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Project Title: Psilocybin vs escitalopram for major depressive disorder: comparative mechanisms

Short title: PSILODEP-RCT

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Contents

1. Aim of study

The aim of this study is to compare the mechanisms, tolerability and efficacy of two high doses of psilocybin versus a 6 week course of a leading antidepressant medication, escitalopram, in major depressive disorder (MDD). This will be a 2-arm, active comparator, double-blind randomised control trial in a total of 60 completing volunteers ('completing' measured by primary outcome measure).

1.1. Basic study design

The main experimental condition (**condition 1**) in this study will involve two high doses of 25mg psilocybin (per os, p.o.), 3 weeks apart. The first dose will be followed by 6 weeks of daily (inert) placebo capsule ingestion (condition 1, fig. 1). The control condition (**condition 2**) will involve two dosing sessions, also 3 weeks apart, with a presumed inactive dose of

psilocybin (1mg p.o.). The first dose will be followed by 6-weeks of daily escitalopram capsule ingestion (fig. 1).

Thus, there will be a dedicated on-site dosing day for both conditions (named here 'initial dosing session') followed by 6 weeks of daily capsule ingestion at home and a second dosing session 3 weeks after the first. The primary endpoint for assessing efficacy is 6 weeks after the initial dosing session, when the blind will be broken at the final study visit. Unblinded follow-up will occur for a further 6 months to assess safety and any potential enduring effects.

The main purpose of this design is to test the hypothesis that two doses of psilocybin, a design similar to what may be done in future therapy, will show a superior efficacy to escitalopram and crucially, a different *mechanism of action*. Secondarily, we predict that conditions 1 and 2 will show comparable efficacy at 6 weeks but with a different side-effect profile, e.g. we predict that changes in sexual dysfunction will be different across conditions and that psilocybin will act more rapidly to alleviate depressive symptoms.

Regarding the primary outcome, we will use functional magnetic resonance imaging (fMRI) at baseline and six weeks after the initial dosing session to identify how brain activity changes before and after two doses of 25mg psilocybin vs 6 weeks of daily escitalopram.

We predict that fMRI measured amygdala blood oxygen level dependent (BOLD) responses to emotional faces after-versus-before treatment will be greater in condition 1 (psilocybin) than in condition 2 (escitalopram).

This trial promises to significantly advance our knowledge of the safety, efficacy and mechanism of action of psilocybin for MDD by comparing it with a major conventional treatment for depression. The comparison with escitalopram adds an important component to this trial which may ultimately lead to the development of psilocybin as an alternative treatment option for patients with MDD.

1.1 Background of the study

This study is designed to test the efficacy of psilocybin as a treatment for major depression. The burden of depression is severe and increasing. Preventing relapse is a major challenge in depression; first line medications and psychotherapy can decrease symptom severity but large numbers of patients fail to respond and/or relapse when these are discontinued. Psilocybin is a naturally occurring compound that is structurally similar to the endogenous

neurotransmitter serotonin. Psilocybin had a brief history of use in psychotherapy in the 1960s but this was cut short before its efficacy could be properly assessed. In recent years, a growing number of studies, including several of our own, have shown that psilocybin can be safely administered to human subjects and there are now consistent reports of persistent improvements in depressive symptoms in depressed patients and other patient groups after just one or two exposures to psilocybin [1; 2; 3; 4; 5]. Our recent open-label feasibility study [1] has provided further preliminary support for the safety and efficacy of psilocybin for treatment-resistant depression, however the data remains inconclusive because of the lack of a control condition. It remains possible that psychological expectations and/or the concomitant psychological support the patients received played a significant role in determining outcomes. It is now important therefore that psilocybin be tested against an appropriate control condition and this is what we propose here.

2. Project outline

2. Main study design

This will be a two-*arm,* active comparator, *double-blind*, *randomized controlled*, between-subjects, design in up to *60 completing* patients meeting DSM-IV criteria for *major depression* of a moderate to severe degree (17+ on the 21-item Hamilton Depression Rating Scale, HAM-D). The patients will be randomly allocated to two groups. Groups will receive either: 1) two on-site dosing sessions with 25mg p.o. psilocybin, 3 weeks apart, the first dosing session being followed by 6 weeks of daily inert placebo ingestion, 2) two dosing sessions with 1mg psilocybin (to our knowledge, sub-psychoactive), 3 weeks apart, the first dosing session being followed by 6 weeks of daily escitalopram (10 mg for the first 3 weeks then increasing to 20 mg for 3 weeks, in line with prescribing guidelines [79] and similar to previous literature [98]). See Figure 1 for details.

Condition one is the main experimental condition and condition 2 is a control condition. Condition 2 involves 6-weeks of treatment with a gold-standard antidepressant, escitalopram, adding an important comparative efficacy component to this trial. Both groups will receive equal preparation and follow-up before and after the dosing session. The blind is broken after 6 weeks, after which normal treatment ensues.

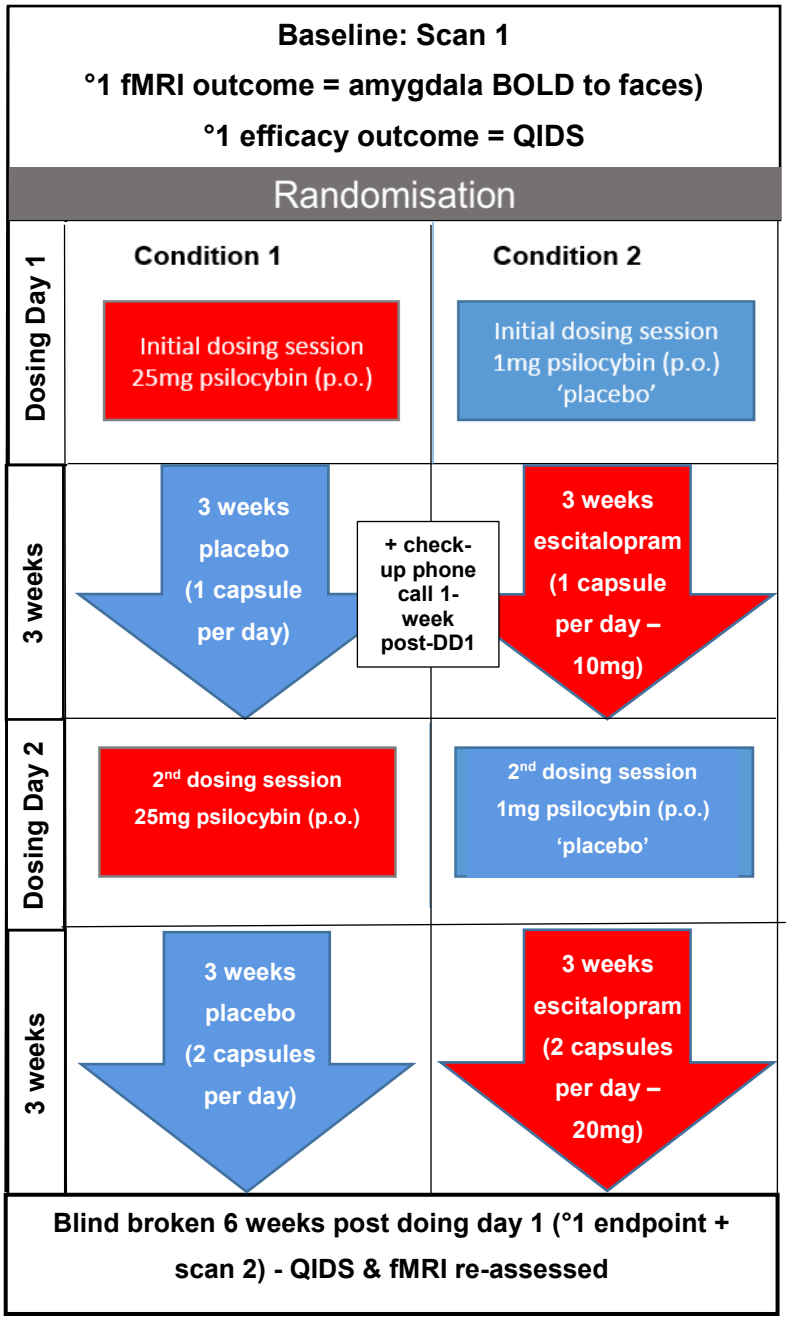

Figure 1. Basic design. Active components are highlighted in red. Please note, the psilocybin 'dosing sessions' are variously called 'dosing days' in what follows

2.1. Dose

2.1.1. Psilocybin

Patients in condition 1 will receive two doses of 25mg, 3 weeks apart from each other. In our recent open label feasibility study, this dose was well tolerated by all of the patients; no serious or unexpected adverse events occurred, and the mean patient rating of intensity of drug effects

was 7.5 (+2.5) out of 10, which was what we had planned to achieve. Based on these observations we feel confident that this dose maximises the potential for therapeutic benefit, whilst minimising the risk of acute adverse events. This view has been further supported by our conversations with other researchers working with psilocybin, such as those at Johns Hopkins University.

Regarding the control group, 1mg psilocybin has been chosen because evidence indicates it is pharmacologically 'inert' and yet capable of serving as an effective placebo [4], producing effects via expectancy alone, to a similar degree as a non-active placebo. Positive expectation is the major psychological factor underlying the 'placebo' effect, so the merit of using psilocybin in both conditions is that study staff and patients can be briefed to expect psilocybin in all conditions. Patients and therapy staff will be encouraged to expect and prepare for up to 25mg of psilocybin; thus, standardizing preparation and expectations prior to the dosing session.

2.1.2. Escitalopram

Escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) that was licensed in the US in 2002 as an approved treatment for major depressive disorder. It has since been prescribed to millions of people worldwide, becoming a gold-standard medication for depression. Meta-analyses have indicated that escitalopram is one of the best performing SSRIs in terms of tolerability and efficacy [77] and it is one of the most selective SSRIs [78].

Patients in condition 2 who receive an inactive dose of psilocybin (1mg) during the first dosing day, will subsequently receive 6 weeks of daily escitalopram. For the first 3 weeks they will receive 10mg-daily (1 capsule per day). After 3 weeks they will have a second 1mg psilocybin dosing day (without interrupting the daily escitalopram dosing schedule). After this, they will subsequently take 20mg of escitalopram daily (2 capsules per day) for three further weeks. The dose of 20mg is the recommended maximum dose for this commonly prescribed primary treatment for depression, and thus we would expect the patient's symptoms of depression to decrease. It would be expected that patients starting a course of SSRIs would report some improvements in depressive symptoms after even this relatively brief treatment period of 6 weeks [80, 81].

The dose of escitalopram can be lowered to 10mg from 20mg if patients appear not to be tolerating 20mg and ask to lower the dose or withdraw from the trial. This would be simple to implement as we would just instruct patients to take 1 capsule daily instead of 2. If, when the blind is broken at the 6 week endpoint, it transpires that the patient was actually in condition 1 and not in fact in the escitalopram condition, this would be logged.

We will be monitoring patients' response to escitalopram via weekly self-report measures, and measures of side effects. FDA guidelines report the following possible side-effects with escitalopram: headaches, dizziness, nausea, insomnia, dry mouth, impotence, decreased appetite, weight gain, vomiting, vivid dreams and a tingling sensation in arms, hands, feet and legs [79]. Insomnia and diarrhea are the most common side-effects, affecting 15% of individuals at 20mg [79].

When the blind is broken at the end of the 6-week course, the study psychiatrist will conduct individual consultations with patients in condition 2 to discuss whether they would like to continue with escitalopram or return to treatment as usual after controlled withdrawal. The patient's GP/psychiatrist will be included in treatment planning/medication withdrawal.

Patients in condition 1 will receive daily placebo (inert) instead of escitalopram over the same 6-week period following the psilocybin dose (fig. 1). The study psychiatrist will also advise patients in condition 1 about treatment options after the trial.

2.2 Data Collection

2.2.1 Outcome Measures

The primary efficacy outcome measure will be the Quick Inventory of Depressive Symptoms (QIDS) and changes from baseline to 6-weeks after the psilocybin dosing session. The QIDS measures internal states including most of the diagnostic criteria for depression and is sensitive to treatment effects [6].

The 16-item QIDS will be collected weekly from the moment of enrolment up to 6 weeks after dosing [12]. It will also be done one day before dosing and one day after dosing (using a version of this scale tailored to daily use [82]). After 6 weeks, measures will be collected monthly, up to 6 months post-dosing. Secondary outcomes include (but are not limited to): additional patient (BDI) and clinician (HAM-D) depression rating scales, well-being (WEMWBS), anxiety (STAI), optimism (LOT-R), personality (BIG-5) and others, plus all imaging outcomes (e.g. anatomical measures, including: morphometry, cortical thickness and tractography; functional measures, including: CBF, BOLD RSFC, signal variance and entropy/complexity, and activations to emotional faces). After the 6-week post dosing day primary end-point, subsequent follow-up will be done remotely with the exception of a structured interview at 1 month and 6 months.

2.2.2 Automated prompts for data completion and participant duties

The Psychedelic Survey platform (psychedelicsurvey.com) is an external software that was created for a recent cohort study conducted by our group (results still unpublished). It was

used to automate reminder emails to a large number of participants over the course of a few months. These emails linked participants to questionnaires contained within the separate Survey Gizmo platform, where we stored our data. This was found to be an efficient way to optimise collection and safe storage of questionnaire data, so this procedure will be repeated for this trial. Using these platforms is an effort to minimise the chance of human error and ensure the large volumes of data are collected correctly over the course of the trial.

For this study, the Psychedelic Survey platform will be programmed to send automatic patient reminders, including:

1. Reminding patients to take escitalopram/placebo every morning, promoting compliance
2. Reminding patients to complete their weekly/monthly QIDS questionnaires. This reminder will have a link to the Survey Gizmo platform, where patients will have an individual login and can complete the questionnaires online.
3. Reminding patients of any extra questionnaires to be completed
4. Reminding patients of onsite meetings

Reminders will be sent by both text message and email at specific times programmed by the study researchers. A limited number of study staff will be able to login to the Psychedelic Survey to amend or update patient reminders.

The Psychedelic Survey platform will only have access to patient email addresses and phone numbers, no other personal/medical data. This data is considered personal but not sensitive, so this project will be in accordance with Schedules I and II of the Data Protection Act [94]. Patient consent will be obtained and will not be necessary for inclusion in the study (see patient consent form). In accordance with the Data Protection Act [94], this personal data will only be used for the purposes of sending reminders and will be deleted after the study is over. More information is available on the Psychedelic Survey's Privacy Policy (attached as an appendix).

Questionnaire data will be stored within the Survey Gizmo platform and not the Psychedelic Survey platform. This has been done in previous studies by our group [95 and unpublished cohort study which launched the Psychedelic Survey platform]. Only study staff will have access to this information and both staff and patients will have individual logins for the website. The Research Data Manager for this study (Ms Bruna Giribaldi) will keep track of incoming data and patient reminders via these two platforms throughout the clinical trial period.

2.3. Recruitment

2.3.1. Key entry criteria

Key inclusion criteria:

1. Major depressive disorder (DSM-IV)
2. Depression of moderate to severe degree (17+ on the 21-item HAM-D).
2. No MRI contraindications
3. No SSRI contraindications
4. Has a GP or other mental healthcare professional who can confirm diagnosis
5. 18-80 years of age
6. Males and females
7. Sufficiently competent with English language

Key exclusion criteria:

1. Current or previously diagnosed psychotic disorder
2. Immediate family member with a diagnosed psychotic disorder
3. Medically significant condition rendering unsuitability for the study (e.g., diabetes, epilepsy, severe cardiovascular disease, hepatic or renal failure e.g. CLRC < 30 ml/min etc.)
4. History of serious suicide attempts requiring hospitalisation.
5. Significant history of mania (determined by study psychiatrist and medical records)
6. Psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin, e.g. borderline personality disorder
7. Blood or needle phobia
8. Positive pregnancy test at screening or during the study, women who are planning a pregnancy and/or women who are nursing/breastfeeding.
9. Participants who do not agree to use an acceptable contraceptive method throughout their participation in study (see section 7.2.1).
10. Current drug or alcohol dependence
11. No email access
12. Use of contraindicated medication
13. Patients presenting with abnormal QT interval prolongation at screening or with a history of this (QTc at screening above 440ms for men and above 470ms for women)

2.3.2. Drug interactions [86]

- Specifically for escitalopram:

MAOIs (escitalopram should not be started until 2 weeks after stopping MAOIs, and MAOIs can not be started until one week after stopping escitalopram), TCIs, Amiodarone, Artemether with Lumefantine, Artenimol with Piperaquine, Chloroquine, Cimetidine, Disopyramide, Dronedarone, Erythromycin, Haloperidol, Metoprolol, Mizolastine,

Moxifloxacin, Pentamidine Isetionate, Phenothiazines, Pimozide, Quinine, Sotalol, Sumatriptan. Caution with Omeprazole (increases plasma concentration of escitalopram), and Metoprolol (escitalopram increases plasma concentration of metoprolol).

- Additional for SSRIs in general – and thus also for escitalopram:
$5HT_3$-receptor antagonists, Antiepileptics, Aspirin (should be avoided), Coumarins, Cyproheptadine, Dabigatran, Dapoxetine, Duloxetine, Fentanyl, Lithium, Methylphenidate, Methylthioninium, Metoclopramide, NSAIDs (should be avoided), Naratriptan, Pimozide, Rasagiline, Ritonavir, St John's Wort, Tramadol, Vortioxetine.

Patients currently receiving any of these medications will either be asked to discontinue them in an appropriate way (where indicated), or they may be excluded from the trial.

Contraindicated medications for escitalopram include [86, 87]:
- MAOIs
- Procarbazine
- NSAIDs (including) Aspirin should be avoided during the course of the trial, as they may cause GI bleeding [86].
- Medicines that prolong QT interval, including [99]:
    - Cardiac medications: Class 1a (Quinidine, Procainamide, Disopromide) and Class III (Dofetilide, Ibutilide, Sotalol) Antiarrythmic drugs
    - Antihistamines (Terfenadine, Astemizole)
    - Antipsychotics: Haloperidol, Droperidol, Thioridazine, Sertindole*, Ziprasidone, Risperidone, Zimeldine, Chlorpromazine
    - Antidepressants: Citalopram, Amitriptyline, Desipramine, Imipramine, Maprotiline, Doxepin, Fluoxetin
    - Antibiotics: Quinolone (Sparfloxacin, Levofloxacin, moxifloxacin, grepafloxacin) and Macrolide (Erythromycin, Clarithromycin)
    - Antimalarials (Quinine, halofantrine)
    - Antiprotozoal (Pentamidine)
    - Antifungal (Azole group)
    - Antimotility agents (Cisapride)
    - Methadone

Antipsychotic medications and mood stabilisers may attenuate the effects of psilocybin and so are also contraindicated for this reason. However, such medications are usually only prescribed for manic and/or psychotic illness, and patients presenting with such histories

would be excluded from the study. Details regarding discontinuation of antidepressant medications can be found below (2.4.1).

2.3.3. Recruitment strategy

To minimise/address pre-study biases, recruitment will predominantly be via referrals (we have good links with Clinical Research Networks (CRNs), Improving Access to Psychological Therapies (IAPT), local clinics and clinicians) and Clinical Record Interactive Search systems (CRIS Health Ltd). A Facebook page has also been created for the trial in order to aid recruitment, which will be managed by the team: https://www.facebook.com/Psilodep-RCT-334207224132116/. Prior attitudes to treatments will be collected at baseline and entered into regression analyses. Patients will be randomly allocated to one of the two conditions after eligibility is confirmed post screening. We will endeavour to recruit patients who are currently unmedicated for their depression. Where patients are medicated, withdrawal from antidepressants would be required prior to participation and this process would be done with adequate washout and appropriate titration and carefully monitored in collaboration with the patient and their primary care giver

2.4 Ethical considerations

Similar ethical considerations will apply to this trial as applied in our feasibility study with psilocybin, with the additional consideration that half of the patients will receive two psychedelic doses of psilocybin (i.e. 25mg), 3 weeks apart, the first one followed by daily placebo for 6 weeks, and half will receive two inactive doses of psilocybin (1mg), 3 weeks apart, the first one followed by 6 weeks of daily escitalopram (10mg for three weeks and 20mg for three weeks). Knowledge gained from our feasibility study [1], discussions with researchers leading other randomized control trials in this area [5] and previous clinical trial literature on escitalopram [98] has directed the design of this trial.

The main study risks include: standard risks associated with an acute high dose of psilocybin (e.g. potential acute anxiety and the need for psychological support and supervision during the experience), standard side-effects associated with escitalopram (e.g. drowsiness, dizziness, sleep problems and potential for withdrawal symptoms upon cessation), and standard concerns regarding placebo treatment in depression [7]. Establishing a good connection with referring clinicians, and following standard procedures for psilocybin research [70], will help to manage and mitigate its particular risks.

2.4.1 Managing risks related to withdrawal from antidepressants

Serotonergic antidepressants are known to attenuate the acute psychological effects of psychedelics [8] and thus, we feel it is necessary that patients withdraw from these medications in order to experience the full effects of the 25mg dose of psilocybin. This washout component of the design is consistent with our recent pilot study, as this was done safely and effectively in that trial. Withdrawal symptoms and a worsening of depressive symptoms can occur with antidepressant-withdrawal [9]; thus, we will incorporate a number of contingency measures to reduce associated risks, namely:

1) Patients will be free to leave the study at any point and return to their treatment as usual if they, their mental-health care-giver or the study team feel this is the right course of action.
2) The study blind will be broken at 6-weeks after the initial dosing session (fig 1), enabling patients to return to pre-study treatment/s if they so choose.
3) Study clinicians will offer telephone contact to patients during the withdrawal period, if this is required.

It is important to note that since recruitment to this trial is not restricted to patients with treatment-resistant depression, potential volunteers may well be unmedicated at the time of study entry. Thus, we can anticipate that challenges relating to withdrawal from medication will be less than in our previous open-label trial in treatment-resistant depression. Even so, antidepressant medication withdrawal was managed safely and effectively in that trial and we foresee that the same will be true in this trial.

2.4.2 Managing risks related to psychedelic treatment

Before, during and after the dosing sessions, patients will receive psychological support from clinicians with experience of providing psilocybin treatment in the context of research studies, including clinical trials. On the dosing day, patients will only be allowed to return home once the study psychiatrist is confident they are fit to do so, and signs the patient out. Taxis will be ordered to take patients home. Patients will be asked to text or call us when they return home.

We will ask that the patient have a friend or family member at home, when they return. We will ask for this ‘chaperone’s’ contact details so that we can contact them if we cannot manage to contact the patient themselves.

Both the patient and their chaperone 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. Twenty-four-hour emergency contact numbers will be provided.

Overnight accommodation facilities are available onsite at Imperial, which are booked in advance. Patients who do not have a chaperone at home will be encouraged to take advantage of the onsite accommodation. Similarly, patients who travel to us from outside of London will be encouraged to take advantage of the onsite accommodation and a friend or family member can also be accommodated.

2.5 Procedures

The patient's immediate care team will be made aware of the study and will identify a patient and ask them if they are willing to be contacted by us. The primary caregiver will then inform us of any patients who are interested in participating and provide a contact telephone number and/or email. The patient will be issued with an A4 summary sheet containing a brief summary of the study and our contact details. The more comprehensive information sheet will also be made available to them. After the patient has initiated contact with us, we will inform them of the nature of the study and organise an appropriate time for an initial telephone screen. We will ask the patient if we can contact their GP/psychiatrist and this will be done via an email using a standard letter template.

Eligibility will be principally determined by the study psychiatrist who will thoroughly screen all patients to identify and confirm the presence of major depression and exclude other conditions. Supporting information from relevant mental health professionals and/or general practitioners will be sought prior to entry into the trial to confirm diagnosis and ensure that all patients meet the inclusion criteria.

If the patient appears to be eligible (post-telephone screen and post-contact with their GP/psychiatrist), a date for the first screening visit will be arranged. This will be a meeting with the study psychiatrist to review patient history, current symptoms, and to further check inclusion and exclusion criteria.

There will be around 4 weeks from first screening visit to the first study day visit to allow analysis of screening data (e.g. blood tests) to determine eligibility and enable contact to be made between their GP and/or mental health practitioners, and so that proper and cautious washout of antidepressant (4 weeks for fluoxetine and 2 weeks for other antidepressants) can be done, where applicable. If no medication washout is required, the time from screening to study day one can be shorter than 4 weeks, although we will strive to acquire weekly QIDS ratings as soon as the patient's entry into the trial is confirmed. In cases where medication washout is required, if symptoms show a marked increase in relation to the cessation/tapering

of medications, we will discuss with the patient and their GP or mental health caregiver whether the patient should withdraw from the trial so that previous medications can be resumed or new ones given. There will be ~7 weeks from the first (post-screening) study visit (**visit 2, scan 1**) to the primary end point/blind broken (**visit 7**), after which patients may return to their normal treatments if they so wish.

Patients will be required to make **7 visits** (see fig. 2). Patients will be assessed for up to six months after the initial dosing session; however, the study blind will be broken 6 weeks after the dosing session. Treatment as normal can then take place after the study blind has been broken.

2.6. Visits

Visit 1: **Screening**

Screenings typically take up to **4.5 hours** and include a physical examination by the study doctor, an ECG, and a period of MRI scanner acclimatisation, i.e. the patient will be invited to spend a period lying in an MRI scanner to assess whether they can tolerate the environment/conditions. Consent to enter the study will be sought from each participant after a full explanation has been given, the study information sheet has been issued and time allowed for consideration. Signed informed consent will be obtained for each patient.

We will know whether or not the patient is eligible for the trial ~3-days post screening (depending on receipt of relevant confirmation of diagnosis from the patient's GP or psychiatrist). As soon as eligibility is confirmed, the patient will be randomly allocated to one of the two study conditions.

If eligible, and if the patient wishes to participate in the trial, as soon as study entry is confirmed, a patient taking antidepressant medication will be required to begin coming off this medication, in a gradual, tapered fashion. We will ask that they inform their primary care giver of their decision to do this and we will manage medication withdrawal with their awareness. Medication withdrawal is typically done via gradual titration (e.g. halving of dose in first week) and the study psychiatrist will oversee this process in correspondence with the patient's GP and/or psychiatrist.

As soon as entry into the trial is confirmed, patients will be asked to complete the weekly QIDS-16 [12].. Patients will complete this up until the 6-week post dosing day, when the blind is broken. Use of the QIDS-16 [12] will enable us to track patient's mental health for the duration of the trial, facilitating patient monitoring and safety, while providing potentially useful data on weekly mood cycling pre versus post treatment [42].

Blood will be collected at baseline for the following routine blood tests:

- Full Blood Count (haemoglobin, total white cell count, lymphocytes, neutrophils, platelets)
- Renal panel (creatinine, urea, estimated GFR)
- Biochemistry (Sodium, potassium, adjusted calcium, phosphate, albumin and total protein)
- Liver panel (total bilirubin, alanine transaminase, GGT)
- Amylase

We will exclude participants on the basis of a clinical significant abnormality in any of the above tests at screening. In particular, we will aim to exclude participants with any form of renal or hepatic impairment, in accordance with the cautions raised in the escitalopram SmPC [100], see section 7.2.1.

As well as collecting blood for the above, we will also ask participants if we can acquire a sample for subsequent genetic analysis (not required for enrolment, only encouraged). Whole blood for genetic analysis will be collected in 2 x 8.5ml 'PAXgene' tubes and frozen at -20C. At the end of the study, samples will be transferred to the labs of the MRC Social, Genetic & Developmental Psychiatry (SGDP) Centre at The Institute of Psychiatry, Psychology and Neuroscience (IoPPN) in Denmark Hill, South London, with whom we have a material transfer agreement. Dr James Rucker and Dr Gerome Breen will act as custodians for the samples and both tissue bank and HTA licenses are already in place. The samples will be stored in locked -80C freezers in the SGDP labs, to which access is only given to authorised personnel and with full audit capabilities.

The purpose for collecting whole blood is to enable genetic analysis in the longer term. Candidate gene and genome wide association analyses require high numbers of samples to achieve adequate statistical power in analysis. Therefore, these samples form the first batch of a larger sample acquisition effort in this area. Our main aim is to perform association testing between functional polymorphisms of the 5-HT2A receptor, hypothesising that these may be associated with response to treatment. For example, the T102C polymorphism of the 5-HT2A receptor has been associated both with suicidality in depression [92] and schizophrenia [93] raising the interesting question of whether the 2 alleles at this locus may have a bidirectional association with response to psychedelics.

Whole blood samples for genetic analysis will be stored for up to 5 years in the first instance, however this will be subject to renewal depending on the progress of the wider project. Participants may request that their samples be destroyed at any time by notifying the PI of the

study in writing. Samples would then be destroyed by incineration. Participants will not receive results of genetic testing, as candidate gene analysis is vanishingly unlikely to have any clinically significant outcome for individuals.

Visit 2: Scan 1/Prep

The scanning procedure takes approximately 2.5 hours, with the scan itself lasting for no longer than 90 minutes. The scan session will be followed by psychological preparation with the therapy team (two individuals) who will sit with the patient during their dosing session. Psychological preparation will take approximately 3 hours, with two breaks. This visit will take approximately **5.5 hours** in total.

Visit 3: Dosing session 1

The dosing session will take place the day after scan 1. Depending on the results of randomisation, the patient will receive either 25mg (conditions 1) or 1mg psilocybin (condition 2) in the morning. After their dosing session is over, they will be given either placebo capsules (condition 1) or 10mg escitalopram capsules (condition 2) to take home with them. The dosing day will typically run for ~8 hours and involve: arrival at 9am, initial preparation, including relaxation techniques. Dosing at 10:30am. Drug effects (25mg only) are typically experienced for 5-6 hours (i.e. subsiding to a low-negligible level at 3:30-4:30pm). Depending on the magnitude of residual drug effects, patients will be asked to complete questionnaires from 3:30pm onwards and take part in a filmed and audio recorded structured interview at ~4:30/5pm (consent for this is included in the consent sheet – and with consent, all visits will be filmed as default). A study psychiatrist will assess the patient for potential discharge. If the patient is to travel home, a taxi will be ordered. Patients will typically leave the study centre around 5:30/6:00pm.

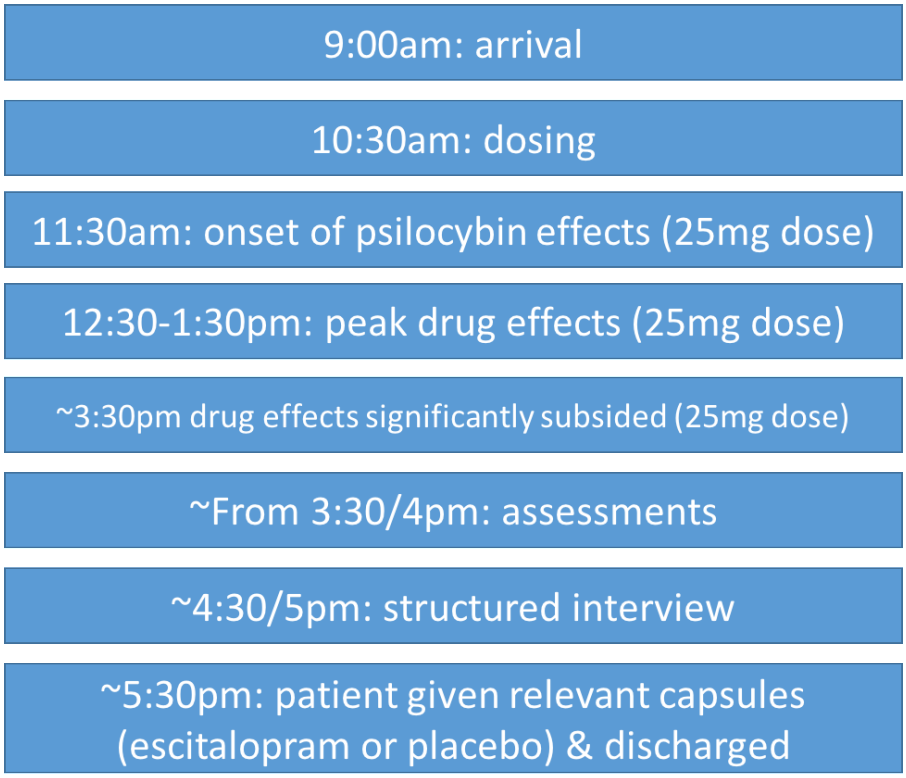

Fig 2. Dosing day timeline

At the end of the first dosing session, patients will be given a course of capsules to be taken daily (upon waking) for the following 6 weeks. Randomisation will determine whether these capsules are to be escitalopram or placebo. Patients will be asked to take their first capsule as close to **8:00am** as possible the morning after the first dosing session and document exactly when it was taken, to ensure standardisation of peak plasma concentration where relevant (i.e. escitalopram condition). N.B. peak plasma concentrations of escitalopram are reached 3-4 hours post-ingestion [10]. Each patient will take one capsule each day for the first 3 weeks and two for the remaining 3 weeks, regardless of whether they are in condition 1 or 2.

Visit 4 (time since first dosing session = 1 day)

One day after dosing, patients will be asked to complete some questionnaires (including a daily version of the QIDS [82]) and will also take part in a structured interview/integration session. Patients will be asked about their experiences the previous day, how they slept, how they have felt today etc. This visit will take approximately 2-3 hours in total.

Interim period (1 week post-treatment): phone call or Skype/Zoom session to check in with patient. Remote assessments of the QIDS also done weekly throughout the trial. Assessments will be cued via email and/or text (using the Psychedelic Survey platform) and completed electronically (on Survey Gizmo), where the study team can access them.

Visit 5 (time since first dosing session = 3 weeks): Dosing session 2

The second dosing session will take place exactly as described in Visit 3/Fig 2 above.

Interim period (4, 5 and 6 weeks post-dosing session 1): remote assessments will continue as before, cued via email and/or text (using the Psychedelic Survey platform) and completed electronically (on Survey Gizmo), where the study team can access them. Patients are free to communicate via email with the study team at any point if issues arise. If additional support is needed, each patient will be allowed a maximum of two additional Skype/Zoom sessions with the study team. This limit is in place in order to avoid an imbalance in the amount of support patients receive.

Visit 6 (1 day post-dosing session 2):

This visit will follow the same structure as visit 4 (1 day post-dosing session 1), described above.

Visit 7 (time since first dosing session = 6 weeks/time since second dosing session = 3 weeks)

The final study visit will take place 6 weeks after the first dosing session. This visit will include a final MRI scan. Patients will arrive at 10am and be scanned at 11am. The scanning session will last for no longer than 90 minutes. After this, patients will be asked to complete some questionnaires and will take part in a structured interview in which they will be asked how they have felt today and the past 6 weeks. The HAM-D and MADRS assessments will be performed which enquire about depressive symptoms over the last week. A comprehensive side-effects questionnaire will also be completed, which asks about side-effects over a 6-week period [11]. A second ECG scan will also be conducted in order to ensure no effect of either drug on heart physiology and a repeat routine blood test will be done (see above for a complete list of tests).This visit will take approximately 5 hours in total. At the end of this visit, we will inform the patient of the condition they **were** enrolled in; thereby breaking the blind. Breaking the blind at this time point will enable us to assess treatment safety and efficacy for both conditions

and provide the patient with information on what they have received - which may then inform future decisions regarding treatment, e.g. whether or not they want to continue with escitalopram if they were in condition 2.

Study Timeline			
Date	**Event**	**Main assessment/s**	**Approximate Duration**
Visit 1	Screening	QIDS, HAM-D MADRS, ECG	5 hours
Visit 2	Scan 1	QIDS, HAM-D, MADRS, scan measures	5 hours
Visit 3	Dosing session 1 (DS1)	ASC, EDI, etc	8 hours
Visit 4	1-day post DS1	QIDS, interview	2-3 hours
Visit 5	Dosing session 2 (DS2)	ASC, EDI, etc	8 hours
Visit 6	1 day post DS2	QIDS, interview	2-3 hours
Visit 7	Final visit + scan 2 6-weeks post DS1	QIDS, HAM-D, MADRS interview, ECG, scan measures	5 hours

At the end of Visit 7: patients will be told by the study team that a documentary is being made about the study that they could participate in if they chose to. If they are interested in finding out more information, they will be taken to meet the Imperial Press Office team in person. The Imperial Press Office team will talk to them about the nature of the documentary and the implications of participating. Participants will be given an information sheet/consent form to read and sign if they are interested, as well as an information sheet about the film producers Grain Media. If participants are keen to be involved or would like to find out more, they can also meet the Grain Media team in person, who can tell them more about the documentary process. If participants agree to sign the consent form, this will prompt the study team to release the footage that has been filmed in the trial to Grain Media. If participants choose to not sign, the footage remains only for use within the Imperial team (the data 'controllers'), for training purposes, as agreed in the initial consent form signed at the start of the study (unless further consent to share is sought from patients).

Assessments at 1-6 months Visit 7: remote assessments of the QIDS-16 will be done monthly at 1-6 months post-treatment. More comprehensive assessments will also be done

1, 3 and 6 months after the initial dosing session. Assessments will be cued by telephone and email and completed electronically and emailed back to the study team. A member of the study team will speak with the patient via telephone or skype at these time points.

1 month post Visit 7: A structured interview will be carried out via Skype, telephone or in person if the patient prefers this. This will focus on the patient's overall experience of the trial, looking back on it as a relatively recent experience, and on how they are doing 1 month later.

6-months post Visit 7: Remote assessments will be done (as at 3 months) and a structured interview will be carried out and recorded, either via skype, telephone or in person, if the patient prefers. This will focus on the patient's perception of the value of the trial with the benefit of 6 months of hindsight and on how they are doing now. See Appendix 1 for semi-structured interview protocol.

If, at any point after the final formal study visit, we become concerned about a patient's mental state and associated risks, we will liaise with their GP and/or mental health practitioners - who may then decide to implement appropriate interventions, if this is indicated.

2.7. Psychological outcome measures

Measures completed before and after treatment will include the following:

- **QIDS-16 (primary efficacy outcome measure) [12]**
- QIDS-16 (daily measure) [82]
- BDI II (two-weekly measure) [13]
- HAM-D [14]
- MADRS [34]
- Spielberger's Trait Anxiety Inventory (STAI) - Trait [15]
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [16]
- Flourishing Scale (FS-8) [102]
- Snaith Hamilton Anhedonia Pleasure Scale (SHAPS) [17]
- Life Orientation Test (LOT-R) [18]
- Meaning in Life Questionnaire (MLQ) [19]
- Brief Resilience Scale (BRS) [20]
- Dysfunctional Attitudes Scale (DAS) [21]
- 44-item Big Five Inventory [22]
- Peters 21-item delusional inventory (PDI) [23]
- EASE anomalous subjective experience [24]

- Ruminative Responses Scale (RRS) [25]
- White Bear Suppression Inventory (WBSI) [26]
- Barrett Impulsivity Scale (BIS) [27]
- Brief Experiential Avoidance Questionnaire [28]
- Modified Tellegen Absoprtion Questionnaire (MODTAS) [29]
- Scale To Assess the Therapeutic Relationship (STAR) [30]
- Credibility/Expectancy Questionnaire [31]
- Connectedness to Nature Scale (CNS) [32]
- Political Perspective Questionnaire (PPQ)
- Social Connectedness Scale (SCS) [33]
- Bech-Rafaelsen Mania Rating Scale (MAS/MRS) [34]
- Revised Santa Clara brief compassion scale (5 items) (SCBCS) [35]
- Gratitude Questionnaire (GQ-6) [36]
- Short Suggestibility Scale (SSS) [37]
- Self-esteem: Rosenberg Self-Esteem Scale [4-items] (RSE) [38]
- Universality subscale of the Spiritual Transcendence Scale (STS) [39]
- Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA) [40]
- Lauks Emotional Intensity Scale (LEIS) [41]
- The Suicidal Ideation Attributes Scale (SIDAS) [84]
- Sexual dysfunction (PRSEXDQ-SALSEX) [83]
- Selected items from Brief Index of Sexual Functioning for Women (BISF-W) [104]
- 2-item Sexual Perceptions Questionnaire (SPQ, self-constructed)
- Barnes Akathisia Rating Scale (BARS) [85]
- Work Productivity and Activity Impairment Questionnaire (WPAI) [87]
- The Work and Social Adjustment Scale (WSAS) [88]
- Self-constructed Connectedness Questionnaire
- Standard Assessment of Personality – Abbreviated Scale (SAPAS) [96]
- Positive and Negative Syndrome Scale (PANSS) [97]
- Mastery Insight Scale (MIS, taken from Therapeutic Realisations Scale [103])
- Self-Reflection and Insight Scale (SRIS) [106]
- Psychological Insight Scale (PIS, self-constructed)
- Metaphysical Beliefs Questionnaire (MBQ, self-constructed)
- Spiritual Bypassing Scale (SBS, self-constructed)
- Adverse Childhood Experience Questionnaire (ACE) [105]
- Therapeutic Music Experience Questionnaire (TMEQ, self-constructed)
- Setting Questionnaire (SQ, self-constructed)
- Selected Items from the Absorption in Music Scale (AIMS - revised)

- Acceptance and Action Questionnaire (AAQ-II) [107]
- CompACT Questionnaire [108]

Although there are a large number of these measures, they are intentionally brief. It will take approximately 75 minutes to complete them. Patients will be encouraged to do this in two or more 'stints' and to take a break if/when they become tired and lose focus.

Measures completed just before treatment will include the:

- Spielberger's Trait Anxiety Inventory (STAI) - State [15]
- The psychedelic predictor scale (self-constructed)
- The surrender scale (self-constructed)

Behavioural tasks will include:

- Emotional processing battery [88]
- Cued autobiographical memory task (AMT) [44]
- Prediction of Future Life Events (POFLE) [45]
- Torrance Test of Creative Thinking (TTCT) [46]
- Emotional response to music [89]
- California Verbal Learning Test (CVLT) [90]
- Digit Symbol Substitution Test (DSST) [91]

The following scales will be used to measure subjective states during the dosing sessions to be filled out at the end of the dosing session:

- Ego Dissolution Inventory (EDI) [47]
- Mystical Experience Questionnaire (MEQ) [48]
- 11 Dimension Altered States of Consciousness Scale (11D ASC) [49]
- Psychotomimetic States Inventory (PSI) [50]
- Visual Analogue Scales (VAS)
- Geneva Emotional Music Scales (GEMS) [51]
- The Challenging Experience Questionnaire [52]
- The Imperial Emotional Breakthrough Inventory (EBI)
- Near-Death Experience (NDE) scale [53]
- Ten Item Personality Inventory (TIPI) [88]

With prior consent, we will also send a patient's significant other a short questionnaire at baseline and at the 6-week end point to enquire how they perceive the patient's depression and whether they have noticed any changes in the patient's behaviour since the intervention.

2.8. Scanning outcome measures

- BOLD response to emotional faces (primary fMRI outcome measure)
- Resting state blood oxygen level dependent (BOLD) signal scan
- Resting BOLD with music as hedonic stimulus
- Anatomical scans (T1 & T2)
- Diffusion Tensor Imaging (DTI) scan

3. Basic safety and scientific background

The LD50 of psilocybin in rats is 280mg/kg [54]; thus, in terms of toxicity, its margin of safety is very large. We intend to give no more than 25mg which equates to less than 0.3 mg/kg. Doses of 30mg and higher have been used in previous research with healthy volunteers and patients without serious adverse events [55; 56]. Common adverse events with high doses of psilocybin include sub-acute headaches which last for 1-2 days maximum, and acute anxiety, which subsides with psychological reassurance or as the acute drug effects subside [1]. 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. Moreover, there is no evidence of subsequent drug abuse, flashback phenomena or prolonged psychoses [57]. We observed no cases of persistent adverse effects of psilocybin in our recent trial of psilocybin for depression in 20 patients. Psilocybin is not habit forming in animals or humans [58] and none of the patients expressed craving for psilocybin.

Reports from the 1960s on the use of psilocybin in psychotherapy indicate clear benefits over harms [59]; however, these studies suffer from a lack of experimental control and standardised assessments. More recently, pilot studies have tested the efficacy of psilocybin in OCD [60] and anxiety related to terminal cancer [3]: In the former study, short-term reductions in compulsive symptoms were reported by all of the patients. In the latter study, trait anxiety was significantly decreased 1 and 3 months post session and depression scores were significantly decreased at 6 months. No clinically significant adverse events were observed in either study. In a large sample of healthy volunteers, orally administered high dose psilocybin induced mystical or spiritual-type experiences in over 60% of subjects [56]. 67% rated their experience as either the single most meaningful experience of their lives – or among the top five. In a

follow-up after 14 months, 64% of the sample maintained that the acute experience had led to a significant improvement in their sense of well-being or life satisfaction [61].

In the last four years, we have completed one pilot study [62], two fMRI studies [63] and one MEG study involving psilocybin [64], as well as a pilot study in treatment resistant depression (n = 20) [65]. We have carried out around 100 dosing sessions in total most with a dose equivalent to that proposed here and have seen no serious adverse events.

4. Study design

4.1. Primary outcomes

4.1.1 Primary outcome measure and endpoint

The primary fMRI outcome will be change in amygdala BOLD response to emotional faces from baseline (prep, 1 day pre-DD1) to scan 2 at 6-weeks post-DD1. Change after psilocybin (condition 1) vs change after escitalopram (condition 2).

4.1.2. Primary efficacy outcome measure and endpoint

Change in QIDS score from baseline (screening) to 6 weeks post initial dosing session (primary endpoint). Change after psilocybin (condition 1) vs change after escitalopram (condition 2). The criteria for determining response will be a reduction of 50% in the QIDS scores and remission will be scores of ≤5 on the QIDS, as per convention [12].

4.2. Volunteers

4.2.1. Sample size

A baseline versus 5-weeks post-treatment reduction of -9.2 (SD = 5.6) on the QIDS was observed in our recent pilot study. To inform what can be expected with 1mg psilocybin, we can refer to the recent end-of-life anxiety trial of Griffiths et al. [66] in which the reduction in scores on another standard scale (BDI) seen with the control condition (1-3mg/ 70kg psilocybin) was 50% that of the active condition, i.e. a reduction of 10.7 (22-30mg/70kg, active) versus 5.5 (1-3mg/70kg, control) at 5-weeks post-treatment. If 1mg psilocybin is equally as effective as the 1-3mg/70kg in the Griffiths study, i.e. 50% of the active dose (which is a conservative prediction, given that the difference in doses is greater, and the time since treatment is shorter), we can expect a mean reduction in QIDS scores of 9.2/2 = 4.7 points for

the 1mg condition. If we assume equal variance for both conditions, we would require 20 patients per condition to achieve the desired power of 80%, $p < 0.05$. We therefore propose to recruit a minimum of 30 patients per condition (60 completers in total for the RCT). These are appropriate numbers for the imaging, given that significant baseline v one-day post-treatment effects are being observed in BOLD resting-state functional connectivity, amygdala activations to emotional faces and CBF with just 15 patients in my recent pilot study (papers in preparation). Significant fMRI findings have been reported with escitalopram in similar paradigms and with similar sample sizes [67]. Equivalent efficacy (primary outcome) is predicted for the escitalopram vs 25mg psilocybin conditions but with different mechanisms of action. For example, we predict greater improvements in wellbeing (WEMWBS) with 25mg psilocybin vs escitalopram at 6-weeks post dosing day 1.

4.2.2 Recruitment of volunteers

Regarding recruitment, we will endeavour to recruit via referrals. We have good links with a number of potential referring centres. We will also utilise word of mouth however, as we did effectively in our previous trial.

We will aim to recruit a similar number of male and female patients. Patients will be at least 18 years of age with an acceptable level of physical health as determined by a medical screening that will include: routine blood tests, ECG, blood pressure and heart rate, neurological exam and psychiatric assessment (MINI). Patients with cardiovascular abnormalities, epilepsy, personal or family histories of psychosis or psychotic symptoms (including mania), or histories of suicide attempts, will not be allowed to participate. As in previous trials, we will include patients that have previous experience with psychedelic drugs, although it is anticipated that most will have never had an experience with a psychedelic. All patients will have a good command of the English language. Patients will have HAM-D scores of at least 17.

General practitioners will be contacted in every case to inform them of the details of the trial and to enquire whether they have any concerns about their patient entering the trial. Until we have confirmed their background medical and psychiatric history, patients will not be allowed to enter the trial. Psychiatric diagnosis is principally determined by one of our study psychiatrists but confirmation will be sought in every case from past/current practioners and a decision will need to be made by the study clinical team about persisting with a given patient if confirmation of diagnosis is not initially forthcoming. In our recent pilot study, patients were successful at obtaining their medical records from their GP, but this can take time and so incur delays.

4.2.3 Screening procedure: Initial screening visit

1. Informed consent
2. Full history-taking and physical examination
3. Psychiatric assessment (MINI)
4. Routine blood screen and sample
5. ECG
6. Urine drug screen
7. Urine pregnancy test if woman of childbearing potential (see section 7.2.2)
8. Height & weight recorded
9. Breathalyser
10. Completion of clinician administered rating scales (HAM-D)
11. Completion of secondary outcome measures

4.2.4 Withdrawal Criteria

1. Withdrawal of Consent
2. Development of concurrent physical illness that necessitates their removal from the trial
3. Deterioration of mental health warranting additional input and support
4. Dependency or problematic alcohol or illicit substance use
5. Positive pregnancy test in women of childbearing potential (see section 7.2.2) at any point during study

GPs and all relevant health professionals will be informed of their patient's involvement in the trial. Any misgivings or reservations they have about their patient entering and continuing the trial can be responded to by the study psychiatrist.

On entering the trial, should there be any deterioration in the patient's physical or mental health that may compromise their ability to continue in the trial then we will reach an informed decision, once we have the contacted the relevant health professionals, about whether their continued participation is prudent. This will all be done in discussion with the patient and the extended research team.

5. Regulatory Issues and informed consent

5.1 Ethical Approval

The study will be conducted according to the revised declaration of Helsinki (2000), the International Committee on Harmonisation Good Clinical Practice guidelines and NHS Research Governance Framework. Ethics and R&D approval will be obtained.

5.2 Consent

Consent to enter the study will be sought from each participant after a full explanation has been given, the study information sheet has been issued and time allowed for consideration. Signed participant consent will be obtained for each patient. It is the right of the patient to refuse to participate without giving reasons and this will be respected. All patients are free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment.

5.3 Confidentiality

Patient's identification data will be required for the registration process and will be held in the screening CRF only. The research team will maintain patient confidentiality at all times. Unique, anonymous patient identifiers will be issues after screening when a patient is enrolled in the study. Identifiers will be issues in a regular ordinal manner, e.g. P1, P2, P3 etc. and these identifiers will be issued to the manager of the randomisation (Invicro, previously Imanova) to determine the relevant condition and task/test versions for each patient (see randomisation, section 12).

5.4 Audits and Inspections

The study may be subject to inspection and audit by Imperial College London and/or Imperial College Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP.

5.5. Monitoring

The study will be monitored internally by the Centre for Neuropsychopharmacology, through the Trust via InForm and it may also be audited by the MHRA and imperial JRCO. Any trial-related regulatory inspections will be permitted and direct access to source data and documents will be provided.

Prof Guy Goodwin (former President of the European College of Neuropsychopharmacology and British Association of Psychopharmacology) has agreed to Chair a Trial Steering Committee and Imperial's Joint Research and Compliance Office (JRCO) and Clinical Research Facility (CRF) both conduct audits of the trial. A Data Monitoring Committee is

currently being compiled consisting of senior figures within the Centre for Psychiatry at Imperial.

6. Patient recruitment strategy

Primary recruitment will be via referrals from mental health practitioners working in the field who have knowledge of the trial and feel that their patients fulfill the inclusion criteria. This study will be adopted by the Mental Health Research Network (MHRN) as well as a number of Clinical Research Networks (CRNs). We have links with the Improvement of Access to Psychotherapy Treatments (IAPT) scheme which runs out of the Camden and Islington Trust. We will also liaise with fellow mental health practitioners working in other London Mental Health Trusts and in satellite towns and cities, with whom we have links. We will also use Clinical Record Interactive Search systems (CRIS Health Ltd). In every case, patients will be thoroughly screened by the study psychiatrist to ensure that they comply with our inclusion criteria before entry into the trial.

7. Drug specific ethical and safety considerations

7.1 Psilocybin safety

We have run close to 100 dosing sessions with psilocybin without serious adverse event, 40 of these were in patients with treatment resistant depression. Recent independent assessments of the harms of popular drugs of abuse, conducted by international experts and experienced drug users have consistently rated magic mushroom as one of the least harmful recreational drugs [68]. 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% [57]), even with very high doses [55], and **none** have been reported in modern studies or studies with patients. We have observed no prolonged psychotic reactions with psilocybin in any of our studies and acute psychotic symptoms, such as paranoia, are also quite rare. The risk of flashback phenomena is minimal-negligible and has **no cases** have been observed in our or other studies with psilocybin. Periods of psychological challenge, e.g. involving anxiety, are more common [56; 65]. Although evidence indicates that challenging experiences under psychedelics can be predictive of positive clinical outcomes [69].

Common (>20% at 25mg):

1) Increased anxiety, particularly at the onset of the drug effects
2) Mild-moderate increased in heart rate
3) Visual hallucinations
4) Transient headaches, lasting for 1 to 2 days (max) post-dosing

Less common (<15%):

1) Paranoia or suspiciousness.
2) Nausea
3) Dizziness
4) A 'bad trip' i.e. negative thoughts and mood during the acute drug effects

Rare (prevalence unknown but likely < 2%):

1) HPPD/flashbacks
2) Worsening of mental state after the drug experience

It is not uncommon for people to experience some negative psychological content during a psilocybin 'trip', particularly if they suffer from ongoing psychological distress, as is characteristic of depression. Typically, this is best deal with by good preparation and support during the experience and integration afterwards. In our sample of 20, while challenging episodes were relatively common within the patients' trips, none were entirely characterized by dysphoric or distressing content, and when challenging content did arise, it was often worked through and contributed to a psychological 'breakthrough' on the part of the patient. Recent evidence indicates that challenging psychological experiences can produce therapeutic benefits, improving psychological well-being in the long-term [69].

Negative aftereffects of challenging psychological experiences under psychedelics are thought to be a consequence of inadequate 'set and setting' and post-session integration work – and they may also relate to the duration of the challenging period [69]. We shall reduce these risk through good psychological preparation and integration work, good patient-staff rapport and a positive environment. Research and medical staff will plan carefully for such eventualities however. Challenging experiences/periods are best managed psychologically. Injectable lorazepam, as a 'rescue medication', will be available but would only be used in cases of severe panic that were unresponsive to psychological intervention, and where the patient's behavior was putting themselves and/or staff in danger. Consent for such medication will be sought from the patient ahead of study participation. Detailed protocols are available on the safe management of clinical research with psychedelics [70].

7.2. Escitalopram safety

7.2.1 Side-effects and SmPC Cautions

In a meta analysis of 22 clinical trials comparing various antidepressant medications, escitalopram was found to compare favourably in terms of achieving acute response,

remission of symptoms and low trial withdrawal rates [71]. As with all SSRI's, side effects are commonly reported. Specific side effects that have been associated with escitalopram include:

Common (i.e. ~10% at 20mg):

1) Agitation or restlessness
2) Diarrhea
3) Difficulty sleeping
4) Drowsiness
5) Dry mouth
6) Headache
7) Nausea
8) Sexual difficulties (decreased sexual ability or desire, ejaculatory delay)
9) Dizziness
10) Sweating

Less common (< 10%)

1) Frequent urination
2) Indigestion
3) Increased or decreased appetite
4) Taste alterations
5) Tremor (shaking)
6) Tingling in arms or legs
7) Weight changes
8) Influenza-like symptoms and pain in neck or shoulders
9) Serotonin syndrome
10) Suicidal thinking and behavior
11) Abnormal bleeding
12) Seizures
13) Manic episodes
14) Low sodium
15) Angle closure glaucoma

The MHRA recommends that escitalopram should not be used in patients with known QT interval prolongation (above 440ms in men and above 470ms in women) or in combination with other medicines known to prolong the QT interval. An ECG during the screening visit will ensure that such individuals will be excluded from the study. To prevent antidepressant discontinuation syndrome, gradual withdrawal from escitalopram will be managed by the study psychiatrist in consultation with the patient's GP/psychiatrist.

In the event of signs of cardiac arrhythmia (fluttering in chest, tachycardia, bradycardia, chest pain, shortness of breath, lightheadedness, etc), patients will be advised to contact us and their GP immediately and stop escitalopram dosing. In this case, we would schedule an extra visit and perform an extra ECG.

Additionally, the Summary of Product Characteristics (SmPC) for escitalopram [100] advises caution in patients with severely reduced renal function (CLCR less than 30 ml/min). We are aiming to recruit depressed patients who are otherwise physically healthy and will be excluding patients with severely reduced renal function as per exclusion criteria.

The SmPC for escitalopram [100] also raises cautions about its use in patients with hepatic impairment. In the case of mild or moderate hepatic impairment, dose reduction is necessary. For consistency, patients with any form of hepatic impairment will be excluded (see section 4.2.4). Liver Function Tests (LFTs) conducted in screening will provide the study medical doctor with the necessary information to make this assessment.

Furthermore, the escitalopram SmPC [100] highlights potential dangers of using SSRIs in pregnancy (especially late pregnancy) and does not recommend its use during lactation. Additionally, because psilocybin does not currently have a marketing authorization and has not undergone extensive testing in-utero and during lactation (as enforced by the HMA guidelines [101]), we will avoid this issue by administering pregnancy tests throughout and excluding any participants who test positive, are currently breastfeeding, planning a pregnancy and/or are not using reliable birth control (unless they are not deemed to be of childbearing potential, see section 7.2.1 below and exclusion criteria for details).

7.2.2 Pregnancy, Breastfeeding and Contraception

A woman who is not of childbearing potential is considered to be postmenopausal (at least 48 consecutive weeks without menstruation) or permanently sterilized (eg hysterectomy and/or bilateral salpingectomy).

The following methods of contraception, if used properly and used for the duration of the study, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (eg hysterectomy and/or bilateral salpingectomy), vasectomized partner, or sexual abstinence. Periodic abstinence (i.e. calendar, symptothermal, or postovulation methods and tubal ligation/occlusion) are not an acceptable form of contraception for this study.

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

If the participant or the female partner of a male participant becomes pregnant within 30 days of receiving psilocybin the investigator should be notified and information will be reported to

sponsors and COMPASS Pathways, the providers of the IMP, within 24hrs of discovery. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion in order to determine outcome. This information is important for both drug safety and public health concerns. If any adverse event occurs in pregnancy (i.e. post-partum complications, spontaneous or induced abortions, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus) it will be reported as an SAE.

7.3 Suicide and persistent adverse events

There have been no cases of increased suicidality in modern trials with psilocybin and we did not observe any such cases in our recent trial in 20 patients; in fact, mean suicidality scores for the sample were significantly reduced at all follow-up time points. A large population survey in the US found a selective association (i.e. among drugs of potential misuse) between psychedelic-use and **reduced** suicidality [72].

There is some evidence of slightly increased suicidality (i.e. suicidal thoughts and behaviours) in adults taking SSRIs over those taking placebo [73], although not all meta-analyses have found this relationship [74]. Suicidality may be elevated in adolescents treated with SSRIs/SNRIs (i.e. from 2% with placebo to 4% with active treatment) [75] but escitalopram was not included in the most recent meta-analysis, and we will exclude individuals under the age of 18 for this trial.

The risk of suicide with placebo treatment is low (0.7% suicide attempts) [76]. The risk of suicide will be further minimized by excluding patients with histories of suicide attempts. We will also give patients a study psychiatrist's and psychotherapist's contact number in cases of emergency. We have written a standard operating procedure for dealing with both adverse events and any unexpected suicide attempt.

7. 4 Definitions and reporting of Adverse Events & Reactions

1. **Adverse Event** (**AE**): Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
2. **Adverse Reaction** (**AR**): All untoward and unintended responses to a medicinal product related to any dose administered
3. **Unexpected Adverse Reaction** (**UAR**): An AR, the nature or severity of which is not consistent with the applicable product information.

4. **Serious Adverse Event** (**SAE**) or Serious Adverse Reaction: Any untoward medical occurrence or effect that at any dose i) results in death ii) is life-threatening iii) requires inpatient hospitalisation or prolongation of existing hospitalization iv) results in persistent or significant disability or incapacity or v) is a congenital anomaly/birth defect
5. **Suspected Unexpected Serious Adverse Reactions** (**SUSAR**): any suspected adverse reaction related to a medicinal product that is both unexpected and serious

Most AEs and ARs that occur in this study, whether they are serious or not, will be expected treatment-related effects of the drugs in this study. The assignment of the causality will be made by the team including using the following definitions:

1. Unrelated: There is no evidence of any causal relationship
2. Unlikely: There is little evidence to suggest there is a causal relationship and there is another reasonable explanation for the event.
3. Possible: There is some evidence to suggest a causal however the influence of other factors may have contributed to the event
4. Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely
5. Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out
6. Not Assessable: There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

Should any uncertainty exist regarding causality, we will discuss within the team and farther afield with local clinicians and representatives. In the event that no agreement is made, the MHRA will be informed of competing points of view.

7.5. Reporting Procedures

All adverse events will be collected from signing of informed consent until the end of the study. Depending on the nature of the event the following reporting procedures will be followed.
1. **Non serious AR/AEs**: All such toxicities, whether expected or not, will be recorded as part of a case report and sent to the research team within one month.
2. **Serious AR/AEs**: Fatal or life threatening SAEs and SUSARs will be reported on the day that the research team is aware of the event. The SAE form requires nature of event, onset, severity, corrective treatment given, outcome and causality. Additional information will be sent

within 5 days if the reaction has not resolved at the time of reporting. An SAE form will be completed for all SAEs and reported to the CI/Sponsor (JRCO.CTIMP.TEAM@imperial.ac.uk) within 24 hours.

3. **SUSARs**: Only serious and unexpected adverse drug reactions are subject to expedited reporting. A SAE report form will be completed by the staff at the site of where the adverse reaction occurred and sent immediately signed and dated to the research team with relevant treatment forms and anonymised copies of all relevant investigations. We will ensure that the MHRA, REC and the Sponsor are notified of all SUSARs occurring during the study according to the following timeline: fatal and life threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Any serious adverse events or reactions that are expected or otherwise will be reported to the sponsor immediately.

Due to the limited safety information available for psilocybin, in addition to reporting all adverse events in line with the requirements of this protocol, the study team will be recording adverse events separately. These AEs will be transferred to Worldwide Clinical Trials for adding into a safety database, managed by both Worldwide Clinical Trials and COMPASS Pathways, allowing for the continued development of safety data around psilocybin. Patients will be asked to consent for this aspect of the research; patients who do not consent will **not** be excluded from study participation.

8. Standard Operating Procedure (SOP) for managing adverse events under psilocybin

- Prior to administration of the drug, we aim to fully prepare each participant to ensure that they are aware what to expect. We will also ensure that they are met by all members of the research team. We have used this approach before and believe it to significantly reduce the possibility of any psychological adverse events following administration and serve to put patients at ease in the process. If patients know what to expect beforehand and are comfortable within their surroundings prior to receiving the drug, then this will reduce the risk of any untoward events.
- Patients will be escorted and chaperoned by a member of the research team at all times throughout their participation in the study and for the period during which they will be under the acute effects of psilocybin, they will always be supported by a team member.
- The acute effects of the drug subside 5-6 hours following administration; however, we will carefully monitor the patient for the duration of their stay at the study centre.
- We do not envisage any serious side-effects from administration of the drug; however, patients 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 manner and by using behavioural techniques such as guided imagery. This was used effectively in our pilot study to facilitate calm. We will also offer patients the opportunity for a member of the therapy team to provide reassuring 'arm holding'. This is where, upon the patient's request, a therapist will place their hand on the patient's wrist/ arm, as a way of helping the patient feel secure during drug administration. This exercise will have been previously practiced during the preparation session. Many patients in our previous feasibility study reported feeling reassured by having the option of arm holding if they felt anxious.

- In the unlikely event that a patient becomes behaviourally disturbed, and the use of de-escalation techniques are not sufficient, medical personnel from the research team and/ or CRF will be on hand to administer tranquillisation if necessary. Patients will be asked to consent to this ahead of time. Tranquilising medication was never used in our pilot study and would only be used as a very last resort.
- Typical doses administered would be PO 1-2mg Lorazepam initially then titrated to effect, but any benzodiazepine or tranquilising medication may be administered. This medical decision lies with the full-time trial clinicians present at the time, all ILS trained.
- If such an adverse event was to occur, a member of staff will accompany the patient at all times and in no circumstances will they be permitted to leave the unit until the psychiatrist is satisfied that they are in a fit state to do so.
- We foresee the majority of patients being able to return home approximately 6 hours after receiving the drug; however, there may be patients who we feel are not in the appropriate frame of mind to be discharged from the clinical research facility at that time. If this was to occur, a psychiatrist would remain in the department for as long as is necessary to ensure the patient's recovery back to their previous level of functioning.
- Prior to a patient's discharge from the unit, an assessment of their current level of risk will be conducted to determine whether it is safe for them to leave.
- Should we have any reservations about discharging a patient, they will be offered the option of an overnight stay at a nearby facility until the following day. They will be supported overnight by the psychiatrist and research nursing staff.
- Patients will be reviewed the next morning to establish whether they have returned to their normal level of functioning and we will decide whether they can return home.
- Phone numbers for each member of the research team will be provided to the patient and this responsible other to ensure immediate contact if required. We will also have contact details for the patient and their responsible other, if we need to be in contact.
- Appropriate follow-ups are in place for monitoring the patient's status throughout the study and afterwards. We will therefore be able to detect any prolonged or delayed adverse events.

- Patients and their relatives will be encouraged to contact us should their mental or physical health deteriorate. Although our options of managing their current difficulties will be limited after the trial is complete, we will be able to offer referral to the relevant services. If indicated, we will offer a further follow-up at the clinical research facility so that we can review the patient in person.

9. Purchasing, manufacturing and storing drug

Psilocybin free-base will be purchased and made to Good Manufacturing Practice standards in accordance with Medicines and Healthcare Products Regulatory Agency (MHRA) regulations. The drug will be stored in a secure laboratory in a locked fridge. Home Office permission for possession and storage will be obtained.

The API psilocybin is being synthesised to GMP standard by Onyx pharmaceuticals (UK) and encapsulated to GMP standards by Juniper pharmaceuticals (UK) and blinded by Fisher pharmaceuticals (UK). This route will provide both the 25mg and 1mg doses of psilocybin for the dosing session. Regarding 6 weeks of escitalopram versus 6 weeks of placebo, relevant doses of escitalopram and placebo are to be encapsulated in accordance with GMP guidelines by Guys and St Thomas' (GSTT) manufacturing pharmacy (UK). Labelling will be done entirely by GSTT. All of the relevant parties possess Home Office schedule 1 drugs licenses.

10. Analysis

The data collected from this study will be used to gather new information and inform future studies. Data will be tabulated and descriptive parameters derived. The study is powered for a baseline vs week 6 t-test on the QIDS-16 (condition 1 vs condition 2) and this is the primary efficacy outcome and endpoint.

11. Dosing procedure and patient management

It is strongly advised that psychedelic drugs only be taken in a positive environment where the patient feels comfortable and relaxed [70]. 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.

Patients will arrive in the morning at 9am but the dosing itself will take place at 10:30am. Patients will have been strongly advised to refrain from alcohol for a minimum of 24 hours prior to their arrival as alcohol may compound the effects of the drug and potentially interfere

with its effects. Patients will be psychologically prepared for the experience at screening. We will advise the patient to surrender to the experience and relaxing music will be used to facilitate calm and a relaxed, accepting mind-set. We will caution patients to expect some anxiety, and they will be encouraged to let us know if they feel this. Consistent with published guidelines on managing psychedelic-drug sessions, patients will be advised to accept feelings of anxiety and to allow the experience to unfold naturally, without psychological resistance [70].

Based on our experience in the feasibility study, we will not initiate conversation with the patient. However, we will respond to them if they initiate contact. It is advised that active intervention is kept to a minimum during the acute experience. The patient is encouraged to explore their own mental space. Simple guided imagery may be used to assist relaxation.

Sessions will take place in a purpose built clinical research facility with extensive nursing and emergency support, Invicro (previously called Imanova). All sessions will be supervised by at least 2 individuals. A study medical doctor will administer the drug/placebo and be available on site during the dosing sessions. If required, he/she can attend the therapy room within less than 5 minutes.

After approximately 5 hours post dose, most of the acute subjective effects of psilocybin will have subsided and we will begin a thorough debriefing. This will involve encouraging the patient to give a detailed descriptive account of the experience. With the patient's prior consent, dosing sessions will be video and/or audio recorded. Post-session interviews will also be video and audio recorded for qualitative analyses. At the end of the dosing day, a study medical doctor will assess the patient for potential discharge and the relevant capsules of escitalopram or placebo will be given, depending on the results of the randomisation.

12. Randomisation

Patients will be randomly allocated to one of the 2 conditions using a random sequence generator such as can be found online: (https://www.random.org/sequences/?min=1&max=66&col=3&format=html&rnd=new). The sequence can be initiated and managed by the dispensing pharmacist and schedule 1 license holder (Invicro, previously Imanova). Blinding and labelling will be done in collaboration with the manufacturing pharmacy (e.g. GSTT, Juniper and Fisher pharmaceuticals). An example of a random sequence for 2 conditions is provided below:

Condition 1	Condition 2
2	1
3	4
5	6
8	7
10	9
12	11
13	14
15	16
18	17
19	20
22	21
24	23
25	26
27	28
30	29
32	31
34	33
35	36
38	37
40	39
41	42
43	44
46	45
48	47
50	49
51	52
54	53
56	55
57	58
60	59

Table 1. Example of a random sequence by which patients recruited to the trial enter the relevant conditions. This sequence is held by the dispensing pharmacy (at Invicro) who do not disclose the randomisation to the study team until situations where the blind is broken.

Patient numbers will be independently monitored by InForm, the data system used by Imperial's in house Clinical Trials Unit (Imp-CTU). Versions of objective tests will be counterbalanced using the same randomisation code (e.g. to ensure a 50:50 split, versions A and B will alternate, with version A provided first). Invicro will also direct the study team as to what version of tests will be used and they will also keep their own detailed log of which patients enter which condition. The Imp-CTU system uses InForm ITM (Integrated Trial Management) System, a web-based data entry system which builds an Oracle database for each individual clinical trial.

13. Breaking of blind

In the event of a medical emergency where breaking the blind is required to provide medical care to the trial participant, the investigator will have access to a mechanism that permits rapid unblinding should they feel this is necessary. The investigator will have the ability to unblind in an emergency without first discussing this with any other trial personnel or the sponsor. Thus, the blinding code for each participant will be kept in individual sealed, tamper-proof envelopes on site, for such scenarios. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and CRF, along with the date on which the treatment assignment was obtained. If there are no emergencies throughout the trial, unblinding will happen for all patients on Follow-Up 3, 6 weeks after the first psilocybin dosing session. For the purposes of the safety database maintained by Compass Pathways and Worldwide Clinical Trials (see section 7.5 above), they will be informed of the unblinding results at the end of the trial (after the last patient, last visit).

14. Significant other assessment process

We will also ask patients' significant others for brief ratings of the patient's depression symptoms before and 6 weeks after the dosing day. The Significant Other Questionnaire has 10 Likert scale items and will take approximately 10 minutes to complete. Patients and their significant other will be made aware that this is not a compulsory part of the study procedure.

The procedures for obtaining an assessment from a significant other will be as follows: at screening, the patient will be asked if they consent to us contacting their significant other (a relevant item is included in the consent form). We will ask for the name and email address of a significant other. We will contact this person by email to explain that we are seeking ratings of depression symptoms for the patient in question. At the same time, they will be sent an information sheet and consent form to consider. If they choose to consent, they will return the completed consent form to us, after which, we will email them the pre-study questionnaire. We will explain that we will contact them via email at some point in the next six months to complete another rating.

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