure Name	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
	PreScreening (SelfReport Questionnaire)	Screening (Psychiatric) (2)	Screening (Safety) (2)	Baseline	Wk 1A	Wk 1B	Wk 2A	Wk 2B	Wk 3A	Wk 3B	Wk 4A	Wk 4B	Wk 5A	Wk 5B	Wk 6A	Wk 6B	1Wk Follow Up	1M Follow Up	3M Follow Up	6M Follow Up
Dosing																				
Receive dose (3, 4)					X	X	X	X	X	X	X	X	X	X	X					
Drug Absorption Waiting Time (30 mins) before continuing other assessments						X		X		X		X		X						
Psychopathology																				
Alcohol Use Disorders Identification Test (short)	X																			
Drug Use Disorders Identification Test (short)	X																			
Questions about previous diagnoses	X																			
Mini International Neuropsychiatric Interview		X																		
Columbia Suicide Severity Rating Scale		X		X												X	X	X		
Standardised Hamilton Depression Ratings Scale		X		X		X		X		X		X		X		X	X	X		
Sydney Melancholia Prototypic Index		X																		

Assessment / Measure Name	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
	PreScreening (SelfReport Questionnaire)	Screening (Psychiatric) (2)	Screening (Safety) (2)	Baseline	Wk 1A	Wk 1B	Wk 2A	Wk 2B	Wk 3A	Wk 3B	Wk 4A	Wk 4B	Wk 5A	Wk 5B	Wk 6A	Wk 6B	1Wk Follow Up	1M Follow Up	3M Follow Up	6M Follow Up
Columbia Suicide Severity Rating Scale - Brief					X	X	X	X	X	X	X	X	X	X	X				X	X
Depression, Anxiety, Stress Scale				X												X	X	X	X	X
Disability / Impairment Measures																				
Alcohol, Smoking and Substance Involvement				X												X		X	X	X
Driving simulator				X		X									X					
Trail Making Task						X		X		X		X			X					
Sheehan Disability Scale				X												X				
Lost Workplace Productivity				X												X	X	X	X	X
Change in Healthcare Utilisation				X												X		X	X	X
Work and Social Adjustment Scale				X												X	X	X	X	X
Antidepressant Side Effect Checklist (ASEC)																X				
Quality of Life																				
EQ-5D				X												X	X	X	X	X
Edinburgh Mental Wellbeing Scale				X												X	X	X	X	X

Assessment / Measure Name	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
	PreScreening (SelfReport Questionnaire)	Screening (Psychiatric) (2)	Screening (Safety) (2)	Baseline	Wk 1A	Wk 1B	Wk 2A	Wk 2B	Wk 3A	Wk 3B	Wk 4A	Wk 4B	Wk 5A	Wk 5B	Wk 6A	Wk 6B	1Wk Follow Up	1M Follow Up	3M Follow Up	6M Follow Up
Views on Treatment																				
Stanford Expectations of Treatment Scale				X																
Acceptability of Intervention Measure																X				
Intervention Appropriateness Measure																X				
Feasibility of Intervention Measure																X				
Expectancy and Belief Questionnaire				X												X				
Acute Effects																				
Microdosing Effects Rating Scale					X	X	X	X	X	X	X	X	X	X	X					
Drug Effects Questionnaire					X	X		X		X		X		X						
11D-ASC						X								X						
Core - Flow State Scale								X				X								
State Mindfulness Scale								X				X								
Psychotomimetic - States Inventory					X										X					
Affect																				

Assessment / Measure Name	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
	PreScreening (SelfReport Questionnaire)	Screening (Psychiatric) (2)	Screening (Safety) (2)	Baseline	Wk 1A	Wk 1B	Wk 2A	Wk 2B	Wk 3A	Wk 3B	Wk 4A	Wk 4B	Wk 5A	Wk 5B	Wk 6A	Wk 6B	1Wk Follow Up	1M Follow Up	3M Follow Up	6M Follow Up
Short Form Profile of Mood States		X		X		X		X		X		X		X		X	X	X		
Baseline Predictors - Traits																				
Brief Experiential Avoidance Questionnaire				X												X	X	X		
Phenomenological Control Scale				X												X				
Modified Tellegen Absorption Scale				X												X	X	X	X	X
Short Big Five Inventory				X												X	X	X	X	X
Mind Wandering Questionnaire				X												X	X	X	X	X
Baseline Predictors - Reasoning/Beliefs																				
Comprehensive Thinking Style Questionnaire				X												X	X	X	X	X
Cognitive Flexibility Scale				X												X	X	X		
Conspiracy Mentality Scale				X												X	X	X	X	X
Cognitive Reflection Test				X																

Assessment / Measure Name	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
	PreScreening (SelfReport Questionnaire)	Screening (Psychiatric) (2)	Screening (Safety) (2)	Baseline	Wk 1A	Wk 1B	Wk 2A	Wk 2B	Wk 3A	Wk 3B	Wk 4A	Wk 4B	Wk 5A	Wk 5B	Wk 6A	Wk 6B	1Wk Follow Up	1M Follow Up	3M Follow Up	6M Follow Up
Baseline Predictors - Pre-existing Cognitive Capacities																				
Digit Symbol Substitution Test				X	X										X	X	X	X		
Sustained Attention to Response Test				X	X										X	X	X	X		
Autobiographical Memory Test					X										X					
Social Cognition / Connection																				
Social Connectedness Scale				X	X											X	X	X	X	X
Social Assurance Scale				X	X											X	X	X	X	X
Short Form Nature Relatedness Scale				X												X	X	X	X	X
Cognitive Enhancement																				
Alternative Uses Test				X	X											X	X	X		
Multisensory Processing																				
Sense of Self Scale				X	X										X	X	X	X	X	X
Neuroimaging (substudy)																				
Visual Longterm Potentiation				X	X															

	Pre-Screening and Screening			Baseline	Treatment											EoT	Follow Up			
Assessment / Measure Name	**PreScreening (SelfReport Questionnaire)**	**Screening (Psychiatric)** (2)	**Screening (Safety)** (2)	**Baseline**	**Wk 1A**	**Wk 1B**	**Wk 2A**	**Wk 2B**	**Wk 3A**	**Wk 3B**	**Wk 4A**	**Wk 4B**	**Wk 5A**	**Wk 5B**	**Wk 6A**	**Wk 6B**	**1Wk Follow Up**	**1M Follow Up**	**3M Follow Up**	**6M Follow Up**
Auditory Oddball				X	X															
Resting State				X	X															
Novelty Attention Task				X	X															
Vanguard Stage only																				
Qualitative interview						X									X					
Blood Sample – Pharmacokinetics (+0 min, +15 min, +30min, +45min, +60 min, +120 min, +180 min, +240 min) (canula)					X															
Drug Effects Questionnaire (+0 min, +15 min, +30min, +45min, +60 min, +120 min, +180 min, +240 min)					X															

Footnotes
(1). Prescreening Consent
(2). Screening may be split across 2 visits
(3). Mandatory medical observation for 4 hours after first dose
(4). Doses must be at least 2 days apart, but no more than 5 days.
(5). AE and SAE reporting – Adverse events will be collected from the time of first dose of IMP until 30 days after the last dose. SAEs will be recorded from the time of informed consent.
(6) For Vanguard Phase participants only. Blood samples will be collected at timepoints post-dose +0 min, +15 min, +30min, +45min, +60 min, +120 min, +180 min, +240 min during visit 1A only.

8. Data collection, management, and analysis

8.1 Data collection

An electronic database (REDCAP) will be used to collect data in this study. The Chief Principal Investigator will be responsible for the data collected in this study and may delegate study staff members to enter the data into the electronic database.

8.2 Data Management

Data management protocols will be in place to protect trial data and the confidentiality and anonymity of participants. Only trial staff will have access to response data, demographic information or any other research document. Unique ID numbers will be utilised in REDCap. Databases will be password protected that are only accessible to trial staff. The system is secured by usernames and passwords. Any written documents will be kept in a lockable cabinet at Macquarie University.

Self-reported questionnaires will be entered directly into REDCap by the participant.

Participant personal and health information will be collected and stored in an electronic medical record system (eMR), called Odyssey eMR. Data and information stored in Odyssey will be kept indefinitely and forms part of the participant's health record.

Biomarker Blood samples will be processed by the Macquarie University Neurogenerative Disease Biobank and stored in an appropriate samples fridge at Macquarie University. Medical safety blood samples will be processed at the local pathology laboratory.

Biomarker blood samples will be labelled with participants' unique ID. Date of birth will be included on the label as a backup identifier in case the ID becomes illegible. Blood analysis results will be stored electronically in exclusively coded form.

REDCap will be used to enable collection, storage and maintenance of the research data for this study. REDCap is a secure application designed to support data capture for research studies and is secured according to approved security protocols which conform to electronic data standards. Data should be entered into database within 5 business days of data collection. Please refer to Section 10 for timelines of reporting safety events.

All materials will be kept for at least 15 years from completion of the trial, as per national requirements, and then disposed of by secure destruction methods such as shredding of paper data and overwriting/erasure of computer−stored data.

8.3 Data Analysis

The statistical analysis of the data obtained from this study will be the responsibility of AI Jones.

8.3.1 Sample size and Statistical Considerations

We aim to recruit 266 participants for this study. This will allow us to detect an effect size of .4 for the primary outcome variable GRID-HAMD, with statistical power 90% and statistical significance level .05 (two-tailed). We anticipate a drop-out rate of 10%. Although the analytic approach adopted for this study uses all available data for all enrolled patients, due to the possibility of fewer EOT measurements than expected our actual recruitment target is 293.

8.3.2 Analysis Populations

Modified Intention-to-Treat (mITT) – is defined as all randomised participants who received at one dose of the study treatment.

8.3.3 Analysis of the Primary Outcome

8.3.3.1 Analysis of Primary Outcome for Vanguard Stage

The primary outcome for the Vanguard study is safety of the investigational product and feasibility of the study. The analysis will be completed once 25 participants have completed the 1 month follow up visit. We note that this analysis does not test any study hypothesis and is conducted purely as an early evaluation and safety and feasibility.

8.3.3.2 Analysis of Primary Outcome for Main Stage

The primary statistical analysis involves the change in the primary outcome variable (GRID-HAMD Depression scores) between the baseline visit and the end of treatment (EOT) visit (Week 6B). A contrast of study groups will be made via linear mixed models estimated via maximum likelihood. The model will include the main effects of Visit and Study group and the interaction between them. The interaction term will be statistically tested as it is a direct estimate of the difference in change with

treatment between the active and placebo groups. This approach is known to be unbiased in the presence of missing values. Should the assumption of normality not be met, formal statistical inference will employ the nonparametric bootstrap.

8.3.3.3 Analysis of Primary Outcome for Open Label Extension Stage

The primary statistical analysis for this phase involves the change in the primary outcome variable (GRID-HAMD) between the baseline visit and the end of treatment (EOT) in the Main Stage for the group originally randomised to active treatment, and the change between the baseline visit and end of treatment (EOT) during the Open Label Extension stage for those randomised to the placebo group. In other words, this analysis will compare change in GRID-HAMD scores experienced by participants in the active intervention with the change in GRID-HAMD scores experienced by participants originally randomised to the placebo group during their second intervention, when they are also administered the active drug. Other elements of this analysis will be as 4.2.

8.3.4 Analysis of the Secondary Outcomes

Statistical analysis of quantitative outcomes will be as specified in 4.2. For qualitative outcomes measured on a binary scale, analysis will be via unconditional logistic regression in which the probability of the specified event will be modelled.

8.3.5 Analysis of Adverse Effects

The proportion of patients reporting any adverse event and specific events of a priori relevance will be compared between active and placebo study groups via unconditional logistic regression.

8.4 Data & Safety Monitoring Board (DSMB)

A DSMB will be organised and set up for the MicroDep-01 study. The DSMB Charter will detail the member listing and timelines. The project manager will follow up with the study team to ensure the completeness of the data.

8.5 Data Retention

Data that forms part of the participants health record and entered onto Odyssey eMR will be retained indefinitely. Study data and records collected will be kept for at least 15 years following the

completion of the trial as per Therapeutic Goods Administration (TGA). Following documented consent, participant data and information will be collected and stored up until the point that they withdraw from the study. Following withdrawal no new data will be collected for that participant however any data collected up until withdrawal will be retained for analysis.

9. Monitoring

9.1 Study Monitoring

The MicroDep-01 will be monitored as per the study monitoring plan to ensure compliance with ICH GCP.

The study monitors may review the following areas:

- Study team adherence to the protocol
- Data is being recorded appropriately and accurately in the eCRFs
- Study drug accountability
- Source data verification
- Study team is fulfilling their reporting requirements
- Appropriate safety management – documentation and reporting

10 Safety, Risk & Risk Management

10.1 Overall

The investigators and study team will adhere to the timelines and safety reporting requirements set out by Macquarie University HREC.

10.2 Definitions

10.2.1 Adverse Events (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events will be collected from the time of first dose of investigational product up until 30 days after the last dose of IMP. AEs must be reported in REDCap within 5 business days of notice.

An unexpected AE is one not listed in the current Investigator's Brochure or an event that is more specific or severe than a listed event.

All AEs will be monitored by investigators until resolution or, if the AE persists, a cause is identified. If unresolved by the end of the participant's involvement in the study, a decision will be made by the investigator and/or a study physician as to whether continued follow-up of the AE is necessary.

10.2.1.1 Adverse Events of Special Interest (AESI) associated with psilocybin

Common adverse events associated with psilocybin are listed below. These are of special interest in this clinical study. These are referred to as Adverse Events of Special Interest and will be reported in the eCRFs, as specified in the Assessment Schedule. A summary of all AESIs will be sent to the DSMB on a schedule set by the DSMB along with other safety events.

- Anxiety
- Confusion
- Paranoia
- Psychotic phenomena
- Dizziness
- Nausea
- Abdominal pain
- Tremors
- Loss of appetite
- Muscle aches or weakness
- Restlessness
- Sleep disturbances
- Coordination impairments
- Working memory impairments
- Headache
- Physical discomfort ("body load")

In addition, investigators will monitor for suicidal ideation and thoughts of self-harm, which are not adverse effects associated with psilocybin but are of special interest to the research team.

10.2.1.2 Expected Adverse Events associated with caffeine

Participants in the placebo condition will consume either 60mg or 30mg of caffeine.

The United States Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) have determined that daily intake of up to 400 mg of caffeine is safe for adults (EFSA NDA panel, 2015). Adverse effects that have been associated with caffeine are listed below:

- Restlessness and shakiness
- Insomnia
- Headache
- Dizziness
- Increased blood pressure
- Dehydration
- Anxiety

10.2.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any untoward occurrence that results in:

- Suicide attempt
- Death
- A life-threatening situation (participant is at immediate risk of death)
- Inpatient hospitalisation or prolongation of existing hospitalisation (excluding those for study therapy, or placement of an indwelling catheter, unless associated with other SAEs)
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect in the offspring of a participant who received treatment medication
- Any medically significant event that may not be immediately life-threatening or result in death or hospitalisation but based upon appropriate medical and scientific judgment may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs will be reported from the time of informed consent and until the participant completes the 1 month follow up visit. SAEs must be reported via REDCap within 24 hours of notice. SAEs will not be collected during the optional long-term follow up period.

10.3 Reporting

Safety events will be reported as per institutional and regulatory requirements. Adverse events information will be collected and recorded from the time of first dose. Serious adverse events will be collected and recorded from the time of informed consent.

10.4 Assessment

10.4.1 Severity

The severity of events reported will be classed by the investigator as:

- Mild – no limitation in normal daily activity
- Moderate – some limitation in normal 85daily activity
- Severe – prevention of normal daily activity

10.4.1 Relationship (Causality)

The relationship of the study treatment to an AE will be determined by the principal investigators based on the following definitions:

1. Not Related

The AE is not related if:

- exposure to the treatment has not occurred; or
- its occurrence is not reasonably temporally related; or
- there is no evidence or reasonable argument to suggest a causal relationship between the two; or
- it is more likely to be related to the participant's pre-existing condition

2. Possibly Related

Treatment administration and AE occurrence are reasonably temporally related, and the AE could be explained by causes other than treatment exposure.

3. Probably Related

Treatment administration and AE occurrence are reasonably temporally related, and the treatment is more likely than other causes to be responsible for the AE, or is the most likely cause.

10.5 Safety and Clinical Monitoring

Serotoninergic psychedelics, including psilocybin, have a very low psychopharmacological risk profile, do not lead to addiction or dependency, and are not known to be associated with any long term health deficits (for a review see Nichols, 2016). Recent evidence has even indicated that psychedelic use is associated with reduced psychological distress and suicidality across the lifespan (Hendricks, Johnson, et al., 2015). Nevertheless, some individuals do report psychologically challenging experiences after taking psilocybin and this is more likely for people with mental health conditions (Carbonaro et al., 2016). We note that the doses in this study are dramatically lower than a typical hallucinogenic dose (i.e., a typical clinical dose in a psilocybin study is approximately 25-30mg), and that the subjective experience of microdosing is vastly different from the experience of standard dose psychedelics. It is reasonable to expect that microdosing is significantly safer than dosing with higher doses of psychedelics. A detailed investigation of microdosing safety found no increase in adverse events compared to placebo, no impairments, and no indicators of risk (Family et al., 2020). However, one potential hazard that may be associated with microdosing that is not as apparent with higher dose psychedelic use is that microdosers tend to ingest small doses relatively frequently (whereas most users of high dose psychedelics only consume these substances occasionally). Kuypers et al. (2019) discussed the potential impact of repeated doses of psilocybin on cardiovascular health but concluded that the risks are minimal. Moreover, there is no evidence for repeated doses of psilocybin inducing cases of addiction or dependence (Ross et al., 2020). This is likely due to the nature of its subjective effects and its lack of interference with the mesolimbic reward pathway.

Nevertheless, a critical aspect of this trial will be our comprehensive safety and clinical monitoring protocols. There are four key components of our clinical monitoring plan: 1) a detailed participant screening protocol, 2) comprehensive monitoring and observation following the first dosing session; 3) safety monitoring during the intervention; and 4) our adverse events protocol. Adherence to these protocols and general safety monitoring will be governed by a Data Safety Monitoring Board.

10.5.1 Participant Screening Protocol

The eligibility criteria for this study will exclude any individual with psychological or physiological characteristics that may be contraindications for the use of psychedelics. In particular, we will exclude individuals currently using any psychoactive substances that may have a serotonergic effect; individuals with mental illness profiles that may increase general or specific risks associated with

either ingestion of psychedelic substances or participation in a relatively demanding trial; individuals at risk of self harm or suicide; individuals with indications of poor physical health; and individuals with any moderate to severe comorbidities likely to interfere with completion of the trial. All potential participants will undergo a through multi-step screening process to ensure that these criteria are closely adhered to (as described in Section 5.1).

10.5.2 Monitoring and Observation of the First Dosing Session

In order to respond to any adverse reaction following an individual's first microdose of psilocybin we will monitor participants for four hours on their first dosing day. Monitoring will take place in the clinic rooms at 2 Technology Place. Participants will be monitored by staff from the Clinical Trials Unit who have been trained to identify and respond to any adverse reactions. The study psychiatrist (AI Shannon) will have close oversight of all initial dosing sessions and will be on call to respond to any mental health concerns. Any medical concerns will be escalated to clinician investigators according to the procedure outlined below (see Section 10.5.3.1*).* If additional escalation is required during monitoring sessions, Macquarie University Hospital clinicians can provide support to participants at this location. If any participant shows signs of discomfort during the initial dosing session, the study psychiatrist may specify additional monitoring on subsequent dosing sessions.

10.5.3 Safety Monitoring During the Intervention

As a standard part of our protocol, we will assess cardiac health using electrocardiogram, blood pressure, and heart rate during the baseline, endpoint, and follow-up sessions. In addition, participants will attend the university for a dosing session twice a week during the intervention period. Participants will be provided a wallet card with contact information for the Macquarie University switchboard in case of any distress or discomfort during the study. This service will be able to connect a participant with a psychiatrist, clinician or alternate service provider as appropriate. This emergency number will also be able to contact study staff to unblind a participant if required.

For maximum safety, participants will be provided with Uber or taxi vouchers to cover transport to and from all dosing sessions. Before dosing, each participant will have a brief assessment by a Clinical Trials Coordinator to probe for any Adverse Events that may have since the previous dose. Participants must also provide a report on subjective effects and impairment experienced during the previous dosing session before any additional doses are administered (see 6.1.5.5). The Clinical Trials

Coordinator will escalate any concerns to the study psychiatrist who will advise whether additional action is needed. Before each dosing session participants will also complete a shortened form of the Columbia Suicide Severity Rating Scale to specifically assess any risk of self-harm. Any score increase from the previous visit will result in the participant's immediate referral to the study psychiatrist and the participant will not be administered any further doses until psychiatric consultation. Finally, at all times during the study, a medical officer or psychiatrist will be on call to respond to any Adverse Events, Adverse Reactions, or other concerns that arise during any testing sessions.

10.5.3.1 Responding to Adverse Events

We have a number of mitigation procedures available to respond in a timely way to any adverse events. First, the study psychiatrist AI Shannon, will be onsite during most participant testing sessions and will be available to provide acute assessment and care as required. On occasions when AI Shannon is not available, medical support will be provided by AI Shaheen who is a GP based in Macquarie University Hospital. In addition to these on-site support staff, our clinical expert PIs (Brett and Bayes) will be available for tele-health consultation if appropriate. If emergency psychiatric support is required AI Samuels, a senior psychiatrist, is able to see study participants by tele-health or in person at his St Leonards rooms. As a final option, in a medical emergency participants will be transferred to the Emergency Department of Ryde Hospital (11 minute drive), facilitated by an Investigator or study staff member. Hospital transfers are extremely unlikely and have not been reported across the thousands of psilocybin dosing sessions documented in the literature. Any participant hospitalised after a severe adverse psychological or physiological reaction will be withdrawn from the protocol. Trial staff will arrange support for the participant, drawing on their existing healthcare team where appropriate.

Reporting and management of all Adverse Events (AE) will follow NHMRC Guidelines (National Health and Medical Research Council, 2016).

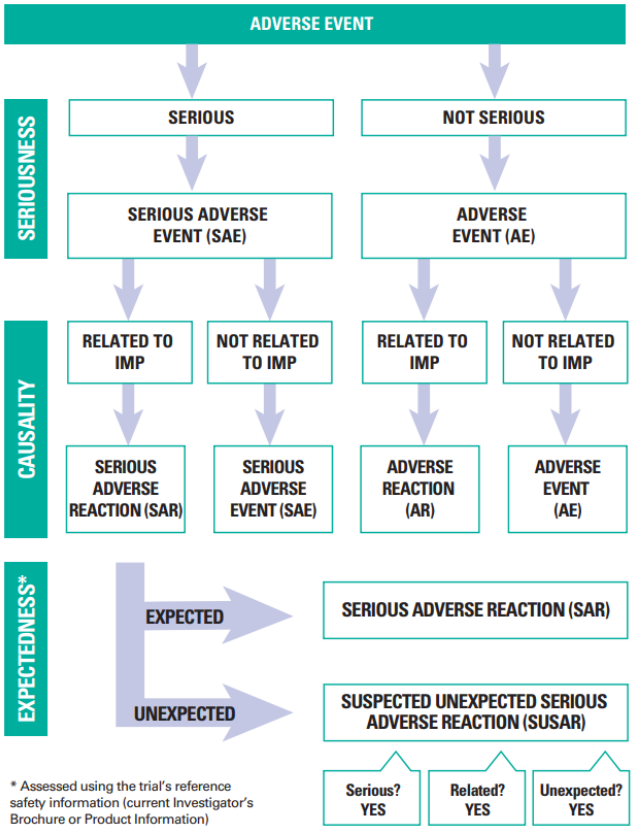


Figure 2: NHMRC Safety Reporting Assessment Flowchart for Investigational Medicinal Products

Specifically, all AEs will be logged and evaluated for seriousness, causality and expectedness. AEs may be identified through reporting during study visits (described in the previous section) or through trial participants independently making contact with a member of the research team. Participants will undergo a detailed safety briefing upon enrolment in the study and will be given contact information allowing them to email or call study staff for any medical or psychological concerns related to the study. All AEs will be referred to the Chief Principal Investigator who will consult with appropriate CIs depending on the nature of the issue (PI Brett for medical issues and PI Bayes for psychiatric issues). These investigators will determine the appropriate course of action, which may include providing additional medical or psychological support. All SAEs (including Suspected and Unexpected Serious Adverse Reactions, and any significant safety issues) will be reported to the TGA, Woke Pharmaceuticals and HREC within the timeframes required by NHMRC (National Health and Medical Research Council, 2016).

11. Ethics and Dissemination

11.1 Research Ethics Approval

This protocol, the consent forms, any information to be given to the patient, and relevant supporting information will be submitted to the HREC for review and approval before the study is initiated and recruiting.

The Chief Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the HREC. Investigators are also responsible for promptly informing and seeking approval from the HREC of any protocol amendments before the changes can be implemented except for changes necessary to eliminate an immediate risk/hazard to participants or changes that are administrative in nature.

Investigators will comply with the requirements for reporting safety events to the HREC and the local health authority, Therapeutic Goods Administration (TGA).

11.2 Essential Documents

Investigators will retain all study records required by Macquarie University Human Research Ethics Committee (HREC), and applicable International Conference on Harmonisation, Good Clinical Practice and local regulations in a secure manner. Essential documents are documents individually and collectively permitting evaluation of a trial's conduct and the quality of data thereby produced. Such documents will be filed according to the stated bodies' regulations in the Investigator Site File.

Essential documents include for our purposes:

- HREC-approved trial protocol and documents
- HREC-approved PICF
- Communications with the HREC
- Copies of signed PICFs
- Regulatory approvals
- Delegation of Duties log
- Safety reports

11.3 Confidentiality

This study will be conducted in compliance with the Privacy Act 1988, ICH-GCP and the National statement as well as other relevant legislation and guidelines.

The participant's identity will be protected; confidentiality will be maintained through the assignment of a unique code to each participant in addition to limiting direct access to participant records, to authorised individuals.

11.4 Declaration of Interests

It is expected that all investigators and any other pertinent personnel involved in the management and oversight of the MicroDep-01 trial will disclose any actual, potential or perceived conflicts between their role within the MicroDep-01 trial and their private or non-study interests as they arise in line with the *Australian Code for the Responsible Conduct of Research* and *National Statement on Ethical Conduct in Human Research*. Any conflict of interest that arises will be openly and completely disclosed to the Institution, ethics committee, governance and to any other group as appropriate.

Conflicts of interest includes both pecuniary (financial loss or gain) and non-pecuniary interests, which may be perceived as having, or possibly have the potential to impact the person's ability to act fairly and impartially in decision-making processes or influence the performance of their research involvement in the study.

Presence of competing interests and/or conflicts of interest do not in themselves imply improper motivation or wrongdoing. After any conflicts of interest are identified, it will be managed as needed with appropriate measures.

11.5 Access to data

Woke Pharmaceuticals may request a de-identified copy of any study data.

Deidentified study data may be published in a scientific repository to facilitate open science.

11.6 Ancillary and post-trial care

The study drugs will not be available at the end of the study. The study drugs will only be available to participants if they meet the eligibility criteria and are enrolled in the study. Participants and their healthcare practitioners will be responsible for their ongoing management.

11.7 Dissemination Policy

11.7.1 Publication Plan

Regardless of the outcome of a trial, the CPI and PIs are dedicated to publishing and disseminating the results of this study. Authorship will be determined by mutual agreement between CPI and PIs who will be jointly responsible for preparing, reviewing and approving any publications and presentations arising from the Microdep-01 study.

At a minimum, a report will be published online on the Open Science Framework. A summary of the results, in non-technical language, will be made be made available to participants and may be discussed in person or via phone/telehealth with participants.

11.7.2 Authorship Criteria

Authorship is to be designated in accordance with the International Committee of Medical Editors recommendations for authorship criteria. Whether an individual is recognised as an author or a non-author contributor will be based on conception or design of the work, data collection, data analysis and interpretation, drafting and critical revision of the article, and final approval of the version to be published.

12. List of Appendices

1. Study Team – Roles and Responsibilities
2. Study Measures (separate document)
3. References

13. List of Tables

Appendix 1: Study Team – Roles and Responsibilities

The interdisciplinary team has expertise in human psychedelic research, clinical trials, toxicology, biomarkers, psychiatry, neuroimaging, statistics, and data management. Investigators on this trial include several of the most experienced psychedelic researchers within Australia, leading clinicians, and prominent senior scientists. Together we have the skills, experience, and capacity to successfully implement this project plan. If our results are consistent with preliminary lab-based, and self-report studies, this world-first clinical trial may provide important new opportunities for the safe and effective treatment of mood disorders.

Name	Title	Location/Institution	Role/Responsibilities
Vince Polito	Dr	Macquarie University	Chief Principal Investigator
Jonathan Brett	Dr	St Vincents Hospital / UNSW	Principal Investigator – Medical
Adam Bayes	Dr	Black Dog Institute / UNSW	Principal Investigator -
Paul Liknaitzky	Dr	Monash University	Principal Investigator
Richard Stevenson	Prof	Macquarie University	Principal Investigator
Anthony Rodgers	Prof	UNSW	Principal Investigator
Joanne Shannon	Dr	Macquarie University	Principal Investigator - Psychiatrist
Ranil Gunewardene	Dr	Northern Beaches Hospital / Macquarie University	Principal Investigator
Mike Jones	Prof	Macquarie University	Associate Investigator - Statistician
Melissa Kang	Assoc Prof	Sydney Medical School	Associate Investigator
Phoebe Holden Kimura	Dr	University of Sydney / Black Dog Institute	Associate Investigator
Paul Sowman	Prof	Macquarie University	Associate Investigator
Nargis Shaheen	Dr	Macquarie University	Associate Investigator
Karen Wells	Ms	University of Sydney	Associate Investigator
Luke Downey	Prof	Swinburne University	Associate Investigator
Owen Samuels	Dr	Ramsay Health	Associate Investigator
Benjamin Heng	Dr	Macquarie University	Associate Investigator
Oscar Nagy	Mr	Macquarie University	Research Officer

Eamon Brown	Mr	Macquarie University	Project Manager
María Alvarado	Dr	Northern Beaches Hospital	Psychiatry Registrar
Timothy Stuckey	Dr	Northern Beaches Hospital	Psychiatry Registrar
Puneet Nanda	Dr	Northern Beaches Hospital	Psychiatry Registrar

Dr Vince Polito (Co-ordinating Principal Investigator) is a Senior Research Fellow in the School of Psychological Sciences and a member of the Biomolecular Discovery Research Centre. He has expertise in cognitive neuropsychiatry, self representation, psychometrics and altered states of consciousness. Dr Polito is a leading expert on microdosing psychedelics. He conducted the first observational longitudinal study of microdosing beginning in 2017 and this research is currently the most cited study on low dose psychedelics (Polito & Stevenson, 2019). Dr Polito is currently conducting the first MEG study of microdosing and is also an Associate Investigator on two Australian trials involving high dose psychedelics. As Chief PI, Vince will have responsibility for the oversight and conduct of the MicroDep-01 study.

Dr Jonathan Brett (Clinical Lead; St Vincents Hospital Sydney / UNSW) is a clinical toxicologist and addiction specialist working for St. Vincent's Hospital, Sydney, clinical director of the Psychiatry and Non-Prescription Drug and Alcohol Unit and a clinical toxicologist for the NSW Poison's Information Centre. He has fellowships with the Royal Australian College of Physicians in clinical pharmacology, toxicology and addiction medicine. He is a Conjoint Associate Professor with St. Vincent's Clinical School and a senior NHMRC Research Fellow at UNSW. He is an editor for the Internal Medicine Journal and sits on the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee. He is the principal investigator on the world's first study of psilocybin-facilitated psychotherapy for methamphetamine use disorder. As Principal Investigator-Medical, Dr Brett be responsible for making decisions to medical suitability of potential participants and participants as well as assessing all adverse events and drug reactions.

Dr Adam Bayes (Black Dog Institute) is a clinical academic psychiatrist with a special interest in mood disorders (depressive and bipolar conditions) including their diagnosis, classification and treatment – with the latter focusing on interventional psychiatry (e.g. rapidly acting antidepressants) and novel neurostimulation (transcranial magnetic stimulation; TMS). Dr Bayes works at the interface of research and clinical application, and has an interest in developing models of care, most recently

establishing the BDI Ketamine Treatment Program which arose out of a clinical trial. Dr Bayes will sit on the trial steering committee and advise on psychiatric aspects of trial design.

Dr Paul Liknaitzky (Monash) is a joint Research Fellow within the Turner Institute (School of Psychological Sciences) and the Dept of Psychiatry (School of Clinical Sciences) at Monash University, and is Head of the Clinical Psychedelic Research Lab. He is the Principal Investigator on a program of psychedelic trials, coordinates Australia's first applied psychedelic therapist training programs, and has obtained the first industry funding and partnership for psychedelics in Australia. Dr Liknaitzky will guide the design and implementation of the study protocol.

Professor Richard Stevenson is an expert in experimental design, hallucinations, imagery and expectation. He will guide overall trial design and selection of psychological measures. He has nearly 30 years' experience as an experimental psychologist, has held 16 research grants from the Australian Research Council, and published over 230 scientific papers, chapters and books. He worked with PI Polito on one of the first studies of microdosing, assisting with research ethics (he has served on multiple ethics committees in senior roles) and in the design of the expectancy bias part of this study. He is currently involved in several other clinical trials relating to depression and low mood. Professor Stevenson will guide the design and implementation of the study protocol.

Professor Anthony Rodgers (UNSW) is a clinical trials expert, with an interest in scale-able interventions to address major risks to health. He is currently Acting Director of the Cardiovascular Division at The George Institute, Australia and Chair of Clinical Epidemiology, Faculty of Medicine, Imperial College of London. He will provide guidance on successful implementation of the planned clinical trial. Professor Rodgers will guide the design and implementation of the study protocol.

Dr Joanne Shannon is a psychiatrist specialising in bipolar and unipolar depression, anxiety, schizophrenia and trauma. She trained at the University of Sydney before practising at St George's Hospital, Kogarah; St Vincent's Hospital, Darlinghurst and the Richmond Clinic, Lismore. She has also worked for the Justice Health & Forensic Mental Health Network, which provides healthcare to vulnerable individuals in contact with criminal justice systems. Her practice uses both traditional and novel therapeutic approaches to treating psychopathology. Dr Shannon will be the study psychiatrist for this trial. She will be responsible for screening participants and clinical monitoring.

Professor Mike Jones trained as a biostatistician and has worked in epidemiology and health psychology for over thirty years in a variety of settings including universities, research institutions and in industry. Mike has focussed on the epidemiology of functional gastrointestinal disorders (FGIDs) and functional somatic syndromes for over 30 years. His current interests in FGID epidemiology include understanding the mechanism of their association with psychological conditions and disorders. Recent papers include those studying potential causal psychological pathways in FGIDs and how cognitive behaviour therapy operates on gastrointestinal symptoms. His previous work in the area of gastroenterology is wide ranging across epidemiological and clinical as well as experimental studies. This work has incorporated the effects of acute and chronic stress on symptoms and gut physiology, determinants of health care seeking behaviour and connections between gastrointestinal symptoms and other health conditions. Professor Jones is the statistician for this trial.

Associate Professor Melissa Kang is Associate Professor in the Specialty of General Practice at the Sydney Medical School. She has an interest in adolescent and young adult health and sexual health, particularly in improving the interactions and engagement between young people and the health system. She teaches into the Sydney Medical School MD program in the community term and contributes to the child and adolescent and perinatal and women's curricula. She regularly teachers GP registrars in consultation skills with adolescents. She has been research supervisor for several academic GP registrars and Higher Degree by Research students. Her research into access to health services for young people spans over 20 years and has contributed to policy and practice in Australia. She is an Associate Editor for Family Practice OUP. Associate Professor Kang will assist in developing partnerships with primary care providers.

Dr Phoebe Holdenson Kimura is a GP with a special interest in Mental Health. She is a lecturer at the University of Sydney and works as a consultant with the Black Dog Institute for the e-Mental Health in Practice Program. Associate Professor Kang will assist in developing partnerships with primary care providers.

Professor Paul Sowman is Associate Professor of Cognitive Science and Director of Research in the School of Psychological Sciences at Macquarie University. As Co-Director of the MQ node of the

Australian National Imaging Facility (NIF) he is involved in facilitating interdisciplinary neuroimaging collaborations and developing novel neuroimaging methodologies. Paul trained as a Physiotherapist at Otago University and later graduated with a PhD in Physiology from the University of Adelaide. He subsequently held fellowships with the NHMRC and ARC in the area of speech motor neuroscience. His research uses magnetoencephalography (MEG) and non-invasive brain stimulation methods to understand neural processes underpinning normal and abnormal cognitive development. Professor Sowman will guide the design and implantation of the neuroimaging sub-study.

Dr Nargis Shaheen is a Geriatrician with an interest in acute general medicine, slow stream rehabilitation and peri-operative care. She trained at Concord, Royal Prince Alfred and completed her final year of training at Royal North Shore Hospital. She has worked as a rapid response registrar and worked extensively with GP's in the Hunter's Hill area. She is currently appointed as a staff specialist at Concord Hospital, VMO at Macquarie University Hospital, Mosman Private Hospital and Hunters Hill Private Hospital. She is a member of Royal Australian College of Physicians and the Australia and New Zealand Society for Geriatric Medicine. Dr Shaheen will provide clinical support to the trial.

Ms Karen Wells is a PhD candidate at the University of Sydney, investigating the experiences of individuals receiving non traditional health treatments. She is also a consumer advocate for people with mental illness. Ms Wells will contribute to developing a lived experience advisory panel to advise this project. Ms Wells will assist in developing partnerships with mental health service consumers.

Professor Luke Downey leads the Drugs and Driving Research Unit at Swinburne University examining psychopharmacology. He also conducts research in emotional intelligence and has developed tools for its effect measurement, which have been used to predict longitudinal outcomes. Professor Downey will guide the design and implementation of driving impairment measures.

Dr Owen Samuels is a psychiatrist trained in both general and forensic psychiatry. Alongside clinical practice, he carries out medico-legal assessment for both criminal civil matters. He is a Fellow of the Royal Australian and New Zealand College of Psychiatrists and is also accredited by the College as a Forensic Psychiatrist. In addition to private psychiatric practice, he is a Senior Staff Specialist and the

Clinical Director for the Northern Sydney Local Health District, providing clinical leadership to services at Royal North Shore, Ryde, Manly and Hornsby Hospitals. Dr Samuels will provide psychiatric support for the trial.

Dr Benjamin Heng is a post-doctoral researcher in the Centre for Motor Neuron Disease Research, within Macquarie Medical School. He has expertise in blood based biomarkers and pharmacokinetic analysis.

Dr Ranil Gunewardene is a clinical associate professor in Macquarie University School of Medicine. Alongside this, he set up and has been the Director of Mental Health Services at Northern Beaches Hospital since its inception in 2018. He has psychiatric expertise and will provide clinical guidance for the project as well as emergency psychiatric support for patients.

Mr Oscar Nagy is a psychology graduate with experience in psychopharmacology and with clinical populations who will act as the research officer for this project. Mr Nagy will assist with research administration of the trial.

Dr María Alvarado is a psychiatry registrar based at Northern Beaches Hospital. Ms Alvarado will aid in administering clinical measures.

Dr Timothy Stuckey is a psychiatry registrar based at Northern Beaches Hospital. Dr Stuckey will aid in administering clinical measures.

Dr Puneet Nanda is a psychiatry registrar based at Northern Beaches Hospital. Dr Nanda will aid in administering clinical measures.

Appendix 2: Study Measures

(Included in a separate document, MicroDep-01 Protocol Appendix 2 v3.3, 04-06-2024)

Appendix 3: References

Aghajanian, G. K. (2009). Modeling “psychosis” in vitro by inducing disordered neuronal network activity in cortical brain slices. *Psychopharmacology*, *206*(4), 575–585. https://doi.org/10.1007/s00213-009-1484-9

Allen, J. P., Litten, R. Z., Fertig, J. B., & Babor, T. (1997). A review of research on the Alcohol Use Disorders Identification Test (AUDIT). *Alcoholism, Clinical and Experimental Research*, *21*(4), 613–619.

Amsterdam, J. van, Opperhuizen, A., & Brink, W. van den. (2011). Harm potential of magic mushroom use: A review. *Regulatory Toxicology and Pharmacology*, *59*(3), 423–429. https://doi.org/10.1016/j.yrtph.2011.01.006

Arbuckle, R., Frye, M. A., Brecher, M., Paulsson, B., Rajagopalan, K., Palmer, S., & Degl’ Innocenti, A. (2009). The psychometric validation of the Sheehan Disability Scale (SDS) in patients with bipolar disorder. *Psychiatry Research*, *165*(1–2), 163–174. https://doi.org/10.1016/j.psychres.2007.11.018

Bachmann, S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. *International Journal of Environmental Research and Public Health*, *15*(7), 1425. https://doi.org/10.3390/ijerph15071425

Badia, X., Roset, M., Herdman, M., & Kind, P. (2001). A Comparison of United Kingdom and Spanish General Population Time Trade-off Values for EQ-5D Health States. *Medical Decision Making*, *21*(1), 7–16. https://doi.org/10.1177/0272989X0102100102

Berman, A. H., Bergman, H., Palmstierna, T., & Schlyter, F. (2005). Evaluation of the Drug Use Disorders Identification Test (DUDIT) in Criminal Justice and Detoxification Settings and in a Swedish Population Sample. *European Addiction Research*, *11*(1), 22–31. https://doi.org/10.1159/000081413

Bershad, A., Preller, K., Lee, R., Keedy, S., Wren-Jarvis, J., Bremmer, M., & de Wit, H. (2020). Preliminary Report on the Effects of a Low Dose of LSD on Resting-State Amygdala Functional Connectivity. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *5*(4), 461–467. https://doi.org/10.1016/j.bpsc.2019.12.007

Bershad A., Schepers S., Bremmer M., & de Wit H. (2019). Subjective and Behavioral Effects of Microdoses of LSD in Healthy Human Volunteers. *Biological Psychiatry*, *85*(10), S345. https://doi.org/10.1016/j.biopsych.2019.03.876

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology*, *29*(3), 289–299. https://doi.org/10.1177/0269881114565144

Bonomo, Y., Norman, A., Biondo, S., Bruno, R., Daglish, M., Dawe, S., Egerton-Warburton, D., Karro, J., Kim, C., Lenton, S., Lubman, D. I., Pastor, A., Rundle, J., Ryan, J., Gordon, P., Sharry, P., Nutt, D., & Castle, D. (2019). The Australian drug harms ranking study. *Journal of Psychopharmacology*, *33*(7), 759–768. https://doi.org/10.1177/0269881119841569

Brooks, R. (1996). EuroQol: The current state of play. *Health Policy*, *37*(1), 53–72. https://doi.org/10.1016/0168-8510(96)00822-6

Brown, R. T., Nicholas, C. R., Cozzi, N. V., Gassman, M. C., Cooper, K. M., Muller, D., Thomas, C. D., Hetzel, S. J., Henriquez, K. M., Ribaudo, A. S., & Hutson, P. R. (2017). Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults. *Clinical Pharmacokinetics*, *56*(12), 1543–1554. https://doi.org/10.1007/s40262-017-0540-6

Cameron, L., Nazarian, A., & Olson, D. (2020). Psychedelic Microdosing: Prevalence and Subjective Effects. *Journal of Psychoactive Drugs*, *52*(2), 113–122. https://doi.org/10.1080/02791072.2020.1718250

Cardeña, E., & Terhune, D. B. (2014). Hypnotizability, personality traits, and the propensity to experience alterations of consciousness. *Psychology of Consciousness: Theory, Research, and Practice*, *1*(3), 292–307. https://doi.org/10.1037/cns0000026

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal of Medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Carhart-Harris, R., Leech, R., Hellyer, P., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D., & Nutt, D. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience*, *8*. https://www.frontiersin.org/articles/10.3389/fnhum.2014.00020

Cavanna, F., Muller, S., de la Fuente, L. A., Zamberlan, F., Palmucci, M., Janeckova, L., Kuchar, M., Pallavicini, C., & Tagliazucchi, E. (2022). Microdosing with psilocybin mushrooms: A double-blind placebo-controlled study. *Translational Psychiatry*, *12*(1), Article 1. https://doi.org/10.1038/s41398-022-02039-0

Cohen, S. (1960). LYSERGIC ACID DIETHYLAMIDE: SIDE EFFECTS AND COMPLICATIONS. *The Journal of Nervous and Mental Disease*, *130*(1), 30–40. https://doi.org/10.1097/00005053-196001000-00005

Cremonini, F., Nicandro, J. P., Atkinson, V., Shringarpure, R., Chuang, E., & Lembo, A. (2012a). Randomised clinical trial: Alosetron improves quality of life and reduces restriction of daily

activities in women with severe diarrhoea-predominant IBS. *Alimentary Pharmacology & Therapeutics*, *36*(5), 437–448. https://doi.org/10.1111/j.1365-2036.2012.05208.x

Cremonini, F., Nicandro, J. P., Atkinson, V., Shringarpure, R., Chuang, E., & Lembo, A. (2012b). Randomised clinical trial: Alosetron improves quality of life and reduces restriction of daily activities in women with severe diarrhoea-predominant IBS. *Alimentary Pharmacology & Therapeutics*, *36*(5), 437–448. https://doi.org/10.1111/j.1365-2036.2012.05208.x

Cuijpers, P., Cristea, I. A., Karyotaki, E., Reijnders, M., & Huibers, M. J. H. (2016). How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *15*(3), 245–258. https://doi.org/10.1002/wps.20346

Curran, S. L., Andrykowski, M. A., & Studts, J. L. (1995). Short Form of the Profile of Mood States (POMS-SF): Psychometric information. *Psychological Assessment*, *7*, 80–83. https://doi.org/10.1037/1040-3590.7.1.80

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *78*(5), 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

de Wit, H., Molla, H. M., Bershad, A., Bremmer, M., & Lee, R. (2022). Repeated low doses of LSD in healthy adults: A placebo-controlled, dose–response study. *Addiction Biology*, *27*(2), e13143. https://doi.org/10.1111/adb.13143

DeMuro, C., Cole, T., Coon, C., McLeod, L., & Gnanasakthy, A. (2014). Psychometric evaluation of the Sheehan Disability Scale in adult patients with attention-deficit/hyperactivity disorder. *Neuropsychiatric Disease and Treatment*, 887. https://doi.org/10.2147/NDT.S55220

Deppe, K. D., Gonzalez, F. J., Neiman, J. L., Jacobs, C., Pahlke, J., Smith, K. B., & Hibbing, J. R. (2015). Reflective liberals and intuitive conservatives: A look at the Cognitive Reflection Test and ideology. *Judgment and Decision Making*, *10*(4), 18.

Dinis-Oliveira, R. J. (2017). Metabolism of psilocybin and psilocin: Clinical and forensic toxicological relevance. *Drug Metabolism Reviews*, *49*(1), 84–91. https://doi.org/10.1080/03602532.2016.1278228

Dittrich, A. (1998). The Standardized Psychometric Assessment of Altered States of Consciousness (ASCs) in Humans. *Pharmacopsychiatry*, *31*(S 2), 80–84. https://doi.org/10.1055/s-2007-979351

Edmondson, D., Park, C. L., Chaudoir, S. R., & Wortmann, J. H. (2008). Death Without God. *Psychological Science*. https://journals.sagepub.com/doi/full/10.1111/j.1467-9280.2008.02152.x?casa_token=xSzP3JgzNGwAAAAA%3Ao7Hr8c7-qN8sV_gbPcTEIJERyyX7Q88HNatIkaCx3QoDrXY8LPeP3NmzDHj8KLHhkxLnGGU7MfqVQQ

EFSA NDA panel. (2015). EFSA panel on dietetic products, scientific opinion on the safety of caffeine. *EFSA*, *13*, 4102.

Family, N., Maillet, E., Williams, L., Krediet, E., Carhart-Harris, R., Williams, T., Nichols, C., Goble, D., & Raz, S. (2020). Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers. *Psychopharmacology*, *237*, 841–853. https://doi.org/10.1007/s00213-019-05417-7

Frederick, S. (2005). Cognitive Reflection and Decision Making. *Journal of Economic Perspectives*, *19*(4), 25–42. https://doi.org/10.1257/089533005775196732

Frokjaer, V. G., Mortensen, E. L., Nielsen, F. Å., Haugbol, S., Pinborg, L. H., Adams, K. H., Svarer, C., Hasselbalch, S. G., Holm, S., Paulson, O. B., & Knudsen, G. M. (2008). Frontolimbic Serotonin 2A Receptor Binding in Healthy Subjects Is Associated with Personality Risk Factors for Affective Disorder. *Biological Psychiatry*, *63*(6), 569–576. https://doi.org/10.1016/j.biopsych.2007.07.009

Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*, *99*(6), 686–696. https://doi.org/10.1111/j.1360-0443.2004.00744.x

Gámez, W., Chmielewski, M., Kotov, R., Ruggero, C., Suzuki, N., & Watson, D. (2014). The Brief Experiential Avoidance Questionnaire: Development and initial validation. *Psychological Assessment*, *26*(1), 35–45. https://doi.org/10.1037/a0034473

Giddens, J. M., Sheehan, K. H., & Sheehan, D. V. (2014). The Columbia-Suicide Severity Rating Scale (C–SSRS): Has the "Gold Standard" Become a Liability? *Innovations in Clinical Neuroscience*, *11*(9–10), 66–80.

Goldberg, S. B., Pace, B. T., Nicholas, C. R., Raison, C. L., & Hutson, P. R. (2020). The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. *Psychiatry Research*, *284*, 112749. https://doi.org/10.1016/j.psychres.2020.112749

Griffiths, R., Johnson, M., Carducci, M., Umbricht, A., Richards, W., Richards, B., Cosimano, M., & Klinedinst, M. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Griffiths, R., Johnson, M., Richards, W., Richards, B., Jesse, R., MacLean, K., Barrett, F., Cosimano, M., & Klinedinst, M. (2018). Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *Journal of Psychopharmacology*, *32*(1), 49–69. Scopus. https://doi.org/10.1177/0269881117731279

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, *187*(3), 268–283. https://doi.org/10.1007/s00213-006-0457-5

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Archives of General Psychiatry*, *68*(1), 71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116

Group, W. A. W. (2002). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): Development, reliability and feasibility. *Addiction*, *97*(9), 1183–1194. https://doi.org/10.1046/j.1360-0443.2002.00185.x

Guilford, J. P. (1967). *The nature of human intelligence*. McGraw-Hill.

Haden, M., & Woods, B. (2020). LSD Overdoses: Three Case Reports. *Journal of Studies on Alcohol and Drugs*, *81*(1), 115–118. https://doi.org/10.15288/jsad.2020.81.115

Hägg, D., Brenner, P., Reutfors, J., Li, G., DiBernardo, A., Bodén, R., & Brandt, L. (2020). A register-based approach to identifying treatment-resistant depression—Comparison with clinical definitions. *PLOS ONE*, *15*(7), e0236434. https://doi.org/10.1371/journal.pone.0236434

Hamilton, M. (1960). A RATING SCALE FOR DEPRESSION. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(1), 56–62.

Hasler, F., Grimberg, U., Benz, M. A., Huber, T., & Vollenweider, F. X. (2004). Acute psychological and physiological effects of psilocybin in healthy humans: A double-blind, placebo-controlled dose-effect study. *Psychopharmacology*, *172*(2), 145–156. https://doi.org/10.1007/s00213-003-1640-6

Hendricks, P. S., Johnson, M. W., & Griffiths, R. R. (2015). Psilocybin, psychological distress, and suicidality. *Journal of Psychopharmacology*, *29*(9), 1041–1043. https://doi.org/10/gfv253

Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology*, *29*(3), 280–288. https://doi.org/10.1177/0269881114565653

Hidaka, B. H. (2012). Depression as a disease of modernity: Explanations for increasing prevalence. *Journal of Affective Disorders*, *140*(3), 205–214. https://doi.org/10.1016/j.jad.2011.12.036

Hodgins, D. C. (2013). Reliability and validity of the Sheehan disability scale modified for pathological gambling. *BMC Psychiatry*, *13*(1), 177. https://doi.org/10.1186/1471-244X-13-177

Holze, F., Caluori, T. V., Vizeli, P., & Liechti, M. E. (2021). Safety pharmacology of acute LSD administration in healthy subjects. *Psychopharmacology*. https://doi.org/10.1007/s00213-021-05978-6

Hutten, N., Mason, N., Dolder, P., Theunissen, E., Holze, F., Liechti, M., Feilding, A., Ramaekers, J., & Kuypers, K. (2020). Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose-effect finding study. *European Neuropsychopharmacology*, *41*, 81–91.

Hutten, N. R., Mason, N., Dolder, P., Theunissen, E., Holze, F., Liechti, M., Varghese, N., Eckert, A., Feilding, A., Ramaekers, J., & Kuypers, K. (2021). Low Doses of LSD Acutely Increase BDNF Blood Plasma Levels in Healthy Volunteers. *ACS Pharmacology & Translational Science*, *4*, 461–466. https://doi.org/10.1021/acsptsci.0c00099

Jackson, S. A., & Marsh, H. W. (1996). Development and Validation of a Scale to Measure Optimal Experience: The Flow State Scale. *Journal of Sport and Exercise Psychology*, *18*(1), 17–35. https://doi.org/10.1123/jsep.18.1.17

Jakobsen, J. C., Gluud, C., & Kirsch, I. (2020). Should antidepressants be used for major depressive disorder? *BMJ Evidence-Based Medicine*, *25*(4), 130–130. https://doi.org/10.1136/bmjebm-2019-111238

Jamieson, G. A. (2005). The modified tellegen absorption scale: A clearer window on the structure and meaning of absorption. *Australian Journal of Clinical & Experimental Hypnosis*, *33*(2), 119–139.

Johnson, M., Richards, W., & Griffiths, R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, *22*(6), 603–620. https://doi.org/10.1177/0269881108093587

Klerman, G. L. (1989). Increasing Rates of Depression. *JAMA: The Journal of the American Medical Association*, *261*(15), 2229. https://doi.org/10.1001/jama.1989.03420150079041

Klock, J. C., Boerner, U., & Becker, C. E. (1974). Coma, Hyperthermia and Bleeding Associated with Massive LSD Overdose. *Western Journal of Medicine*, *120*(3), 183–188.

Krebs, T. S., & Johansen, P.-Ø. (2013). Psychedelics and Mental Health: A Population Study. *PLOS ONE*, *8*(8), e63972. https://doi.org/10.1371/journal.pone.0063972

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2002). The PHQ-15: Validity of a New Measure for Evaluating the Severity of Somatic Symptoms: *Psychosomatic Medicine*, *64*(2), 258–266. https://doi.org/10.1097/00006842-200203000-00008

Kuypers, K. P. C. (2020). The therapeutic potential of microdosing psychedelics in depression. *Therapeutic Advances in Psychopharmacology*, *10*, 204512532095056. https://doi.org/10.1177/2045125320950567

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, 0269881119857204. https://doi.org/10.1177/0269881119857204

Lee, R., & Robbins, S. (1995). Measuring Belongingness: The Social Connectedness and the Social Assurance Scales. *Journal of Counseling Psychology*, *42*, 232–241. https://doi.org/10.1037/0022-0167.42.2.232

Leganger, A., Kraft, P., & R⊘ysamb, E. (2000). Perceived self-efficacy in health behaviour research: Conceptualisation, measurement and correlates. *Psychology & Health*, *15*(1), 51–69. https://doi.org/10.1080/08870440008400288

Lorenzo-Luaces, L., Rutter, L. A., & Scalco, M. D. (2020). Carving depression at its joints? Psychometric properties of the Sydney Melancholia Prototype Index. *Psychiatry Research*, *293*, 113410. https://doi.org/10.1016/j.psychres.2020.113410

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, *33*(3), 335–343. https://doi.org/10.1016/0005-7967(94)00075-U

Lush, P., Scott, R. B., Seth, A. K., & Dienes, Z. (2021). The Phenomenological Control Scale: Measuring the Capacity for Creating Illusory Nonvolition, Hallucination and Delusion. *Collabra: Psychology*, *7*(1), 29542. https://doi.org/10.1525/collabra.29542

Luszczynska, A., Gutiérrez-Doña, B., & Schwarzer, R. (2005). General self-efficacy in various domains of human functioning: Evidence from five countries. *International Journal of Psychology*, *40*(2), 80–89. https://doi.org/10.1080/00207590444000041

Madsen, K. E. (2016). The differential effects of agency on fear induction using a horror-themed video game. *Computers in Human Behavior*, *56*, 142–146. https://doi.org/10.1016/j.chb.2015.11.041

Madsen, M. K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., Johansen, S. S., Lehel, S., Linnet, K., Svarer, C., Erritzoe, D., Ozenne, B., & Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology*, *44*(7), Article 7. https://doi.org/10.1038/s41386-019-0324-9

Manicavasagar, V. (2012). A review of depression diagnosis and management. *InPsych*, *34*(1). https://www.psychology.org.au/publications/inpsych/2012/february/manicavasagar

Manly, T., & Robertson, I. H. (2005). CHAPTER 55—The Sustained Attention to Response Test (SART). In L. Itti, G. Rees, & J. K. Tsotsos (Eds.), *Neurobiology of Attention* (pp. 337–338). Academic Press. https://doi.org/10.1016/B978-012375731-9/50059-8

Marks, I. M. (1986). *Behavioural psychotherapy: Maudsley pocket book of clinical management* (pp. x, 133). Wright/IOP Publishing.

Marschall, J., Fejer, G., Lempe, P., Prochazkova, L., Kuchar, M., Hajkova, K., & van Elk, M. (2022). Psilocybin microdosing does not affect emotion-related symptoms and processing: A preregistered field and lab-based study. *Journal of Psychopharmacology*, *36*(1), 97–133. https://doi.org/10.1177/02698811211050556

Martin, M. M., & Rubin, R. B. (1995). A New Measure of Cognitive Flexibility. *Psychological Reports*, *76*(2), 623–626. https://doi.org/10.2466/pr0.1995.76.2.623

McClain, C. S., Rosenfeld, B., & Breitbart, W. (2003). Effect of spiritual well-being on end-of-life despair in terminally-ill cancer patients. *The Lancet*, *361*(9369), 1603–1607. https://doi.org/10.1016/S0140-6736(03)13310-7

Mehling, W. E., Acree, M., Stewart, A., Silas, J., & Jones, A. (2018). The Multidimensional Assessment of Interoceptive Awareness, Version 2 (MAIA-2). *PLOS ONE*, *13*(12), e0208034. https://doi.org/10.1371/journal.pone.0208034

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., & Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLOS ONE*, *7*(11), e48230. https://doi.org/10.1371/journal.pone.0048230

Melartin, T. K., Rytsala, H. J., Leskela, U. S., Lestela-Mielonen, P. S., & Isometsa, E. T. (2002). Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *The Journal of Clinical Psychiatry*, *63*(2), 3977.

Morean, M. E., de Wit, H., King, A. C., Sofuoglu, M., Rueger, S. Y., & O'Malley, S. S. (2013). The drug effects questionnaire: Psychometric support across three drug types. *Psychopharmacology*, *227*(1), 177–192. https://doi.org/10.1007/s00213-012-2954-z

Moreno, et al. (n.d.). *Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder*. 6.

Morilak, D. A., & Frazer, A. (2004). Antidepressants and brain monoaminergic systems: A dimensional approach to understanding their behavioural effects in depression and anxiety disorders. *International Journal of Neuropsychopharmacology*, *7*(2), 193–218. https://doi.org/10.1017/S1461145704004080

Mrazek, M., Phillips, D., Franklin, M., Broadway, J., & Schooler, J. (2013). Young and restless: Validation of the Mind-Wandering Questionnaire (MWQ) reveals disruptive impact of mind-wandering for youth. *Frontiers in Psychology*, *4*. https://www.frontiersin.org/articles/10.3389/fpsyg.2013.00560

Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. M. (2002). The Work and Social Adjustment Scale: A simple measure of impairment in functioning. *British Journal of Psychiatry*, *180*(5), 461–464. https://doi.org/10.1192/bjp.180.5.461

Murray, C. H., Tare, I., Perry, C. M., Malina, M., Lee, R., & de Wit, H. (2022). Low doses of LSD reduce broadband oscillatory power and modulate event-related potentials in healthy adults. *Psychopharmacology*, *239*, 1735–1747. https://doi.org/10.1007/s00213-021-05991-9

National Health and Medical Research Council. (2016). *Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods* (No. EH59). National Health and Medical Research Council.

Newton, C., Feeney, J., & Pennycook, G. (2021). *The Comprehensive Thinking Styles Questionnaire: A novel measure of intuitive-analytic thinking styles* [Preprint]. PsyArXiv. https://doi.org/10.31234/osf.io/r5wez

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, *68*(2), Article 2. https://doi.org/10.1124/pr.115.011478

Nisbet, E. K., Zelenski, J. M., & Murphy, S. A. (2009). The Nature Relatedness Scale: Linking Individuals' Connection With Nature to Environmental Concern and Behavior. *Environment and Behavior*, *41*(5), 715–740. https://doi.org/10.1177/0013916508318748

Nisbet, E., & Zelenski, J. (2013). The NR-6: A new brief measure of nature relatedness. *Frontiers in Psychology*, *4*. https://www.frontiersin.org/articles/10.3389/fpsyg.2013.00813

Nutt, D., King, L. A., Saulsbury, W., & Blakemore, C. (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *The Lancet*, *369*(9566), 1047–1053. https://doi.org/10.1016/S0140-6736(07)60464-4

Olfson, M., Fireman, B., Weissman, M. M., Leon, A. C., Sheehan, D. V., Kathol, R. G., Hoven, C., & Farber, L. (1997). Mental Disorders and Disability Among Patients in a Primary Care Group Practice. *American Journal of Psychiatry*, *154*(12), 1734–1740. https://doi.org/10.1176/ajp.154.12.1734

Parker, G., Fletcher, K., Barrett, M., Synnott, H., Breakspear, M., Rees, A.-M., & Hadzi-Pavlovic, D. (2010). Inching toward Bethlehem: Mapping melancholia. *Journal of Affective Disorders*, *123*(1), 291–298. https://doi.org/10.1016/j.jad.2009.10.001

Parker, G., Fletcher, K., & Hadzi-Pavlovic, D. (2012). Is context everything to the definition of clinical depression? A test of the Horwitz and Wakefield postulate. *Journal of Affective Disorders*, *136*(3), 1034–1038. https://doi.org/10.1016/j.jad.2010.11.021

Parker, G., McClure, G., & Paterson, A. (2014). Melancholia and Catatonia: Disorders or Specifiers? *Current Psychiatry Reports*, *17*(1), 536. https://doi.org/10.1007/s11920-014-0536-y

Parker, G., McCraw, S., Fletcher, K., Friend, P., & Futeran, S. (2013). Validation of a new prototypic measure of melancholia. *Comprehensive Psychiatry*, *54*(7), 835–841. https://doi.org/10.1016/j.comppsych.2013.02.010

Pennycook, G., Cheyne, J. A., Seli, P., Koehler, D. J., & Fugelsang, J. A. (2012). Analytic cognitive style predicts religious and paranormal belief. *Cognition*, *123*(3), 335–346. https://doi.org/10.1016/j.cognition.2012.03.003

Petitmengin, C., Navarro, V., & Le Van Quyen, M. (2007). Anticipating seizure: Pre-reflective experience at the center of neuro-phenomenology. *Consciousness and Cognition*, *16*(3), 746–764. https://doi.org/10.1016/j.concog.2007.05.006

Petitmengin, C., van Beek, M., Bitbol, M., Nissou, J.-M., & Roepstorff, A. (2019). Studying the experience of meditation through Micro-phenomenology. *Current Opinion in Psychology*, *28*, 54–59. https://doi.org/10.1016/j.copsyc.2018.10.009

Petranker, R., Anderson, T., Maier, L., Barratt, M., Ferris, J., & Winstock, A. (2020). Microdosing psychedelics: Subjective benefits and challenges, substance testing behavior, and the relevance of intention. *Journal of Psychopharmacology*, 0269881120953994. https://doi.org/10.1177/0269881120953994

Polito, V. (2021). *Sense of Self Scale*. https://doi.org/10.17605/OSF.IO/654BG

Polito, V., & Liknaitzky, P. (2022). The emerging science of microdosing: A systematic review of research on low dose psychedelics (1955-2021) and recommendations for the field. *Neuroscience & Biobehavioral Reviews*, *139*, 104706. https://doi.org/10.1016/j.neubiorev.2022.104706

Polito, V., & Stevenson, R. (2019). A systematic study of microdosing psychedelics. *PLOS ONE*, *14*(2), e0211023. https://doi.org/10.1371/journal.pone.0211023

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S., & Mann, J. J. (2011a). The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. *American Journal of Psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Primi, C., Morsanyi, K., Chiesi, F., Donati, M. A., & Hamilton, J. (2016). The Development and Testing of a New Version of the Cognitive Reflection Test Applying Item Response Theory (IRT): A New Version of the Cognitive Reflection Test Applying IRT. *Journal of Behavioral Decision Making*, *29*(5), 453–469. https://doi.org/10.1002/bdm.1883

Prochazkova, L., van Elk, M., Marschall, J., Rifkin, B. D., Fejer, G., Schoen, N., Fiacchino, D., Kuchar, M., & Hommel, B. (2021). *Microdosing psychedelics and its effect on creativity: Lessons learned from three double-blind placebo controlled longitudinal trials*.

Ramaekers, J., Hutten, N., Mason, N., Dolder, P., Theunissen, E., Holze, F., Liechti, M., Feilding, A., & Kuypers, K. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, *35*(4), Article 4. https://doi.org/10.1177/0269881120940937

Reitan, R. M., & Wolfson, D. (1995a). Category test and trail making test as measures of frontal lobe functions. *The Clinical Neuropsychologist*, *9*(1), 50–56. https://doi.org/10.1080/13854049508402057

Reitan, R. M., & Wolfson, D. (1995b). Category test and trail making test as measures of frontal lobe functions. *The Clinical Neuropsychologist*, *9*(1), 50–56. https://doi.org/10.1080/13854049508402057

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). `Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*, *35*(6), 747–758. https://doi.org/10.1016/S0028-3932(97)00015-8

Rodríguez Arce, J. M., & Winkelman, M. J. (2021). Psychedelics, Sociality, and Human Evolution. *Frontiers in Psychology*, *12*, 729425. https://doi.org/10.3389/fpsyg.2021.729425

Ross, S., Agin-Liebes, G., Lo, S., Zeifman, R. J., Ghazal, L., Benville, J., Franco Corso, S., Bjerre Real, C., Guss, J., Bossis, A., & Mennenga, S. E. (2021). Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. *ACS Pharmacology & Translational Science*, *4*(2), 553–562. https://doi.org/10.1021/acsptsci.1c00020

Ross, S., Agrawal, M., Griffiths, R. R., Grob, C., Berger, A., & Henningfield, J. E. (2022). Psychedelic-assisted psychotherapy to treat psychiatric and existential distress in life-threatening medical illnesses and palliative care. *Neuropharmacology*, *216*, 109174. https://doi.org/10.1016/j.neuropharm.2022.109174

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom

reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, *30*(12), 1165–1180. https://doi.org/10.1177/0269881116675512

Santos, R. (2022, September 8). What Does Microdosing Drugs Feel Like Anyway? *Vice*. https://www.vice.com/en/article/4axn7d/microdosing-drugs-experience-effects-lsd-pscyhedelics

Sanz, C., Cavanna, F., Muller, S., de la Fuente, L., Zamberlan, F., Palmucci, M., Janeckova, L., Kuchar, M., Carrillo, F., García, A. M., Pallavicini, C., & Tagliazucchi, E. (2022). Natural language signatures of psilocybin microdosing. *Psychopharmacology*. https://doi.org/10.1007/s00213-022-06170-0

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*, *88*(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Schaeuffele, C., Knaevelsrud, C., Renneberg, B., & Boettcher, J. (2021). Psychometric Properties of the German Brief Experiential Avoidance Questionnaire (BEAQ). *Assessment*, 107319112110109. https://doi.org/10.1177/10731911211010955

Schwarzer, R., & Jerusalem, M. (n.d.). *The General Self-Efficacy Scale (GSE)*. 2.

Schwarzer, R., Mueller, J., & Greenglass, E. (1999). Assessment of perceived general self-efficacy on the internet: Data collection in cyberspace. *Anxiety, Stress & Coping*, *12*(2), 145–161. https://doi.org/10.1080/10615809908248327

Shacham, S. (1983). A shortened version of the Profile of Mood States. *Journal of Personality Assessment*, *47*, 305–306. https://doi.org/10.1207/s15327752jpa4703_14

Sheehan, D. V. (n.d.). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *J Clin Psychiatry*, 12.

Sheehan, D. V. (1986). *The anxiety disease*. Bantam Press.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Sirota, M., Dewberry, C., Juanchich, M., Valuš, L., & Marshall, A. C. (2021). Measuring cognitive reflection without maths: Development and validation of the verbal cognitive reflection test. *Journal of Behavioral Decision Making*, *34*(3), 322–343. https://doi.org/10.1002/bdm.2213

Sirota, M., & Juanchich, M. (2018). Effect of response format on cognitive reflection: Validating a two- and four-option multiple choice question version of the Cognitive Reflection Test. *Behavior Research Methods*, *50*(6), 2511–2522. https://doi.org/10.3758/s13428-018-1029-4

Soto, C. J., & John, O. P. (2017). Short and extra-short forms of the Big Five Inventory–2: The BFI-2-S and BFI-2-XS. *Journal of Research in Personality*, *68*, 69–81. https://doi.org/10.1016/j.jrp.2017.02.004

Squires, N. K., Squires, K. C., Steven, & Hillyard, A. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography and Clinical Neurophysiology*, 387–401.

Stojanov, A., & Halberstadt, J. (2019). The Conspiracy Mentality Scale: Distinguishing Between Irrational and Rational Suspicion. *Social Psychology*, *50*(4), 215–232. https://doi.org/10.1027/1864-9335/a000381

Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric Evaluation of the Altered States of Consciousness Rating Scale (OAV). *PLoS ONE*, *5*(8), e12412. https://doi.org/10.1371/journal.pone.0012412

Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. X. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: A pooled analysis of experimental studies.

Journal of Psychopharmacology, *25*(11), 1434–1452. https://doi.org/10.1177/0269881110382466

Sumner, R. L., Spriggs, M. J., Muthukumaraswamy, S. D., & Kirk, I. J. (2020). The role of Hebbian learning in human perception: A methodological and theoretical review of the human Visual Long-Term Potentiation paradigm. *Neuroscience & Biobehavioral Reviews*, *115*, 220–237. https://doi.org/10.1016/j.neubiorev.2020.03.013

Tamas, A. (2020). COGNITIVE REFLECTION TEST - NEXT GENERATION. *International Journal of Teaching & Education*, *VIII*(1). https://doi.org/10.20472/TE.2020.8.1.006

Tellegen, A., & Atkinson, G. (1974). Openness to absorbing and self-altering experiences ('absorption'), a trait related to hypnotic susceptibility. *Journal of Abnormal Psychology*, *83*(3), 268–277. https://doi.org/10.1037/h0036681

Teyler, T. J., Hamm, J. P., Clapp, W. C., Johnson, B. W., Corballis, M. C., & Kirk, I. J. (2005). Long-term potentiation of human visual evoked responses. *European Journal of Neuroscience*, *21*(7), 2045–2050. https://doi.org/10.1111/j.1460-9568.2005.04007.x

Thomson, K. S., & Oppenheimer, D. M. (2016). Investigating an alternate form of the cognitive reflection test. *Judgment and Decision Making*, *11*(1), 15.

Toplak, M. E., West, R. F., & Stanovich, K. E. (2014). Assessing miserly information processing: An expansion of the Cognitive Reflection Test. *Thinking & Reasoning*, *20*(2), 147–168. https://doi.org/10.1080/13546783.2013.844729

Uher, R., Farmer, A., Henigsberg, N., Rietschel, M., Mors, O., Maier, W., Kozel, D., Hauser, J., Souery, D., Placentino, A., Strohmaier, J., Perroud, N., Zobel, A., Rajewska-Rager, A., Dernovsek, M. Z., Larsen, E. R., Kalember, P. Giovannini, C., Barreto, M., McGuffin, P.,, & Aitchison, K. J. (2009). Adverse reactions to antidepressants. *The British Journal of Psychiatry*, *195*(3), 202-210.

van Amsterdam, J., Opperhuizen, A., Koeter, M., & van den Brink, W. (2010). Ranking the Harm of Alcohol, Tobacco and Illicit Drugs for the Individual and the Population. *European Addiction Research*, *16*(4), 202–207. https://doi.org/10.1159/000317249

van Amsterdam, J., & van den Brink, W. (2022). The therapeutic potential of psilocybin: A systematic review. *Expert Opinion on Drug Safety*, *0*(0), 1–8. https://doi.org/10.1080/14740338.2022.2047929

van Elk, M., Fejer, G., Lempe, P., Prochazckova, L., Kuchar, M., Hajkova, K., & Marschall, J. (2022). Effects of psilocybin microdosing on awe and aesthetic experiences: A preregistered field and lab-based study. *Psychopharmacology*, *239*, 1705–1720. https://doi.org/10.1007/s00213-021-05857-0

Van Oekelen, D., Luyten, W. H. M. L., & Leysen, J. E. (2003). 5-HT2A and 5-HT2C receptors and their atypical regulation properties. *Life Sciences*, *72*(22), 2429–2449. https://doi.org/10.1016/S0024-3205(03)00141-3

Vázquez-Morejón, R., León Rubio, J. M., Martín Rodríguez, A., & Vázquez Morejón, A. J. (2019). Validation of a Spanish version of the Brief Experiential Avoidance Questionnaire (BEAQ) in clinical population. *Psicothema*, *31.3*, 335–340. https://doi.org/10.7334/psicothema2019.60

Visser, A., Garssen, B., & Vingerhoets, A. (2010). Spirituality and well-being in cancer patients: A review. *Psycho-Oncology*, *19*(6), 565–572. https://doi.org/10.1002/pon.1626

Vivanti, G., Hocking, D. R., Fanning, P. A. J., Uljarevic, M., Postorino, V., Mazzone, L., & Dissanayake, C. (2018). Attention to novelty versus repetition: Contrasting habituation profiles in Autism and Williams syndrome. *Developmental Cognitive Neuroscience*, *29*, 54–60. https://doi.org/10.1016/j.dcn.2017.01.006

Voluse, A. C., Gioia, C. J., Sobell, L. C., Dum, M., Sobell, M. B., & Simco, E. R. (2012). Psychometric properties of the Drug Use Disorders Identification Test (DUDIT) with substance abusers in outpatient and residential treatment. *Addictive Behaviors*, *37*(1), 36–41. https://doi.org/10.1016/j.addbeh.2011.07.030

Wackermann, J., Wittmann, M., Hasler, F., & Vollenweider, F. X. (2008). Effects of varied doses of psilocybin on time interval reproduction in human subjects. *Neuroscience Letters*, *435*(1), 51–55. https://doi.org/10/c25c34

Weiner, B. J., Lewis, C. C., Stanick, C., Powell, B. J., Dorsey, C. N., Clary, A. S., Boynton, M. H., & Halko, H. (2017). Psychometric assessment of three newly developed implementation outcome measures. *Implementation Science*, *12*(1), 108. https://doi.org/10.1186/s13012-017-0635-3

Williams, J., Kobak, K., Bech, P., Engelhardt, N., Evans, K., Lipsitz, J., Olin, J., Pearson, J., & Kalali, A. (2008). The GRID-HAMD: Standardization of the Hamilton depression rating scale. *International Clinical Psychopharmacology*, *23*, 120–129. https://doi.org/10.1097/YIC.0b013e3282f948f5

Williams, J. M. G., & Broadbent, K. (1986). *Autobiographical Memory Test*. https://doi.org/10.1037/t13835-000

Yanakieva, S., Polychroni, N., Family, N., Williams, L., Luke, D. P., & Terhune, D. B. (2019). The effects of microdose LSD on time perception: A randomised, double-blind, placebo-controlled trial. *Psychopharmacology*, *236*(4), 1159–1170. https://doi.org/10.1007/s00213-018-5119-x

Yoon, S., Park, K., & Choi, K.-H. (2020a). The ultra brief checklist for suicidality. *Journal of Affective Disorders*, *276*, 279–286. https://doi.org/10.1016/j.jad.2020.07.037

Younger, J., Gandhi, V., Hubbard, E., & Mackey, S. (2012). Development of the Stanford Expectations of Treatment Scale (SETS): A tool for measuring patient outcome expectancy in clinical trials. *Clinical Trials*, *9*(6), 767–776. https://doi.org/10.1177/1740774512465064

Zijlema, W. L., Stolk, R. P., Löwe, B., Rief, W., White, P. D., & Rosmalen, J. G. M. (2013). How to assess common somatic symptoms in large-scale studies: A systematic review of questionnaires. *Journal of Psychosomatic Research*, *74*(6), 459–468. https://doi.org/10.1016/j.jpsychores.2013.03.093