Imperial College London

PsiloIMAGINE

Investigating the effects of a psychedelic-augmented mental imagery-based intervention for young people with self-harm behaviour: an experimental medicine study

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This study is funded by the Economic and Social Research Council (ESRC).

This protocol describes the PsiloIMAGINE study: a psilocybin-augmented mental imagery intervention for young people who self-harm and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AAT	Approach/Avoidance Task
ACE	Adverse Childhood Experience
AE	Adverse Event
ASA	Anhedonia Scale for Adolescents
AUDIT	Alcohol Use Disorders Identification Test
BP	Blood Pressure
CEQ	Challenging Experience Questionnaire
CEQ-SH	Craving Experience for Self-Harm
CI	Chief Investigator
COHS	Creature of Habit Scale
CRF	Case Record Form
CUDIT-R	Cannabis Use Disorders Identification Test Revised
DASS-21	Depression Anxiety Stress Scale (21)
DERS-SF	Difficulty in Emotional Regulation Scale Short Form
EBI	Emotional Breakthrough Inventory
ECG	Electrocardiogram
GP	General Practitioner
HR	Heart Rate
ICRF	Imperial College Research Facility
ImRS	Imagery Re-Scripting
MEQ	Mystical Experience Questionnaire
MINI	Mini-International Neuropsychiatric Interview
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
NART	National Adult Reading Test
PIS	Participant Information Sheet
PIT	Positive Imagery Task
PRL	Probabilistic Reversal Learning
RT	Reaction Time

SAE	Serious Adverse Event
SCS	Self-Compassion Scale
SH	Self-harm
SH-DPT	Self-harm Dot Probe Task
SHII	Self-harm Images Interview
SITBI	Self-Injurious Thoughts and Behaviours Interview
SM-SH	State Motivation for reducing Self-harm Scale
STAI-S	State-Trait Anxiety Inventory – State
S-UPPS-P	Impulsive Behaviour Scale
UDS	Urine Drug Screen
WIMI	Waterloo Images and Memories Interview
YSQ-SF	Young Schema Questionnaire Short Form
5-HT	5hydroxytryptaminergic

KEYWORDS
Self-harm, psilocybin, mental imagery, imagery re-scripting, young people

STUDY SUMMARY

Title: Investigating the effects of a psychedelic-augmented mental imagery-based intervention for young people with self-harm behaviour: an experimental medicine study

Design: Double-blind placebo-controlled pharmacological enhancement experimental study

Aims: To investigate if, compared to Imagery Re-Scripting (ImRS) alone, ImRS plus psilocybin (5-HT2A agonist) can modify psychological and cognitive processes underpinning repetitive self-harm behaviour in young people aged 16-25, with a focus on mental images that drive self-harm and associated maladaptive emotions and cognitions

Outcome Measures:

Primary Outcomes:
- Frequency, vividness, compellingness, emotions' intensity and cognitions believability scores on a 1-10 Likert scale related to self-harm and novel adaptive mental imagery
- Scores on Young Schema Questionnaire Short Form (Young et al., 1994)

Secondary Outcomes:
- Performance (e.g., reaction time, accuracy) to self-harm vs neutral pictures and positive vs neutral pictures on the Approach Avoidance task (Loijen et al., 2020)
- Performance (e.g., RT, accuracy, learning rate) on the Probabilistic Reversal Learning task (Dombrovski et al., 2010) and the Self-harm Dot Probe Task (Constantinou et al., 2010)
- Scores on the Difficulty in Emotional Regulation Scale (Hallion et al., 2018); and the Self-compassion scale (Neff, 2003)
- Scores on the State Motivation for Reducing Self-harm scale (Robinson et al., 2016)
- Scores on questionnaires related to the psychedelic experience: Mystical Experience questionnaire (Barrett et al., 2015), Challenging Experience questionnaire (Barrett et al., 2016), Emotional Breakthrough inventory (EBI; Roseman et al., 2019)
-- Feasibility outcomes: participants' recruitment rate, the retention rate for primary and secondary outcomes

Population: Young people with a history of self-harm behaviour and experience of self-harm-related mental imagery.

Eligibility: Individuals aged 16-25 years old who experienced >=2 episodes of self-harm behaviour lifetime, and at least 1 in the last 4 weeks, and self-harm-related imagery in the last 6 weeks and have no contra-indication to taking psilocybin.

Study Duration: 30 month

1. INTRODUCTION

1.1. Background

1.1.1. Self-harm behaviour

Self-harm, 'any act of self-poisoning or self-injury carried out by a person, irrespective of their motivation' (www.nice.org.uk/guidance/qs34), often functions to reduce negative affect, increase positive affect, or gain social support (Nock & Prinstein, 2005). It is a common problem, with approximately 20% of young people report having self-harmed in their life (Gillies et al., 2018) with rates increasing (McManus et al., 2019). The incidence of self-harm has been conceptualised using an iceberg model, with fatal suicide at the tip, hospital presenting self-harm in the middle, and the greatest incidence of self-harm at the bottom occurring within the community and going undetected by clinical services (Geulayov et al., 2018). Importantly, the frequency and severity of self-harm have been shown to increase over time (Nixon et al., 2002).

1.1.2. Targets for intervention in self-harm

Treatment innovation should be based on modifying the underlying mechanisms that maintain symptoms (Holmes et al., 2014), including psychological mechanisms such as cognition. However, little is known about the underlying cognitive processes maintaining repetitive self-harm behaviour, which presents a challenge for effectively targeting interventions.

Current interventions for self-harm focus primarily on improving emotion regulation strategies and interpersonal skills, which helps to minimise the negative emotions often triggering self-harm. However, the efficacy of these interventions for reducing the number of young people engaging in self-harm remains mixed (Saunders & Smith, 2016).

Mental imagery is the experience commonly referred to as "seeing through the mind's eye" and is equal to a form of "weak perception". Across psychopathology mental imagery can "amplify" emotions motivation particularly when it's vivid and compelling (i.e. encourages acting on its content) (Ji et al., 2019).

Young people who self-harm report vivid mental imagery of hurting themselves, such as details of tools and the action sequence to be performed, or the consequence (blood gushing) and the sensation of intense relief often generated by the actual act. Mental images of self-harm can drive the urge to enact the behaviour and are a promising target for intervention (Di Simplicio et al., 2020; Hasking et al., 2018). A recent study confirmed this by using ecological momentary assessment for 14 days and showing that the presence of self-hrm imagery and predicted future urges to self-harm and the likelihood of engaging in the behaviour (Ji et al., 2024). Evidence from the integrated motivational-volitional model indicates that self-harm is associated with deficits in setting attainable goals (O'Connor et al., 2012) and anticipating rewarding experiences (O'Connor et al., 2008). The ability and motivation to engage in goals and rewarding behaviours are sustained by future positive goal-oriented imagery, e.g., imagining going for a run and enjoying the fresh air (Kavanagh et al.,

2005). It is possible that maintaining strong positive goal imagery can act as a protective factor in the motivational phase of self-harm by counteracting feelings of entrapment. Thus, reinforcing motivation away from self-harm and towards adaptive behaviour may represent a novel therapeutic approach.

Imagery Re-Scripting (ImRS) is a well-established cognitive technique used across disorders from post-traumatic stress disorder to depression (Holmes et al., 2007). During ImRS, individuals bring to mind a target ('unhelpful') image associated with their symptoms (such as the ones preceding self-harm) and are guided to modify the image content in a way that will change the associated emotions, cognitions, and the impact on behaviour (Holmes et al., 2007; Schaitz et al., 2020). For example, a self-harm image of a blade triggering emotions of relief, craving and shame and appraisals that there is no other way than self-harming to feel better can drive enacting the behaviour. Re-scripting can modify the image so that a friend appears, puts the blade away and takes the young person's hand instead, eliciting alternative emotions that would stop the individual from self-harming. For example, in our pilot study ('iMAGine', IRAS: 19/SC/0275), ImRS often introduces self-compassion-themed mental imagery or positive goal imagery, in a personalised participant-guided way, instead of the self-harm related image.

During ImRS individuals are guided to identify maladaptive core beliefs or schemas that are associated with their unhelpful image and encouraged to introduce more adaptive beliefs or challenge the maladaptive ones via the re-scripting procedure. Such changes in maladaptive cognitions could weaken the association of the image with psychopathological symptoms (Strachan et al., 2020), i.e., self-harm behaviour. Further proposed mechanisms of ImRS focus on the concepts that mental imagery of salient situations can elicit the same neural response as the one evoked by the real experience itself (Kosslyn et al., 2001) and that imagining a future act can influence future behaviour (Knäuper et al., 2011).

In summary, initial findings suggest that self-harm imagery is associated with engaging in self-harm, and positive goal imagery and/or other imagery encapsulating adaptive beliefs could attenuate self-harm. Thus, ImRS constitutes a promising therapeutic intervention for self-harm behaviour, as it has the potential to disrupt the emotional, cognitive, and motivational drive to self-harm that the self-harm image carries, and it could disrupt the underlying beliefs that maintain self-harm.

However, emotional avoidance and fear of bringing negative images to mind can hinder full engagement in therapy, and deeply ingrained cognitions linked to repeated intrusive mental imagery may require several therapy sessions to become malleable or may resurface after therapy ends.

1.1.3. Psychedelics in therapy

Psychedelic-assisted therapy has shown the potential to produce dramatic psychological change across a number of mental disorders and improve wellbeing (Roseman et al., 2018). Psychedelics, including psilocybin, have been shown to facilitate confronting difficult emotions, which underpins their treatment effect, e.g., in depression, and report feeling more

emotionally re-connected and accepting (Goodwin et al., 2022; Roseman et al., 2018). Following psilocybin therapy, increased trait openness has been observed, reflecting an active approach of individuals to try novel ways of doing things, new experiences, or to consider other people's opinions and world views (Erritzoe et al., 2018). Cognitive flexibility, the capacity to shift between different mental states, has also been shown to increase following psilocybin therapy for major depressive disorder, possibility opening a window of plasticity that could facilitate psychological interventions (Doss et al., 2021).

Further, psilocybin has been shown to modulate neural activity in brain areas part of the core mental imagery network (Hassabis et al., 2007), suggesting synergistic mechanisms to be exploited. Based on this evidence, we propose that psychedelics could facilitate access to and re-scripting of dysfunctional mental imagery and consolidate change in the cognitive processes maintaining self-harm.

Here we propose an acute pharmacological augmentation of a psychological intervention (ImRS) approach where psilocybin will be acting as a mechanistic therapeutic enhancer to improve ImRS outcomes (Nord et al., 2023).

1.1.4. Psilocybin

Psilocybin was used in general psychiatric research and in psychodynamic-orientated psychotherapy during the early to mid-1960s up until its scheduling as a controlled substance in 1970 in the United States, and up until the 1980s in Germany (Passie, 2005; Passie et al., 2002). Research into the effects of psilocybin resumed in the mid-1990s, and it is currently the preferred compound for use in clinical research on 5hydroxytryptaminergic (5-HT) hallucinogens (see for example (Carter et al., 2005; Gouzoulis-Mayfrank et al., 1999; Hasler et al., 2004). Furthermore, clinical observations indicate that it is associated with less anxiety, fewer panic reactions and affective disturbances and milder vegetative side effects than other similar drugs (Carhart-Harris & Nutt, 2010).

Psilocybin or 3[2(Dimethylamino)ethyl]1Hindol4yldihydrogenphosphate, is a tryptamine, and one of the major psychoactive constituents in mushrooms of the Psilocybe genus. Psilocybin is a high-affinity agonist of the 5HT2A receptor (Nichols, 2004). It shows good selectivity for this receptor over other 5HT receptors and other receptor classes. Psilocybin the highest affinity for the 5HT2A > 5HT1A > 5HT2C (Table 8.2.1.1.) (McKenna et al., 1990). Human studies showed that administering psilocybin after pre-treatment with 5HT2A receptor antagonist, such as ketanserin or risperidone, attenuated or completely abolished the subjective and perceptual effects of psilocybin (Carter et al., 2004; Vollenweider et al., 1998) as well as the drug's positive mood effects (Kometer et al., 2013), while Haloperidol did not significantly influence the subjective effects of psilocybin (Vollenweider et al., 1998).

Studies in humans and preclinical species indicate that psilocybin is safe and has low toxicity (Nichols, 2004; Passie et al., 2002). Psilocybin containing mushrooms have been used for thousands of years with artefacts and historical documents suggesting that ritual use of psilocybin-containing mushrooms occurred as early as 3000 years ago, with documented use in 16th Century Mexico, prior to Spanish prohibition on their use. Psilocybin has been given

to several hundred patients and volunteers in modern studies. In a thorough review of dosing sessions in 110 healthy subjects, dysphoric experiences/bad trips were rare and dose-dependent and there was no evidence of subsequent drug abuse, flashback phenomena or prolonged psychoses (Erich Studerus et al., 2011). The majority of recreational magic mushroom users described their experiences as enriching, insightful and beneficial, but not something they would regularly repeat (Carhart-Harris & Nutt, 2010). The Imperial College Psychedelics Research Group (PRG) team has substantial experience administrating psilocybin safely both to healthy psychedelic-naïve and psychedelic-experienced individuals and to patients with moderate to severe depression, in doses larger (oral doses up to 25mg) than proposed in the current study (oral dose of 5mg).

Detailed information about psilocybin and its use can be found in section ***Experimental manipulation*** - Drug effects and the Psilocybin Investigators Brochure (IB) ‘‘Psilocybin Investigator’s Brochure January 2017”.

1.2. Rationale for current study

Self-harm is a major public health issue with health and societal impacts and the greatest risk factor for suicide (Morgan et al., 2017). Current treatments are long, costly and do not suit all young people (Glenn et al., 2019), highlighting the need to develop innovative and scalable interventions that are accessible to young people in the community that could offer a means of reducing the escalation of repetitive self-harm behaviour, which could prevent future suicide attempts.

ImRS guides individuals to manipulate unhelpful mental images (such as the ones preceding self-harm) in a way that will change the associated emotions and the impact on behaviour (Holmes et al., 2007). However, emotional avoidance and fear of bringing negative images to mind can hinder full engagement in therapy. Due to psilocybin’s ability to enhance emotional acceptance, cognitive flexibility, and trait openness (Carhart-Harris et al., 2018), we propose that psychedelics could facilitate access to and re-scripting of dysfunctional mental imagery and consolidate change in the cognitive processes maintaining self-harm.

Based on the above, we aim to test the cognitive processes by which a psychedelic-augmented cognitive intervention may reduce self-harm behaviour, laying a mechanistic foundation for treatment development.

We will examine the effect of a sub-hallucinogenic dose (5mg) of the psychedelic psilocybin compared to placebo, in combination with the cognitive-behavioural therapy technique Imagery Re-Scripting (ImRS) on cognitive processes that contribute to self-harm, in particular self-harm related mental imagery.

Our overall hypothesis is that changes in imagery characteristics, cognitive processes (self-report measures as well as performance on tasks) and self-reported symptomatology in the direction of more adaptive characteristics/performance will be greater following the psilocybin-augmented ImRS experimental manipulation compared to the ImRS + placebo.

We will use a placebo-controlled randomised design, where participants are allocated to either psilocybin-augmented ImRS or ImRS + placebo and primary outcomes are collected after 4 weeks. At 12-weeks, we will be collecting our secondary outcomes (see Flowchart below, figure 1).

Findings from this study will inform cognitive and psychological mechanism for the development of a highly innovative combined pharmacological and cognitive intervention targeting self-harm in young people.

2. OBJECTIVES

2.1. Primary Objectives

Our primary objectives are to measure if, compared to ImRS + placebo, ImRS + psilocybin:

- Reduces the frequency, vividness, and compellingness of self-harm mental imagery, the intensity of associated negative emotions and the believability of associated negative cognitions, within the ImRS session and measured over 2-weeks and at 4-weeks after the experimental manipulation compared to baseline.
- Enhances the frequency, vividness, and compellingness of novel adaptive mental imagery generated during ImRS, the intensity of associated adaptive emotions and the believability of associated adaptive cognitions, within the ImRS session and measured over 2-weeks and at 4-weeks after the experimental manipulation.
- Modifies cognitive constructs that maintain self-harm, such as core cognitive schemas at 4-weeks after the experimental manipulation compared to baseline.

2.3. Secondary Objectives

Our secondary objectives are to measure if, compared to ImRS + placebo, ImRS + psilocybin:

- Reduces self-report measures of depression, anxiety, and stress.
- Reduces self-harm cognitions (e.g., urge, craving, and motivation) and behaviour.
- Modifies motivational biases related to self-harm measured via cognitive tasks.
- Facilitates reward-based learning and cognitive flexibility measured via cognitive tasks and their computational models.
- Increases self-compassion measured via a self-report questionnaire.
- Generates altered state of consciousness and mystical experiences that are associated with self-harm imagery and novel adaptive imagery characteristics.

Our secondary objectives will be measured at 4 weeks and 12 weeks post the experimental manipulation. Our overall hypothesis is that changes in imagery characteristics, cognitive processes (self-report measures as well as performance on tasks) and self-reported symptomatology in the direction of more adaptive characteristics/performance will be greater following the psilocybin-augmented ImRS experimental manipulation compared to the ImRS cognitive manipulation only.

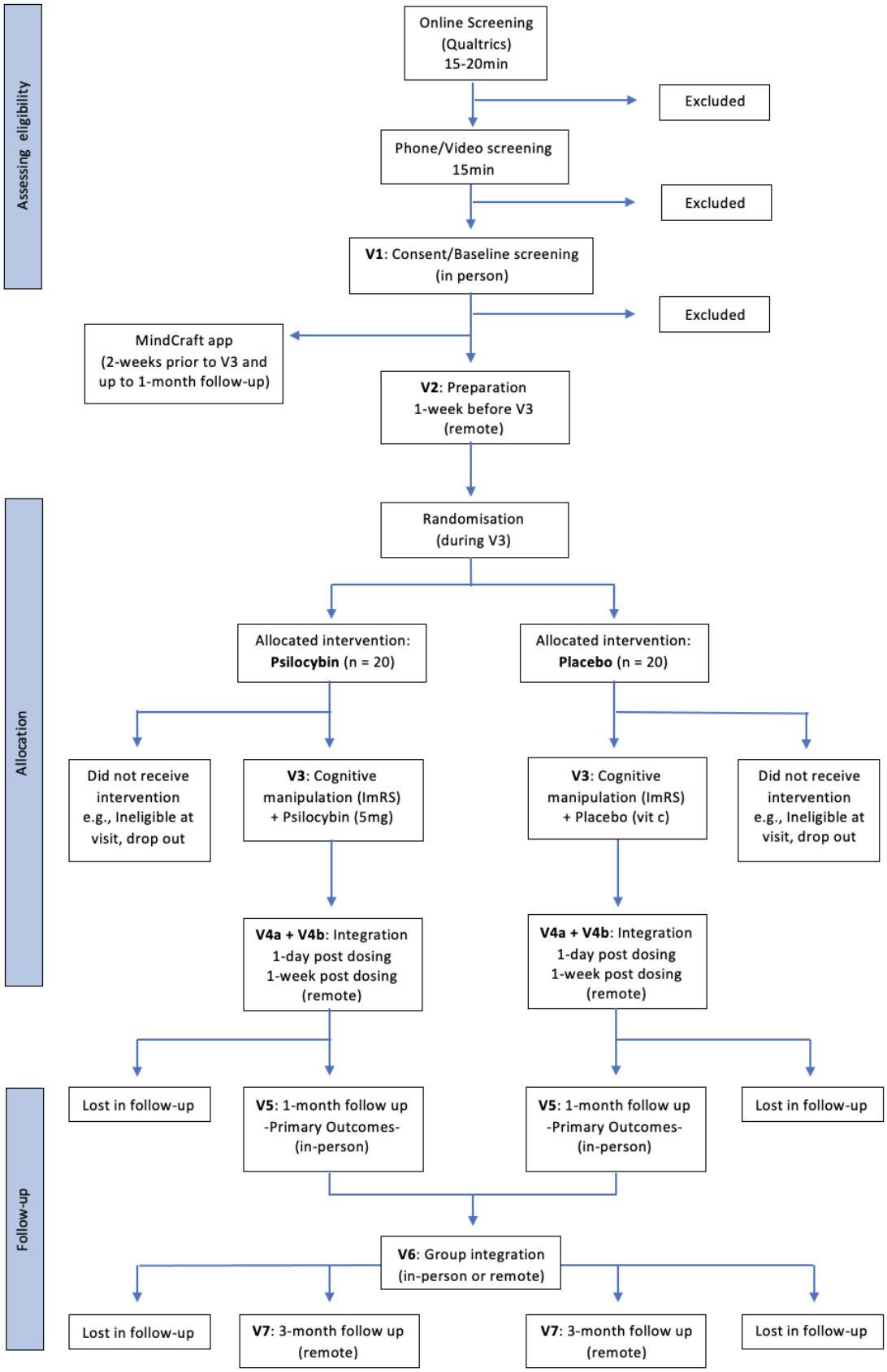

Figure 1: Flowchart of study procedures and visits

In addition, further objectives are to measure if:
- In participants randomised to psilocybin-augmented ImRS, the effects on mental imagery, cognitive schemas, depression, anxiety, stress, self-harm cognitions and behaviour and self-compassion (as above) are maintained at 12-weeks after experimental manipulation.
- To explore if changes in mechanistic outcomes correlate with any change in self-harm behaviour.

3. STUDY DESIGN

We will conduct a double-blind placebo-controlled study that will compare 5mg of psilocybin + ImRS (psilocybin-augmented ImRS) to placebo (vitamin C) + ImRS on N = 20/group participants with an experience of self-harm behaviour and associated mental imagery.

Participants will undergo three in-person visits at the NIHR Biomedical Research Centre Imperial College Clinical Research Facility (ICRF) (baseline, experimental manipulation, 1-month outcome assessment), four remote visits (preparation, integration, 3-month follow-up), and digital assessment using a smartphone app MindCraft for the duration of the study. Following the 1-month primary outcomes, a group integration will be implemented, either remotely or in-person, according to participant preference.

3.1. ENDPOINTS

All endpoints are calculated as between-group differences in change from baseline to 4-weeks (primary outcomes) and 12-weeks (secondary outcomes) post-experimental manipulation, or as simple between-group differences for measures only collected post-experimental manipulation (e.g., ratings of novel imagery characteristics).

3.1.1. Primary endpoints

- Frequency, vividness, compellingness, emotions intensity and cognitions believability scores on a 1-10 Likert scale related to self-harm and novel adaptive mental imagery
- Scores on Young Schema Questionnaire Short Form (YSQ-SF; Young, 1994)
-
- Feasibility outcomes: participants' recruitment rate, retention rate for primary and secondary outcomes.

3.1.2. Secondary endpoints

- Task performance (e.g., reaction time [RT], accuracy) to self-harm vs neutral pictures and positive vs neutral pictures on the Approach Avoidance task (AAT; (Loijen et al., 2020)
- Task performance (e.g., RT, accuracy, learning rate) on the Probabilistic Reversal Learning (PRL; (Dombrovski et al., 2010) task and the Self-harm Dot Probe Task (SH-DPT; based on (Constantinou et al., 2010)
- Scores on the Difficulties in Emotion Regulation Scale (DERS ; (Hallion et al., 2018); and the Self-compassion scale (SCS; (Neff, 2003)
- Scores on the SM-SH (state motivation for reducing self-harm scale) (Robinson et al., 2016)

- Scores on measures of psychedelic experience on based on scores on the mystical experience questionnaire (MEQ; (Barrett et al., 2015), challenging experience questionnaire (CEQ; (Barrett et al., 2016), and emotional breakthrough inventory (EBI; (Roseman et al., 2019).

4. PARTICIPANT ENTRY

4.1. Population

Young people aged 16-25 with at least 2 lifetime self-harm episodes, 1 in the past 4 weeks and who experienced self-harm-related mental imagery in the past 6 weeks.

4.2. Inclusion criteria

- At least 2 lifetime episodes of self-harm measured using the Self-Injurious Thoughts and Behaviours Interview (SITBI, Nock et al., 2007) and at least 1 self-harm episode in the past month
- Self-harm-associated mental imagery in the past 6-weeks measured using the Self-harm Imagery Interview (SHII, Hales et al., 2011)
- Any gender
- Age: 16-25 years old
- Good command of the English language
- Mental capacity to provide written informed consent
- Participant is willing to engage in tasks showing images of self-harm
- Participant is willing to talk about mental health and self-harm behaviour
- Normal ECG and blood pressure (determined by study medic)
- Psychedelic naïve
- No recreational drug use 7 days prior to the dosing visit
- Comfortable using a computer and smartphone app for data collection, access to the internet from home and willing to have some of the study visits via video-link

4.3. Exclusion criteria

- Current or past history of psychosis or mania in themselves or a first-degree relative
- Current severe suicidal ideation that constitutes a risk for their participation
- Have a medically significant condition which renders them unsuitable for the psychedelic component of the study (e.g., hypertension, diabetes, severe cardiovascular disease, hepatic or renal failure etc.)
- Previous psychedelic use
- Current or chronic history of kidney or liver disease
- Have previously experienced a serious adverse response after psychedelic use
- Intoxication on any of the visits, as assessed by difficulty in walking, the slurring of speech, difficulty concentrating or drowsiness.
- Clinically significant head injury (e.g., requiring medical or surgical intervention) that in the opinion of the investigators, contraindicates their participation
- Severe learning disability (including dyslexia/dyspraxia) that needs support to perform daily work/school tasks

- Unwillingness or inability to follow the procedures outlined in the protocol
- Are currently using a psychoactive medication (e.g.,)
- History of psychosurgery
- In the opinion of the study team, they are unlikely to comply with the study protocol and lifestyle restrictions that it imposes
- Unstable physical illness
- Heavy smoker
- Those needing regular specified medication that might interact adversely with psilocybin e.g., selective serotonin reuptake inhibitor, 5HT1 agonists, mirtazapine, trazodone, analgesics that have serotonergic effects (tramadol), MAOI's, antipsychotics with significant 5-HT2A receptor antagonist actions (risperidone, olanzapine, and quetiapine)
- Those unwilling to allow their GP or involved mental health practitioners to be informed of their participation
- Women of childbearing age who are not using reliable contraceptive methods
- Women of childbearing age who are unable to comply with or produce a positive pregnancy urine test

4.4. Withdrawal criteria

Participants may be withdrawn from the study if they are ill, become pregnant or if the investigator or study doctor feels that their participation in the study might be affecting their health. In the unlikely event that the participant's capacity to consent changes during the study, they will also be withdrawn, and their healthcare team will be notified.

5. STUDY PROCEDURES

5.1. Recruitment

The study will be advertised using posters and leaflets that will direct participants to the study website (www.imaginestudy.org), or to email imagine@imperial.ac.uk for more information. Posters will be put up in the local community and public spaces for example in:
community centers, libraries, cafes, cinema toilets, shopping center toilets, schools, colleges, universities, GP surgeries, general hospital areas, A&E departments, Imperial student health, and mental health centers. The study will also be advertised using social media platforms (e.g., Instagram, Twitter, Facebook) that will direct potential participants to the study website. We will endeavour to recruit an equal number of males and females when possible.

5.2. Study Screenings and Visits

Online Screening

Potential participants will visit the study website (www.imaginestudy.org), where they will be directed to the Qualtrics online screening form (https://imperial.eu.qualtrics.com/jfe/form/SV_dhcKgbBJtrSxjxQ). Participants will complete the online screening form, which includes questions on their demographics, mental health, history of self-harm, and smoking status. It also asks participants to complete the alcohol use disorders identification test (AUDIT) and the cannabis use disorders identification test revised

(CUDIT-R) as an initial screen for hazardous alcohol and cannabis use. This will take approximately 15-20 minutes to complete.

Telephone/ video screening

Potential participants will be initially contacted by the study team via text/email to confirm their interest in the study and arrange a short phone or video call to assess initial inclusion/exclusion criteria and answer any questions. Participants will be asked to confirm whether they have a history of self-harm within the past year and to confirm any methods of self-harm used (to prepare stimuli for the AAT). They will be asked to confirm whether they experience mental imagery (visualisation) related to self-harm and if they have experienced it within the past 6-weeks. Participants will also be asked about hobbies and other things they enjoy to prepare for the AAT and positive imagery task (PIT) in advance of the testing session. An overview of the study and testing session will also be given, and they will be sent a participant information sheet (PIS) to read and consider. This will take approximately 20 minutes. Volunteers will be given at least 48 hours to consider the PIS and if they still wish to participate, the team will arrange a date and time for the screening session.

V1: Screening and Baseline Assessment Visit

Consent and screening

The remaining screening will be completed in person at the ICRF, Imperial Centre for Translational and Experimental Medicine, Imperial College London. The screening will consist of an interview where the study will be discussed and explained, and the participants ' understanding of the procedure, requirements and commitments are confirmed.

Participants will be given ample time to take in all study information and to ask any questions and then written informed consent is taken. Consenting participants will be asked for their GP details and permission to inform their GP and any mental health practitioner actively involved in their care in the case the participant is identified as high-risk, and the clinician needs to contact the GP. A 'Summary Care Record' will also be requested from the GP. This will not be optional. This visit must be at least 2 weeks before the first experimental visit (V4).

On location, a urine drug screen (UDS), an alcohol breathalyser test and a psychiatric and physical examination will be conducted by the study doctor. The volunteers will have an electrocardiogram (ECG) and their blood pressure (BP), heart rate (HR), height and weight will be measured. A pregnancy test will be performed for female participants if applicable. They will undergo a routine neurological exam and a standard psychiatric interview (Mini-International Neuropsychiatric Interview v5 [MINI-5; (Sheehan et al., 2016)]).

Any incidental finding from the above medical screening will be communicated by the study clinician to the participant and communicated to the GP with the participant's consent.

The study clinician will also assess the readiness, expectations, and motivation of the participants to take part in the study, blinding (psilocybin/placebo), stability of their environment (e.g., family setting) and taking a psychedelic substance. Usually, readiness for

a psychedelic intervention and generally for psychological intervention is assessed in studies using high doses of psychedelic substances. Despite the low dose (5mg) used in our study, we will incorporate this assessment.

If the volunteer still appears to be suitable for the study, we will then introduce them to the study team, including those who will conduct the experimental sessions. Only subjects meeting all inclusion and none of the exclusion criteria will be included in the experimental phase.

We will encourage participants to have a trusted person (friend or relative) accompany them to the testing facility and back home on the experimental session day (V3), and help them identify one if needed. If a participant feels they do not want this, or do not have a trusted person available to accompany them, a member of staff will offer to take them home after the session or put in place an adequate plan to ensure their safety (e.g. plan phone call to family member at home etc.).

Baseline assessments during V1

Participants will then complete self-report questionnaires on Qualtrics and computerised tasks.

Questionnaires (round 1):

- Visual Analogue Scales (VAS) measuring state affect
- Depression, Anxiety and Stress Scale (DASS-21; Antony et al., 1998)
- SITBI (self-injurious thoughts and behaviours interview) (Nock et al., 2007)
- SHII (Self-harm images interview) (Hales et al., 2011)
- NART (National Adult Reading Test) (Nelson & Willison, 1991)
- YSQ-SF (Young, 1994)
- SCS (Neff, 2003)
- CEQ-SH (Craving experience for self-harm) (Di Simplicio et al., 2020)
- SM-SH (state motivation for reducing self-harm scale) (Robinson et al., 2016)
- Future Imagery Scale

Computerised tasks (round 1):

- Visual Analogue Scales (VAS) measuring state affect
- PRL (Dombrovski et al., 2010)
- Self-harm Dot Probe Task (SH-DPT; based on (Constantinou et al., 2010)

Questionnaires (round 2):

- ACE (Adverse childhood experience) (Felitti et al., 1998)
- ASA (Anhedonia scale for adolescents) (Watson et al., 2021)
- TEPS (Temporal experience of pleasure) (Gard et al., 2006)
- DERS (Difficulty in emotional regulation scale) (Hallion et al., 2018)
- MSI-BPD (McLean Screening Instrument for Borderline Personality Disorder) (Zanarini et al., 2003)
- S-UPPS-P (impulsive behaviour scale) (Cyders et al., 2014)
- COHS (Creature of Habit Scale) (Ersche et al., 2017)

Computerised tasks (round 2):

AAT (Loijen et al., 2020)

Visual Analogue Scales (VAS) measuring state affect

PIT (O'Donnell et al., 2018)

App-based daily monitoring

Participants will then be asked to download the MindCraft app (Kadirvelu et al., 2023) freely available on iOS and Android app stores. Once downloaded, they will be shown how to sign in using their unique participant code. MindCraft is a digital mental health app that enables capturing and tracking subjective experiences and behaviour in young people, as well as passive behavioural indices, and was co-designed with young people by the Faisal Lab at Imperial College London. MindCraft is currently used in research studies by our team in both general and clinical populations. Participants will be instructed to record daily occurrences of self-harm mental imagery, future positive mental imagery, affect, sleep and energy levels (5 mins daily ratings) from 2-weeks prior to their experimental visit for the study duration.

The researcher will also illustrate how to personalise active tracker data collection if any of the participants wants to track additional symptoms/experiences/behaviour that they feel are relevant to their wellbeing (e.g., self-esteem levels, socialisation). Researchers will ask participants to enable permission for the app to collect passive data, such as battery status or steps (these options can be turned off if the participant chooses). They will also show participants how to visualise the graphs tracking activity over time. Finally, they will suggest setting a daily reminder at the time of the day when a participant is most likely to respond and have 5 minutes available to complete the trackers.

Debrief

At the end of the baseline assessment, to minimise the possibility of any negative affect or distress, all participants will complete a positive imagery task (O'Donnell et al, 2018) and have a debrief session ensuring they are safe to go home (see below).

<u>V2: Preparation session</u>

Following the Screening Visit V1, participants will undergo a remote preparation session with one or both of the researchers/clinicians who will conduct the experimental session. This will provide a foundation for psychological preparation for the experimental session and allow additional opportunities for the relationship between the participant and the clinician/research team to develop. The preparatory session will be around 1 week before V3. The preparatory session will be conducted remotely (via phone/Skype/Zoom). Part of the preparation will be to warn the participants to expect some anxiety during the psilocybin administration, and they will be encouraged to let us know if they feel this. Participants will be advised to accept these feelings of anxiety and to allow the experience to unfold naturally, without psychological resistance. They will be informed of the setting and that a member of the team will always be present (see below). VAS scales will be completed at the start and end of the session.

V3: Experimental Session

Participants will be collected from their home either by taxi or car (by a trusted person) and taken to the ICRF, in the early morning. They will be advised to have a light breakfast prior to being picked up. The exact timing will be determined by the distance they need to travel so that they can arrive by 09.00. The participant will be encouraged to be accompanied by a trusted person (e.g., partner, close friend, family member) but this will be left up to the participant.

Screening

On arrival, they will be asked if they agree to carry on participating in the study and their general health and compliance with study-specific restrictions will be assessed by a short interview. Once it is confirmed they are eligible to proceed, participants will undergo: a urinary drug screen, alcohol-breathalyser, and pregnancy test (if applicable) and vital signs (BP and HR). If still eligible, participants will then complete the following questionnaires and tasks.

Baseline assessments during V3:

STAI-S (Spielberger et al., 1983)
DASS-21 (Antony et al., 1998)
CEQ-SH (Craving experience for self-harm) (Di Simplicio et al., 2020)
ABUSI (Alexian Brothers Urge to Self-Injure) (Washburn et al., 2010)

VAS measuring state affect

Experimental manipulation

Participants will be randomised to either psilocybin (5mg) or placebo (vitamin C) (1:1 ratio) using the online software application, Sealed Envelope™, on the day of V3 by a study clinician not involved in the experimental session, who will be unblinded and remain available in case of any adverse reaction/clinical need. The administration of psilocybin or placebo will be recorded in a drug accountability log, given by the research team, and recorded in the Case Record Form (CRF). The psilocybin capsules (GMP) and placebo capsules will be supplied by the USONA Institute and held by the team until required.

Participants will be administered the drug (psilocybin or placebo) by a researcher, followed by a 3 hrs break.

After the break, i.e., approximately 2 hr after the peak psilocybin effect (estimated at 1 hr after administration), participants will complete the cognitive manipulation (ImRS) together with a study clinician (see details below). If any of the participants require more time for the effects of psilocybin to wear off prior to ImRS, we will prolong the waiting time and request support from the Imperial Psychedelic Research Team.

Outcome assessments during V3

After ImRS participants will have a 1 hr break (approximately 5 hrs post-dosing/drug effects wear off), and then complete the post-manipulation outcome assessments, including:

(VAS) measuring state affect
STAI-S (Spielberger et al., 1983)
SCS (Neff, 2003)
CEQ-SH (Craving experience for self-harm) (Di Simplicio et al., 2020)
SM-SH (Robinson et al., 2016)
MEQ (Barrett et al., 2015)
CEQ (Barrett et al., 2016)
EBI (Roseman et al., 2019)

They will be instructed to continue recording daily affect, energy levels, and occurrences of mental imagery, including self-harm imagery, future positive imagery and their novel adaptive image using the MindCraft app.

Debrief and physical health check
Before leaving the session, participants will have a debrief with the researcher, who will check their affect, monitor risk, and make sure they have positive plans for the remainder of the day (see below for details). Participants will be able to leave after a final medical assessment to check they are physically fit to return home in a taxi with a trusted person or in a car driven by their trusted person. Participants will be able to go home within 5 h after dosing or later as soon as they are deemed safe to do so (see 'drug effects' section below).

<u>V4a and V4b: Integration sessions</u>
One day and one week after the experimental session participants will attend an integration session (two sessions in total). They will be asked about their experiences the previous day and of the week following dosing, how they slept, how they have felt etc. These sessions will be audio- and video-recorded (consent taken upon enrolment) for qualitative analysis. Content will follow standard procedures after psilocybin administration in psilocybin-assisted therapy, with an additional focus on mental imagery experiences. V4a and V4b will be conducted remotely (via phone/Skype/Zoom). VAS scales will be completed at the start and end of the sessions.

<u>V5: Primary Outcomes Assessment</u>
Participants will be invited to attend an outcomes assessment session 4-weeks after the experimental session in person at the ICRF. Participants will repeat the baseline assessment measures, plus an additional imagery assessment, see below.

Outcome assessments during V5
Questionnaires:
YSQ
(VAS) measuring state affect
SHII (from last assessment only)
SITBI (from last assessment only)
CEQ-SH (from last assessment only)
ABUSI (from last assessment only)
MINI – Suicidality section

ABUSI (Alexian Brothers Urge to Self-Injure) (Washburn et al., 2010)
SCS
SM-SH
DASS-21
DERS

Computerised asks:
AAT
PRL
SH-DPT

Imagery task:
The participant will be instructed to bring to mind the novel adaptive mental image that they had constructed during the experimental session ImRS procedure. Following 1 min of imaginal exposure, they will be asked to rate the image on vividness, the emotions, and thoughts intensity/believability that they had identified in the experimental manipulation session.

Debrief
At the end of the session, the same debrief procedure as in V1 will be used.

V6: Group integration session
Between V5 and V7, participants will complete a group integration session. Participants will be asked to discuss their drug, mental imagery, and mental health experience in a group setting, led by a trained member of staff. This session will be audio- and/or video-recorded (consent taken upon enrolment) for qualitative analysis. Content will follow standard procedures after psilocybin administration in psilocybin-assisted therapy, with an additional focus on mental imagery experiences. The visit will be held remotely over video call or in person, according to the participant's preference.

<u>V7: Follow-up outcomes assessment</u>
The follow-up assessment will be completed over video call by participants initially allocated to psilocybin-augmented ImRS 12-weeks after the experimental session. It will include self-report questionnaires on Qualtrics and a qualitative feedback interview to collect data on the subjective experience of the psilocybin-augmented ImRS procedures, acceptability, and potential barriers to translating the experimental manipulation into a clinical manipulation.

Outcome assessments during V6
YSQ
(VAS) measuring state affect
SHII (from last assessment only)
SITBI (from last assessment only)
CEQ-SH (from last assessment only)
ABUSI (from last assessment only)
MINI – Suicidality section

ABUSI (Alexian Brothers Urge to Self-Injure) (Washburn et al., 2010)
SCS
SM-SH
DASS-21
DERS

V8: End of study
Participants complete the study after the follow-up and outcomes assessment (V7).

5.3. Experimental manipulation: psilocybin-augmented Imagery Re-Scripting (ImRS)

ImRS is a therapeutic technique in cognitive behavioural therapy that modifies the content and features of maladaptive, often intrusive mental images associated with psychopathology or dysfunctional behaviours. A simplified ImRS procedure has been devised for the purpose of experimental studies (rather than clinical interventions), to standardise the ImRS steps, based on the Waterloo Images and Memories Interview (WIMI), and on clinical procedures (Moscovitch et al., 2011). We have used this procedure on approximately N=30 participants with a history of self-harm (same inclusion criteria as for this study) as part of the IMAGINE project. The procedure lasts approximately 45-60 min. Most participants found the procedure feasible, informative and some even helpful. Two out of 30 participants terminated the procedure early as they found the exposure phase too distressing or found it hard to identify alternative adaptive imagery; however, the distress (one participant) didn't persist and was quickly reverted after completing study measures and the debrief procedures.

Introduction
First, the therapist illustrates the ImRS procedure. Then participants begin with a mental imagery practice exercise, the 'lemon 'exercise, to familiarise themselves with using mental imagery. They are instructed to imagine a lemon; how it looks or feels. After the participant is confident they understand what imagery is and the ImRS procedure they will follow, the re-scripting section begins.

Self-harm mental imagery exposure
The participant is instructed to choose the most significant self-harm-related mental image that they feel comfortable bringing to mind. They are asked to identify and rate retrospectively what emotions and at what intensity (scale 1-100%) are usually associated with this image. They are then asked to bring to mind the image and maintain it in mind making it "as real as usually feels" for 1 min. Following this mental exposure, they are asked to re-rate the emotions previously listed. They are also asked about associated thoughts and beliefs and asked to rate their "believability" (scale 1-100%) during the imaginal exposure.

Identifying 'antidote' emotions and thoughts

The therapist then guides the participant to identify what alternative emotions and thoughts/beliefs would be more helpful to experience at times of self-harm urges (an alternative to the ones associated with the self-harm image), termed 'antidote' emotions and thoughts. Together they brainstorm an alternative image that could encapsulate these and hold a different meaning that would ultimately make the individual less likely to self-harm in real life.

Imagery Re-Scripting

The therapist then guides the participant to bring to mind the self-harm imagery again (1min) then turn it into or switch it for the alternative, 'antidote 'image, holding it in mind for 1 min. This is repeated twice. After each re-scripting the participant is asked to rate the emotions intensity and thoughts/beliefs believability of the self-harm and novel adaptive image (scale; 1-100%).

Adaptive mental image exposure.

Finally, participants are asked to bring to mind and hold in mind only the novel adaptive 'antidote' image for 1 min and emotions and thoughts ratings are repeated for the final time.

Drug effects

The effects of orally administered psilocybin at low-moderate (5mg) doses last for approximately 2-4 hours peaking at 1 hour post-administration. The 5mg dose that we have chosen is low, so we are not expecting any profound or extensive psychedelic experience. However, there is a possibility of differing experiences to be had by the individual participants and so all necessary precautions will be taken.

A trained study team member (researcher, therapist, medic) will be sitting next to the participants for the duration of the drug effect, i.e., 3 hr before ImRS, and approx. 1 hrs after ImRS and will check in hourly with the participant aside from the ImRS, but otherwise, only engage in contact if the participants choose to initiate contact with them. After drug administration, participants will be encouraged to wear an eye mask for the majority of these 4 hrs and encouraged to "go into" the experience, this will include the period during the ImRS. This procedure has been used in previous clinical studies with psilocybin conducted by the Imperial College team.

Current recommendations in the field include that the psychedelic drug only be taken in a positive environment where the participant feels comfortable and relaxed and is supported (Johnson et al., 2008). To that end, efforts will be made to arrange the intervention room to promote relaxation without compromising medical safety. Mobile phones will be switched off during every session and efforts will be made to minimize unexpected interruptions. Relaxing music will be used to facilitate calm and relaxation outside the period of ImRS.

The schedule will afford a minimum of 4 hours of observation after the oral ingestion of psilocybin, which is sufficient time for most psychedelic or physical effects to have disappeared, as most of these effects last no longer than 4 to 6 hours after oral psilocybin is administered (Gouzoulis-Mayfrank et al., 1999; Hasler et al., 2004; Hollister, 1961; Passie et

al., 2002; Vollenweider et al., 1998; Wittmann et al., 2007). If participants are not fit to leave after 4 hours, they will continue to be monitored until they are. It is expected that the participants will be able to return home that day considering the low dose of psilocybin they will receive. In other similar studies, the Imperial PRG have given psilocybin in over 54 dosing sessions to healthy volunteers and other patient groups at differing doses of at least 10mg and all have been safe to leave on the evening of their test day. In two recent psilocybin trials in patients with moderate to severe depression 20 of them had an initial test dose of 10mg, double the dose we are using in our study, after which very few experienced any effects, and these were very mild and resolved within the testing period and were able to go home that day (Carhart-Harris et al., 2016). When they are assessed to be safe to return home, they will be sent home by taxi or in a car. Participants will be accompanied by a trusted person – or if this is not possible by a member of the core study team. This will mitigate problems if any effects of the pharmacological challenge manifest following leaving the ICRF, which is not expected. Participants will be given a card containing the emergency contact details of the study team and information about the study in case they experience any untoward events or issues overnight, or throughout the rest of the study.

5.4. Mood repair and debrief procedures

At the end of the in-person sessions V1, V3 and V5, a study team member will ensure that participants are feeling okay before leaving.

To minimise the possibility of increased negative affect after sessions including discussing mental health issues and showing self-harm-related images, all participants will complete a Positive Imagery Task (PIT) previously shown to improve positive affect (O'Donnell et al, 2018). The task will be completed at the end of the baseline session V1 and outcome assessment session V5, as well as at the end of the experimental session V3 if needed to improve positive affect before participants go home.

In the task, participants are trained in positive imagery generation by combining a picture and a word cue and instructed to rate the vividness and valence of this imagery (e.g., a neutral image of the countryside with the words 'fun walk'). Picture-word cues will relate to activities the participants enjoy (described during the telephone screening). We have successfully used this task in our IMAGINE project (IRAS: 19/SC/0275) where we have tested the same population using the same tasks and ImRS procedure.

Participants will also be given the opportunity to watch a film with calming positive images, from a publicly available series, shown to be soothing (www.projectsoothe.com). They will then be given a drink and asked questions related to current feelings, what they are doing that evening etc., to ensure they have a positive plan. They will also be given the opportunity to ask questions about the study.

For online sessions V2 and V6, participants will be debriefed at the end of the session to ensure they are feeling okay before ending the call and if needed the same debrief procedures will be adopted (PIT and projectsoothe video).

6. MATERIALS

6.1. Experimental tasks

Approach Avoidance Task (AAT; (Loijen et al., 2020) (10 minutes)
Approach and/or avoidance biases will be assessed by the AAT. During this task, participants will see either self-harm images, positive images, or neutral images, and will respond to these by moving the joystick toward themselves (approach) or away from themselves (avoidance). Movement of the joystick is accompanied by zoom-in (approach) or zoom-out (avoidance), strengthening the subjective impression of pulling the picture in or pushing it out. Reaction times will be measured to determine if they show avoidance (longer reaction time) or approach (shorter reaction time) towards the self-harm, positive or neutral stimuli. Self-harm images for the AAT have been reviewed by our YPRG and the task has been used in our IMAGINE study with the same population.

Probabilistic Learning Task (PRL; (Dombrovski et al., 2010) (15 minutes)
During this task, learning from rewards and punishments will be assessed. In this task, participants are required to win as many points as they can. In the first phase of the task, participants learn that responding to certain abstract stimuli results in winning or losing points. In the second phase, associations reverse, and participants are required to adapt their performance. The reward consists in winning 100 points and a 'yay' sound, while the punishment consists in losing 100 points and a 'boo' sound.

Self-harm Dot Probe Task (SH-DPT; based on (Constantinou et al., 2010) (15 minutes)
During this task attention bias to self-harm cues is assessed. Participants are presented with both self-harm and neutral images (cues), which are matched to the self-harm images for complexity, colour, and type. Each participant will be allocated their own task based on their methods of self-harm, where half of the self-harm images will be tailored to their methods. The other half of the images will be the same across all participants to reduce task design variability. In the task, a fixation cross is shown, followed by two images. One of the images will then be replaced by either one or two dots (probe). Participants are instructed to determine as quickly as possible whether one or two dots were showing. A self-harm trial was 'congruent' if the probe replaced the self-harm image or 'incongruent' if the probe replaced the neutral image. Congruent, incongruent, and neutral trials were used to calculate an Attention Bias Index and Disengagement Index for each participant.

Positive Imagery Task (PIT) (O'Donnell et al, 2018) (15 minutes)
See section '5.4. Mood repair and debrief procedures' for task details.

6.2. Questionnaires

Self-Injurious Thoughts and Behaviours Interview (SITBI) (Nock et al, 2007).
Only the non-suicidal self-injury section of this interview will be used, modifying the term 'non-suicidal self-injury' to 'self-harm' as our definition includes all self-harm behaviour regardless of intent. This interview assesses various aspects of self-harm behaviour including frequency, methods, and functions. This interview has excellent inter-rater reliability and

test-retest reliability. One question on recency of self-harm will also be included, for example, 'When was the last time you self-harmed?'

Alexian Brothers Urge to Self-Injure Scale (ABUSI) (Washburn et al, 2010).
The ABUSI measures the intensity of the urge to self-harm over the past week. This measure captures both emotional and cognitive aspects of how motivated someone is to engage in self-harm. It has shown adequate internal consistency, test–retest reliability, sensitivity to change, and convergent, predictive, and incremental validity.

Craving Experience Questionnaire for Self-Harm (CEQ-SH) (Di Simplicio et al., 2020, adapted from May et al, 2014). This measure assesses the frequency and strength of the desire to self-harm over the past week. It contains 11 items giving subscales of Intensity, Imagery, and Intrusiveness.

Self-Harm Images Interview (SHII) (Hales et al., 2011).
The SHII documents the self-harm-related mental images most significant to the individual. The image does not have to be depicting the act of self-harm, but it has to be related to self-harm. Participants are asked to rate the extent to which each emotion was experienced immediately after experiencing the images, on a five-point rating scale ranging from 1 ('very slightly or not at all') to 5 ('extremely'). Participants are also asked to rate on a scale ranging from 0 to 9 several other qualities related to the image, e.g., how vivid or compelling it is.

State Motivation for Reducing Self-harm Scale (SM-SH) (Robinson et al., 2016)
This is a 12-item scale assessing motivation to control self-harm behaviour. Participant are asked to rate from 0 (never) to 10 (constantly), the strength of motivational cognitions "right now..." followed by, for example, "...how strongly do you want to do it?".

Mystical Experience Questionnaire (MEQ30) (Barrett et al., 2015)
This is a 30-item revised Mystical Experience Questionnaire, developed to measure mystical-type experiences occasioned by psilocybin-containing mushrooms. It is comprised of four factors: mystical (including items from the internal unity, external unity, noetic quality, and sacredness scales of the original MEQ), positive mood, transcendence of time and space, and ineffability.

Challenging Experience Questionnaire (CEQ) (Barrett et al., 2016)
This is a validated questionnaire that explores potentially challenging experiences of affective, cognitive, and somatic nature while under the influence of psilocybin. It has 26 questions, five-point Likert scale, and is divided into seven dimensions: (a) Isolation, (b) Grief, (c) Physical distress, (d) Fear, (e) Insanity, (f) Paranoia, and (g) Death, to provide a phenomenological profile of challenging aspects of experiences with psilocybin. Factor scores were associated with difficulty, meaningfulness, spiritual significance, and change in well-being attributed to the challenging experiences.

Emotional Breakthrough Inventory (EBI) (Roseman et al., 2019)
This is a validated questionnaire exploring the phenomenon of experiencing emotional release or breakthroughs under the influence of psychedelic substances. It has 8-items, out of which two were 'negative' items that required reverse scoring. Items were rated using a visual analogue scale (VAS) (0–100, with incremental units of one) with zero defined as 'No, not more than usually', and 100 defined as 'Yes, entirely or completely'. Items include "I faced emotionally difficult feelings that I usually push aside; I felt able to explore challenging emotions and memories" and "I felt emotionally stuck throughout, without breakthrough".

Depression, Anxiety, Stress Scale (DASS-21) (Antony et al., 1998)
This questionnaire measures depression, anxiety and stress and has acceptable to excellent internal consistency validated in both clinical and non-clinical samples. The depression scale measures symptoms associated with dysphoric mood e.g., worthlessness; the anxiety scale measures symptoms associated with physiological arousal such as trembling, as opposed to symptoms of generalised anxiety; and the stress scale measures symptoms of tension and reactivity to stressful events. Participants are asked to rate on a 4-point Likert scale how much 21 items related to them over the past week (e.g., 'I found it hard to wind down').

State-Trait Anxiety Inventory – State (STAI-S) (Spielberger et al., 1983)
This questionnaire measures state anxiety. It has 20 items including, "I am tense; I am worried" and "I feel calm; I feel secure." All items are rated on a 4-point scale (e.g., from "Almost Never" to "Almost Always"). Higher scores indicate greater anxiety.

Difficulties in Emotion Regulation Scale Short Form (DERS-SF) (Hallion et al., 2018)
(Kaufman et al, 2016) This scale measures general emotion regulation ability as well as six subscales that measure various aspects of emotion regulation, for example, difficulties engaging in goal-directed behaviour when upset, and limited access to emotion regulation strategies. The scale has 18 items and has been adapted from the original long version. Participants are asked to rate these items on a 5-point Likert scale. The scale has high internal consistency.

Anhedonia scale for adolescents (ASA) (Watson et al., 2021)
This is a validated 14-item scale designed specifically for adolescents to measure loss of interest and pleasure in previously enjoyable experiences. It has one general factor and three specific factors producing the best fit to the data, (1) Enjoyment, Excitement, and Emotional Flattening (negatively framed); (2) Enthusiasm, Connection, and Purpose (positively framed); and (3) Effort, Motivation, and Drive (negatively framed).

Short Impulsive Behaviour Scale (S-UPPS-P) (Cyders et al., 2014)
This 20-item scale measures five subscales of impulsivity (positive urgency, negative urgency, lack of premeditation, perseverance, and sensation seeking). Participants are required to rate how much they agree or disagree with these items on a 4-point Likert scale. This scale has good internal consistency and has replicated the internal consistency of the original long UPPS-P.

Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993)
This is a 10-item measure of alcohol misuse and possible dependence, in which participants are asked to rate items related to their drinking (e.g., 'How often do you have a drink containing alcohol') on a 5-point scale. The AUDIT is an effective means of identifying hazardous or harmful drinking behaviour.

Cannabis Use Disorder Identification Test Revised (CUDIT-R) (Adamson et al., 2010)
This measure is used to screen for problem cannabis use. Participants are asked to rate a series of eight items relating to their cannabis use (e.g., 'How often do you use cannabis') on a 5-point Likert scale. The measure has excellent internal consistency.

Smoking assessment
Participants will be asked questions about their smoking and vaping, such as:
Do you smoke? Yes/No/Occasionally
If yes, how many cigarettes do you smoke a day?
Do you vape? Yes/No/Occasionally
If yes, how many times do you vape a day?

MINI The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 2016)
It is a short structured diagnostic interview which explores 17 disorders according to DSM diagnostic criteria. This interview will be carried out by trained researchers. Depending on the number of disorders experienced by participants the time taken for interview varies. In the current sample, it is estimated that the interview will take approximately 30-45 minutes.

McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) (Zanarini et al., 2003)
It is a validated 10-item screening measure for Borderline Personality Disorder (BPD) with all items based on the DSM-1V diagnostic criteria for BPD. Two items are based on the ninth DSM-IV criterion of paranoia/dissociation, and each of the remaining eight items is based on the remaining eight DSM-IV criteria.

National Adult Reading Test (NART) (Nelson & Wilson, 1991)
It is a widely used measure of IQ in clinical research. Participants are given a list of 50 predefined words and asked to read these aloud. The number of words correctly and incorrectly pronounced are then scored.

Adverse childhood experience (ACE) (Felitti et al., 1998)
It is a 10-item, widely used questionnaire to define physiological and psychological abuse during childhood and to define violence against the respondent's mother.

Temporal experience of pleasure (TEPS) (Gard et al., 2006)
It was designed to measure individual trait dispositions in both anticipatory and consummatory experiences of pleasure. It contains 18-items, with a 10-item anticipatory pleasure scale and an 8-item consummatory pleasure scale.

Young schema questionnaire short form (YSQ) (Young et al., 1994)
This is a 75-item questionnaire, developed to assess Early Maladaptive Schemas, which account for the dysfunctional beliefs in individuals with personality disorders or maladaptive personality traits.

Self-compassion scale (SCS) (Neff, 2003)
This is a validated and reliable 13-item scale. It measures self-compassion; the notion of being kind and understanding to oneself in instances or pain or failure, rather than being harshly self-critical.

Creature of Habit Scale (COHS) (Ersche et al., 2017)
This scale assesses the tendency towards routine behaviour in everyday life and automaticity in eating behaviour, both of which provide a valid and reliable index of habit proneness. Participants rate on a 5-point Likert scale how much they agree or disagree with 27 items. Participants with restrictive eating disorders will be excluded from part two of the scale (automaticity in eating behaviour) during analysis.

7. ADVERSE EVENTS

7.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.2. Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

7.2.1. Non-serious AEs

All such events, whether expected or not, should be recorded - it should be specified if only some non-serious AEs will be recorded, and any reporting should be consistent with the

purpose of the trial endpoints. Self-harm behaviour (mild to moderate) being the pre-existing condition will not be recorded as a non-serious AE.

7.2.2. Serious AEs

An SAE form should be completed and emailed to the Chief Investigator (Martina Di Simplicio) within 24 hours. However, relapse in self-harm behaviour (severe) including hospitalisation, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', i.e., resulted from the administration of any of the research procedures; and
- 'unexpected', i.e., an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (m.di-simplicio@imperial.ac.uk**)**

Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

8. STATISTICS AND DATA ANALYSIS

8.1. Sample size

As this is an experimental medicine study, we have not conducted a formal sample size power calculation. Recommended sample sizes for feasibility studies range from 20-40 per group (Teresi et al., 2022). Previous first-in-kind studies exploring the effects of psilocybin had samples ranging between 10-20 participants, typically using a within-subject design with placebo or low-dose psilocybin vs. full-dose psilocybin approximately 1-4 weeks apart (Carhart-Harris et al., 2018; Carhart-Harris et al., 2016; Griffiths et al., 2016; Grob et al., 2011). We have chosen a between-subject design as it is unknown if the ImRS manipulation may exert effects on our primary outcomes that may last beyond the above within-subjects interval of 1-4 weeks, which could confound effects in a within-subjects design.

8.2. Statistical analysis

As our study is likely unpowered to run inferential statistics on primary and secondary outcomes, we will primarily run descriptive statistics and measures of effect size in the between-group and within-group differences (post vs pre-experimental manipulation) on our self-report and cognitive measures. We will also explore whether any differences in task performance (e.g., reaction times) are influenced by self-harm, imagery, and psychedelic experience measures. Behavioural data from the learning task will also be explored using computational methods, for example, a reinforcement learning model with free parameters such as i) memory, ii) learning rate from rewards, iii) learning rate from punishments and iv) exploration (Dombrovski et al., 2010). Data will be analysed using software packages such as SPSS, R, Python and Matlab.

8.3. Data storing

Data and all appropriate documentation will be stored for a minimum of 10 years (5 years if ICHT sponsored study) after the completion of the study, including the follow-up period.

9. REGULATORY ISSUES

9.1. Ethics Approval

The study has obtained approval from the NHS xxx Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions.

9.2. Managing risks related to psychedelic treatment

Before, during and after the dosing session, participants will receive psychological support from trained clinicians. On the dosing day, participants will only be allowed to leave the ICRF once the study psychiatrist is confident that they are fit to do so and signs the participant out. We will strongly encourage participants to bring a support person (friend or family member) with them.

The participant will be asked to return home in the company of a support person/next-of-kin and if this is not possible, then to have their support person waiting for them at home. Participants will be asked to text or call us when they return home. We will also have the contact details of their support person/next-of-kin so that we can contact them if we cannot manage to contact the participant themselves.

Both the participant and their support person will be encouraged to contact us should any problems arise. In this way, any concerns in the immediate period or thereafter can be easily brought to our attention. A 24-hour contact card outlining contact with the study team and emergency services will be provided.

9.3. Pharmacological challenge – psilocybin

Psilocybin is a safe drug and has been given to several hundred patients and volunteers in modern studies. In a thorough review of dosing sessions in 110 healthy subjects, dysphoric experiences/bad trips were rare and dose-dependent and there was no evidence of subsequent drug abuse, flashback phenomena or prolonged psychoses (Erich Studerus et al., 2011). In addition, the dose we plan to use in this study is low and any effects are expected to be less as a result of this. However, here are some of the key ethical and safety considerations.

Recent independent assessments of the harms of popular drugs of abuse, conducted by international experts (Nutt et al., 2007; Nutt et al., 2010; van Amsterdam & van den Brink, 2010) and experienced drug users (Carhart-Harris et al., 2011; Morgan et al., 2010) have consistently rated magic mushroom (psilocybin) as one of the least harmful recreational drugs. Commonly cited risks include: prolonged psychotic reactions, flashback phenomena/hallucinogen persisting perceptual disorder (HPPD), and bad trips. Prolonged psychotic responses are extremely rare in clinical studies with psilocybin (< 1 %) (Erich Studerus et al., 2011), even with very high doses (Griffiths et al.,2011) and none have been reported in modern studies or studies with patients (Carhart-Harris et al., 2011; Grob et al., 1996; Moreno et al., 2006). The risk of flashback phenomena is also minimal. Typically, flashbacks or HPPD refers to drug-like visual perceptual effects (e.g., "trails" or geometric patterns) occurring when no drug has been taken. The two largest surveys on this phenomenon found that very few psychedelic drug users (3 – 4 %) report perceptual changes that are distressing to them (Carhart-Harris & Nutt, 2010). There have been no cases of flashback-like symptoms occurring in modern clinical studies with psilocybin (Erich Studerus et al., 2011) – even with very high doses (Griffiths et al., 2016).

Negative acute psychological experiences or 'bad trips' do occur more frequently, but they are strongly dose-dependent (Griffiths et al., 2011; E. Studerus et al., 2011). In a sample of 36 healthy subjects given a high oral dose of psilocybin (30 mg), 11 subjects reported strong anxiety at some point during their session (Griffiths et al.,2011). However, the anxiety was short-lived in every case and no persistent negative mood effects were reported. Most of the subjects reported that their experience had been insightful and beneficial, and this positive appraisal of their experience was sustained (Griffiths et al., 2008). This is consistent with the claim that psychologically 'challenging' psychedelic drug experiences can be especially beneficial – if properly mediated. In work that the Imperial Centre for Psychedelic Research has conducted, when dosing 40+ subjects with 2 mg psilocybin i.v., 30 of which took place in a spatially restrictive and noisy MRI scanner, anxiety scores were not significantly higher after psilocybin than placebo. No subjects showed panic or asked for their scans to be aborted.

Patients with psychiatric vulnerabilities are thought to be more likely to experience bad trips, but we will strive to minimize this risk through psychological preparation, good patient-staff rapport, and a positive environment. Bad trips are best managed psychologically (Griffiths et al., 2008, Johnson et al., 2008) and administration of a benzodiazepine would only be used in cases of severe panic. Detailed protocols are available for the safe management of clinical research with psychedelics (Johnson et al., 2008). The summary of side effects associated with

oral psilocybin can be found below and in the investigator's brochure, which will serve as the reference safety information for this study:

Below is a summary of the prevalence of side effects:
Common:
Visual hallucinations, feelings of unreality and altered sense of time.
Increased anxiety, particularly at the onset of the drug effects.
Increased heart rate and blood pressure (We will check heart function at screening and patients with heart abnormalities will be excluded from the study).
Transient headaches, lasting for 1 to 2 days (max) post-dosing

Less common:
Nausea
Dizziness, drowsiness, fatigue, and sleepiness.
A 'bad trip '/ 'challenging experience ,'i.e., negative thoughts and mood during the short-term drug effects (in other psilocybin studies, good preparation, support during the experience and integration can mitigate negative impacts of this. With support, challenging content can be worked through and contribute to a psychological 'breakthrough 'on the part of the patient. Recent evidence indicates that challenging psychological experiences in supportive environments can produce therapeutic benefits, improving psychological well-being in the long term (Griffiths et al.,2016). The risk of this is also lower with 5mg, a low dose.
Temporary paranoia or suspiciousness

Rare:
Flashbacks or persisting perceptual phenomena (we did not observe any cases of this in our work with psilocybin. However, about 10 % have reported perceptual effects lasting beyond the acute drug effects in experiments with orally administered psilocybin (although they were not reported as distressing and are typically transient), about 35 % of recreational users of psychedelics describe this and less than <5 % describe them as distressing.
Worsening of mental state after the drug experience is rare and was not seen in our work or that of others. However rare cases are reported in the literature.

It is strongly advised that psychedelic drugs only be taken in a positive environment where the patient feels comfortable and relaxed and is supported (Johnson et al., 2008). For this reason, we will arrange the intervention room to promote relaxation without compromising medical safety. In addition, the following precautions will used to minimise any negative events.

Prior to drug administration, we will prepare each participant to ensure that they are aware of what to expect (1 preparation session). We will also ensure that they meet the key members of the research team prior to dosing. Professor Griffith's (Johnson et al., 2008) team have used this approach and believes it to significantly reduce the possibility of any psychological adverse events following administration and serve to put participants at ease in the process. We have also used this approach in previous studies using psilocybin for depression at Imperial College and found the same.

Participants will be escorted and chaperoned by a member of the research team at all times throughout their participation in the study and for the 3 to 4 hours during which they will be under the acute effects of psilocybin they will always be supported by at least one team member.

The acute effects of the drug should be over within 4 hours following administration. We will carefully monitor the participant for the duration of their stay at the ICRF. Staff will be vigilant of any overly unusual behaviour, anxiety, and paranoia. Interpersonal exchanges that would be readily overlooked in a normal state of awareness may assume extreme and confusing meanings for persons under the influence of a psychedelic substance. Staff will be aware of this and adopt an open and non-judgmental manner, allowing the participant to speak freely without challenge.

On occasion, nursing staff or other staff may be called upon to monitor a participant, but this will be rare as there will normally be sufficient personnel from the research team to perform this function.

We do not envisage any serious side-effects from the administration of the drug but, participants may experience anxiety reactions or paranoid thoughts. These are likely to be short-lived and will be managed by psychological approaches such as reassurance and adopting a calm and supportive demeanour and by using behavioural techniques such as guided imagery. There were no serious adverse events in our two previous studies using 10mg and 25mg psilocybin in patients with moderate-severe depression.

If the situation were to deteriorate further, the research team may have to be more proactive in their attempts to calm the patient and reduce distress and this may require an assertive tone of voice and/or the supportive hand-holding of the individual if their behaviour becomes erratic, for example. This would only be done in an attempt to alleviate the participant's distress and maintain their and the research team's safety. This will be discussed with the participants beforehand in the preparation sessions.

In the unlikely event that a participant becomes behaviourally disturbed, medical personnel will be on hand to physically restrain or administer tranquillising medication if necessary. Typical doses administered would initially be PO 5 – 10 mg diazepam, or an equivalent dose of another benzodiazepine, which can be repeated and titrated according to the product license to achieve the required effect. If such an adverse event were to occur, the study psychiatrist will closely monitor the participant at all times and in no circumstances will they be permitted to leave the ICRF until the psychiatrist is satisfied that they are well enough to do so.

A final contingency for the handling of any persisting events that mean the clinical team are unable to allow them to go home on the test day will be to take them to the nearest A&E department (Charing Cross Hospital) for further assessment and treatment.

On discharge from the ICRF, the participant will be reviewed which will encompass an assessment of their current level of risk and whether they have returned to their normal level of functioning. Once this is performed, the psychiatrist, together with the rest of the team, will decide if it is safe for them to leave the unit and return home.

On discharge from testing, phone numbers for key members of the research team will be provided to the participants, along with a leaflet with further information on organisations that can offer support in times of need.

A follow-up after the dosing day and a 1-month follow-up are in place for monitoring the participant's status and mental health condition. We will therefore be able to detect and assess any delayed or persisting adverse events. Participants and their trusted person will be encouraged to contact us should there be a persistent deterioration in their mental or physical health.

Should we have any concerns about the participant's mental health and safety during the study or follow-up the same procedures will be followed as described below.

9.4. Managing risk from exposure to self-harm stimuli, mental imagery of self-harm and assessments of self-harm / suicide and mental health

The tasks and stimuli used in the study are based on tasks and stimuli already used in our previous experimental studies (IRAS: 19/SC/0275) with individuals who self-harm and no incidents were reported attributable to these (Rodrigues et al., 2023). However, theoretically, it is possible that a number of procedures (listed below) included in the study may result in (i) causing serious distress or (ii) may reveal information relevant to the participant's mental health and safety such as risk of self-harm and suicide. If this is the case the necessary steps to manage participants' wellbeing and safety will be taken as described below. The Chief Investigator (CI) is a Consultant Psychiatrist with previous experience in conducting clinical and experimental research with vulnerable young people including young people with self-harm and pharmacological experimental medicine research. The CI and other research clinicians on the team will overview all experimental procedures and be available either on-site or over the phone during the experimental sessions.

<u>Study procedures, which may result in (i) increased perceived distress and/or (ii) disclosure of information relevant to the participant's mental health and safety are as follows</u>:

1) Responding to the MINI questions.
2) Completing questionnaires on mood, self-harm imagery, and self-harm assessment.
3) Recalling mental images related to past negative outcomes associated with self-harm, during ImRS, which may impact on the participants' mood.

While the risk of major distress occurring is minimal based on previous research using similar procedures, researchers will always remain sensitive to signs of participant distress and will terminate any procedure if the participant becomes distressed and wishes to stop. Researchers will also check the participant's mood state and safety upon completion of the

self-report questionnaires and computer tasks. Participants' well-being and safety will be considered as a priority concern at all points in the study, and a clinician will be always available on-site when testing participants to support them if needed. To minimise anxiety to the participants during the study, where possible, the sessions will be conducted by the same study personnel.

The risk of distress occurring will also be minimised in the following ways:

Responding to the MINI assessment and questionnaires:
Participants will be fully informed about the content of the MINI and other questionnaires. The MINI will ask questions about current and prior psychiatric disorders. Questions will also be asked about drug and alcohol use, including illegal drugs. All these questions are a standard component of psychiatric interviews. The participant information sheet will provide information about the type of questions participants should expect in the interview, so they can give genuinely informed consent to participate. All named researchers in the study who will carry out the MINI will receive training for the interview and specific supervision by the research team that will help to manage any distress arising during the interview process.

Viewing images related to self-harm in the computer-based tasks:
Participants will be made fully aware that they will be shown images related to self-harm in the participant information sheet, when completing the online screening, and again during the telephone screening. They will also be required to demonstrate their willingness to view these images during the telephone/video screening, and so will expect to be shown these during the testing session. Participants will be made fully aware before beginning the testing that they do not have to complete the tasks if they feel uncomfortable or distressed.

Risk of distress from bringing to mind self-harm-related images during the imagery manipulation (ImRS):
The clinicians/researchers conducting the ImRS are trained in this technique and have experience in delivering it either or both in clinical and experimental settings, including the iMAGine study (IRAS: 19/SC/0275). Participants are instructed to bring to mind the images as it happens in their daily life but in a way that is tolerable (i.e., to "tune down the image" if needed). The ImRS session will always end with exposure to the new adaptive image. The clinicians/researchers are trained to check that participants' affect has returned to a positive state and if needed will also offer to complete a positive imagery task shown to improve mood. At the end of the session there will be a debrief to ensure participants are okay before leaving. The researchers will be trained to make sure the session ends with the participant feeling supported and endowed with the necessary coping strategies in place to go safely back to their home.

A participant disclosing information relevant to their health and safety such as suicidal risk, or the safety of others, will be addressed in the following ways:
In session, adequately assess the mental state and risk of the participant once information suggesting these may be problematic is disclosed.

Assess current acute severe suicide ideation by asking whether questions C4, C5 and C6 (suicidality section) in the MINI have applied to participants during the past week.
The researcher will call the clinician supervising the testing to assess the participant and advise on further actions, including whether the participant can participate in the remainder of the study. Any review conducted by one of the covering clinicians will be documented in the participant's study file.

In session, carry out all possible interventions to reassure, support, and reduce active distress to the minimum once this has become apparent.
Agree with the participant on a strategy to ensure their needs (in terms of mental state and safety) are met as soon as possible; this is likely to include informing other individuals such as family, friends, and other mental health workers or clinicians; and/or informing via phone, email or letter the participant's GP and/or other health professional (consultant psychiatrist, care coordinator etc.) named by the participant at the time of enrolment in the study (Screening visit). If the situation is deemed as needing urgent intervention, the mental health Single Point of Access service local to the participant will be contacted with a referral for urgent mental health assessment.

All participants will be asked for their address and GP details at the start of the video-call screening, in case the participant is identified as high-risk, and the clinician needs to contact their GP. Participants will be informed that all information is confidential. The limits of confidentiality (e.g., that the researcher may have an ethical duty to disclose information to a third party to protect the immediate safety of the participant or someone else in the rare circumstance in which it is judged that the participant or someone else is at risk of serious harm) are made explicit to participants in both the participant information sheet and the consent form.

Procedures have been developed based on comments (e.g., that we will need to minimise negative emotions after showing self-harm images), feedback and suggestions (e.g., to include a debrief), from the iMAGine/PsiloIMAGINE Young Person's Research Groups. The group included in total 10 young people with lived experience of self-harm and other mental health issues. The group has approved the final protocol and study material.

9.5. Benefits

In our study participants take part in an experimental manipulation that is based on a cognitive behaviour therapy technique (imagery re-scripting) that has been shown to be beneficial as a single intervention or brief intervention with different mental health disorders, including initial evidence with self-harm (Sosic-Vasic & Schaitz, 2020). While this study does not provide a therapeutic context, it is possible that some participants may benefit temporarily or even long-term, by using the technique provided during the experimental manipulation, in their everyday lives to cope when self-harm-related mental imagery is present.

No previous study has used psychedelics in the context of self-harm behaviour, so we are unable to say if augmenting imagery re-scripting with psilocybin will have beneficial effects.

Current literature using psychedelics in a therapeutic/experimental setting for other mental health disorders and maladaptive behaviours indicates that there may be some therapeutic benefit for participants from taking part. Hence participants randomised to psilocybin may experience improvements in various aspects of mental wellbeing in relation to or even regardless of the imagery-re scripting procedure.

All participants will take part in "integration sessions" after the experimental manipulation that can improve emotional awareness and understanding of triggers and mechanism underpinning self-harm.

Finally, while there may also be no personal benefit at all, participants may feel a sense of reward for helping us improve our understanding of self-harm behaviour in young people and develop better treatments for self-harm.

9.6. Participant Reimbursement

Participants will be reimbursed for time dedicated to study assessments at an approximate rate of 10£/hr, i.e., £150 in total, based on previous similar experimental studies conducted by the team.

9.7. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Participants are provided with information about the broad aims of the study, what participation entails, rights to withdraw and terms of confidentiality and data protection. It is clearly stated that the participant is free to withdraw from the study at any time for any reason with no obligation to give the reason for withdrawal. The participant is allowed as much time as needed to consider the information, and the opportunity to question the researchers, their GP, other clinicians involved in their care, or other independent parties to decide whether they will participate in the study.

Consent to participate in the online screening is given by a tick box before completing the online screening questionnaire. When testing is conducted in person, written Informed Consent is then obtained before the testing session by means of the participant's dated signature, and signature of the person who presented informed consent. A copy of the signed Informed Consent form is given to the participant. The original signed form is retained at the study site. Informed consent also includes consent to inform referring clinicians about participation in the study and risk management procedures, which include breaking

confidentiality. Finally, participants will be given the option to also consent to being contacted for future studies at Imperial College London.

9.8. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Participants' confidentiality is only breached in case of disclosure of information relevant to their health and safety, in which case this will be communicated to the participant's GP or other indicated health professional (as detailed above).
Data will be pseudonymised (see below).

9.9. Data Handling and Record Keeping

All data will be pseudonymised. A study-specific participant ID number will identify the participant. The name and any other detail will not be included in any study electronic database compiled for statistical analysis of the research outcomes. Electronic data will be stored on network drives on the Imperial College server.
A document matching identity and participant ID number is centrally managed by the research team and only accessed by named research team members on an encrypted server. Only named researchers will have access to the database that holds the personal information to access contact details while taking part in the study.
Paper-based consent forms and participant questionnaires will be stored at the Division of Psychiatry, Imperial College London in separate locked cabinets. All documents are stored securely and only accessible by study staff and authorised personnel.

Data from the questionnaires will be collected using Qualtrics, a research data collection platform (https://www.qualtrics.com/uk/). This data will be stored on a server owned by Qualtrics, whose data storage is compliant with OECD privacy rules and the European Union Directive on Data Protection. Data will be downloaded from Qualtrics and later stored on Imperial College London secure servers. This data will also be stored in a pseudonymised format with the participant ID.

The data collected by the MindCraft app will be transferred directly from the app to the secure data server located in Imperial College data center only accessed by the research team. This data will also be stored in a pseudonymised format and will be linked to the Qualtrics collected data using the participant ID.

The data will be stored in compliance with GDPR guidelines. Data will be stored for a period of at least 10 years after the date of publication of results in accordance with the minimum standard for journal publications as outlined in the British Psychological Society Good Practice Guidelines for the Conduct of Psychological Research in the NHS, and the American Psychological Association Publication Manual (fifth edition). During the time of storage Dr Martina Di Simplicio will be custodian for the data, and it will be stored in appropriate data archive facilities provided by Imperial College London. Named researchers will have sole access to the data over this time period.

The named research team will undertake analysis of the data from the study. This analysis will take place at the Division of Psychiatry, Imperial College London. Pseudonymised data will be made available to other researchers after the end of the study via data repositories such as Open Science Framework.
22.

9.10. Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study, which apply to this study.

9.11. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.12. Funding

Financing will be provided by the London Interdisciplinary Social Science Doctoral Training Partnership.
Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

9.13. Audits

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

10. STUDY MANAGEMENT

The management of the study will be co-ordinated through Dr Martina Di Simplicio assisted by Prof David Nutt. Ms Ioanna Vamvakopoulou and Dr Bhavika Dulab will oversee the day-to-day running of the project. Dr Balasundaram Kadirvelu will oversee the technical aspects of data collection from the MindCraft app.

11. PUBLICATION POLICY

The results from this study may be reported and disseminated through peer-reviewed journals, conference presentations, and publications on websites including a summary on the Imperial website and other innovative methods.

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