PARTICIPANT INFORMATION SHEET

A randomised, placebo-controlled trial of psilocybin in treatment resistant depression: a feasibility study

You are being invited to take part in a research study called the 'Psilocybin in Depression Resistant to standard treatments (PsiDeR) trial'. You do not have to take part and if you decide not to your care and treatment will not be affected in any way. Before you decide, it is important for you to understand why the research is being done, what your participation will involve and what the potential benefits and risks to you are. Please take time to read the following information and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You can take as much time as you like to decide. Part 1 tells you the purpose of this study and what will happen if you take part. Part 2 gives you more detailed information about the conduct of the study.

Part 1

What is the purpose of this study?

The purpose of this study is to determine whether a proposed treatment for clinical depression called psilocybin is safe and effective.

What is the background to this study?

Clinical depression is a common mental health problem and some people do not get better despite usual medical and psychological treatments. Some go on to suffer for longer than they need to because they cannot find a treatment that is right for them. This is called 'treatment resistant depression'.

Psilocybin is the active ingredient of so-called 'magic' mushrooms. Psilocybin mushrooms have been used in ceremonial or healing rituals stretching back thousands of years. Some people who have used psilocybin mushrooms recreationally have said that they help them to feel better from depression and anxiety. We think that psilocybin may be a new treatment for depression, but we need to test this in a clinical trial.

We completed a smaller trial of psilocybin in 20 patients with treatment resistant depression in 2016. The trial showed that psilocybin was well tolerated and some people experienced long term improvements in their mood. Some people's mood did not improve, but no one experienced a worsening of their mood.

This study will test psilocybin by using a random process to decide whether you receive psilocybin or a placebo. Neither you nor the study team will know what treatment you received until everyone has completed the study. This is the best way of finding out if psilocybin works.

Regardless of whether you receive psilocybin or placebo, everyone will have the opportunity to receive a dose of psilocybin once they complete the main part of the study. This is called the 'open label extension' part of the trial.

We are looking for 60 participants aged 25-80 years with clinical depression that hasn't improved despite the usual treatments to take part in this study.

Why am I being asked to take part?

We are asking you to take part because we think you may be eligible for the study. To be eligible you need to be currently suffering from depression and have not significantly improved despite at least two standard treatments, such as antidepressants or psychological therapy.

In order to confirm your eligibility, we will need to meet you face to face a number of times, perform some routine blood tests and an ECG and get to know you and your current situation. We will also need your GP to provide us with a copy of your medical history.

It's important to emphasise that many people, for various medical or personal reasons, turn out not to be eligible for the study. Whilst we do not want to discourage you volunteering, please take the time to read this information sheet fully so you can decide if this study is right for you. Please feel free to ask us any questions if anything is not clear.

Do I have to take part?

No. If you decide not to take part your care and treatment will not be affected. If you do decide to take part, you can withdraw at any time.

What will happen to me if I take part?

We will send you a link to a short survey you can fill out online. If we think you may be suitable from the survey, we will invite you to a meeting where we will talk to you about your history and current circumstances in depth to help us decide. If we think that you are suitable then you will need to provide a blood sample for routine laboratory tests, have a heart tracing (called an electrocardiogram (ECG)) and consent to your GP or community mental health team sharing the information they hold about you with us. We will also conduct a physical examination at this screening visit and at any other visit if the study doctor think this is necessary. A doctor will then go through this information and make a decision with you about your suitability for the study.

Because we do not know enough about the effects psilocybin might have in pregnancy, all pre-menopausal women will have to take blood and urine pregnancy tests and all sexually active participants will have to use adequate contraception for the duration of the study.

If you are currently taking antidepressants then we will help you to stop taking them, because otherwise psilocybin probably won't have an effect on you. We will talk with you to help you understand how psilocybin might affect you and we will give you information to read and watch on-line.

During the phase where we are withdrawing you from your antidepressants (if you are taking them), we will see you in the research facility each week to review your mood and any problems you are having. If you do not have a care giver then we will make contact with you every 4 days. A psychiatrist will oversee the withdrawal of your medication.

If you have a care giver, then we will ask them to contact us if they think that your mental health is significantly deteriorating or that you are a risk to yourself or others. If this happens, then we may recommend that you restart your previous treatment or another treatment.

Before you receive the treatment, you will be introduced to two people who will be your companions on the day when you receive the treatment. Both will understand the treatment and at least one will be a psychotherapist or a psychiatrist. You will have some time to get to know each other before you receive the treatment and it is important that you feel a sense of trust between you. If you are struggling with this, then please tell us. You will meet with your lead psychotherapist or psychiatrist for at least 3 hours on at least 2 separate occasions before your treatment, but it could be longer if we decide that you need more time to prepare.

Your final eligibility for the study will not be confirmed until shortly before the treatment. This means that you might be excluded from the study even though you thought you were eligible. This usually happens because new information becomes available that we didn't know before. However, it might happen because we decide that it isn't safe for us to give you psilocybin. We can only make this judgement once we have got to know you and you have got to know us. Please consider this point carefully. It might mean this trial is not right for you.

On the day of your treatment, you will come to a comfortable, quiet room in a clinical research facility at King's College Hospital in Denmark Hill, south London. There will be a reclining chair, sofa or bed to lie on

and we will give you eye shades and headphones with calming music to help you relax. Food and drink will be available if you need it and there will be a lavatory nearby.

The treatment will consist of 5 capsules to take by mouth with a glass of water. Before we give you the capsules you will need to tell us that you agree to stay at the hospital with your companions until the doctor is satisfied that you are safe to leave.

Once you've taken the treatment, your companions will stay with you. A doctor will also be available if necessary. We will encourage you to lie back, relax, listen to the music and let your mind go where it needs to.

You have an equal (50:50) chance of receiving psilocybin or placebo in this trial and no one in the study team knows which you will get. This is an important part of the trial that we cannot change.

People who have taken psilocybin have told us the experience is like a 'waking dream'. Like a dream, you might experience a wide variety of sensations and feelings, but none of these experiences are dangerous to you. Psilocybin is not known to be toxic to the body.

If you try to leave the hospital after you have taken the treatment, then we will stop you if we think you are under the influence of the treatment and leaving would be risky for you or others. We will discuss this with you when you sign the consent form, but it is important that you think about this carefully, because it might not be right for you.

The effects of the treatment usually last about 6 hours. Usually, the whole day should last until about 6:30pm, but it could be later. At the end of the treatment a doctor will decide if you are safe to go home. If we don't think you are safe to go home and it is late, then we may ask you to stay in the hospital overnight. If we think that you are safe to go home then we ask that a friend or relative pick you up. We will not give you any psilocybin to take home.

The next day, we will ask you to come back. We will ask you about how you have been feeling, if you have had any side effects to the treatment and ask you to fill out some more questionnaires. We will help you to understand any difficult experiences you might have had. We will also do another heart tracing (ECG) at this visit. You can then go home.

We will ask you to come in for face-to-face meetings with us at 1 week, 3 weeks and 6 weeks after the treatment. We will ask you about how you have been feeling, if you have had any side effects to the treatment and ask you to fill out some more questionnaires. You can then go home.

Your participation in the trial will end 6 weeks after your treatment, unless you want to participate in the open label extension part of the trial, in which case you will stay in the trial for a further 12 weeks. Everyone who takes part in the open label extension will receive a dose of psilocybin. Regardless of when you finish the study, we will help you access whatever care and treatment you feel you need, if any. At the end of your participation in the study, we will ask you whether you would like to share data on sleep and activity from your smartphone or fitness watch, if you have one.

We may use a video or audio recorder to record some of the conversations we have with you during your study visits. This is done so that external assessors can ensure that the study team are performing the study correctly. We may also use the data to perform a thematic (narrative) analysis of the study. This means a member of the study team will transcribe what you and the people with you say into text and then use a computer to pick out the common 'themes' of conversation, without identifying you. Everyone who sees the video or listens to the audio of your conversations with the study team will be bound by the same strict confidentiality agreements, regardless of who they are or where they are based.

Below is a table to help you understand the time needed for you to be a participant in this study. We can be flexible within certain limits (usually between 1 and 3 days) about the specific days that you visit, but if you think you are not going to be able to attend more than 1 of the study visits, then please tell us at the

first visit. We will pay your travel expenses, but we cannot pay you for the time commitment for the study. The total time commitment for you will be about 36 hours spread over 8 visits over the course of 3-5 months, depending on your particular circumstances.

Everyone who completes the 6-week follow up period will have the opportunity to receive a further dose of psilocybin, unless this would not be safe for you. More detail on this is contained within the participant information sheet for the open label extension part of the trial.

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**(8)**
Description	Screening Visit	Baseline Visit	Treatment Visit	Follow Up Visit 1	Follow Up Visit 2	Follow Up Visit 3	Follow Up Visit 4	(Open Label Extension)
Time	1-8 weeks		1 day	6 weeks				(12 weeks)
Location	King's College Hospital, Denmark Hill, London							
Length of Visit	4 hours	4-6 hours	8 hours	4 hours	4-6 hours	4 hours	2 hours	(Variable)
Optional Activities (see below)	Mobile Data	Brain Scan & Bloods	None	Bloods	Brain Scan & Bloods	Bloods	Bloods	(Further psilocybin treatment)

Table 1: Schedule of Visits.

Optional additions to the study

If you are suitable for the study, we will ask you whether you would like to take part in 3 optional parts of the study. You don't have to consent to the additional parts of the study to take part in the main trial, but if you do it will help us understand how the treatment works. The 3 optional parts of the study are as follows:

1. Neuroimaging. We want to understand how psilocybin works in the brain. To do this we need to collect brain scan (MRI) data before and after (but not during) the psilocybin treatment. If you consent to this part of the study we will ask you to have a 1 hour MRI brain scan 1 or 2 days before the treatment and 1 week after the treatment. You will be attending the study site on those days anyway as part of the trial. The information you need to decide about this part of the study is contained within the participant information sheet called 'Participant Information Sheet: Neuroimaging'.

2. Additional blood samples. We want to understand how psilocybin works in the body. To do this we need to collect blood samples before and after the treatment. If you consent, then we will ask you to donate 5 blood samples of about 50mls (10 teaspoons) each over the course of 6 weeks. You will be attending the study site on those days anyway as part of the trial. The tubes containing your blood will be labelled with a code number that is unique to you but does not identify you personally. This means that no one outside of the study team who looks at the tube will know that the blood belongs to you. The tubes will be stored in a secure laboratory freezer at King's College London and might be analysed as part of future research efforts. If we perform analyses on your samples then we will seek separate ethical approval for each project. We will not normally tell you about the results of any analysis that we undertake, because it is very unlikely that this would have individual significance to your health. You may ask us to destroy your samples at any time. Otherwise, we will keep your samples for as long as they may be usefully used in research, but such research will never identify you personally. The Principal Investigator of the trial will be the named custodian of your samples. When they can no longer be usefully used in research they will be securely destroyed.

3. Open label extension. Everyone in this trial who completes the 6 week follow up study visits will have the option to receive a dose of psilocybin, unless there is a reason for you not to. This will be the full treatment dose of psilocybin, regardless of which dose you received before, with a further 12 weeks of follow up. The information you need to decide about this part of the study is contained within the participant information sheet called 'Participant Information Sheet: Open Label Extension'.

What are the possible effects of taking psilocybin?

Psilocybin is called a 'psychedelic' drug and it can have a wide range of effects that depend on the individual person and their circumstances, so it's hard to predict how it will affect you personally. Some of psilocybin's effects will be unfamiliar or strange to people who have not experienced them before.

The following effects may, or may not, happen to you.

1. Heightened emotions. Psilocybin can lead to heightened emotions of any kind, from bliss and ecstasy through to anxiety and, more rarely, panic or paranoia.
2. Vivid, dream-like experiences or memories whilst you are awake. This is a bit like day-dreaming.
3. Visual disturbances such as vivid colours, textures, geometric patterns or illusions. Rarely, psilocybin causes visual hallucinations.
4. Changes in the sense of time. Time may seem to be passing slowly, quickly or may seem not to exist at all.
5. Changes in how your body feels. This can range from aches and pains or feeling the need to use the lavatory to tickling/tingling sensations, or hot/cold sensations running through the inside or on the surface of your body.
6. Changes in your 'sense of who you are'. You may feel as though you 'no longer exist', that you have 'died' or been 'reborn'. This is called 'ego-dissolution'.
7. Other experiences that can have a deep personal significance for you (noetic), but which are hard to put into words (ineffable).

Most people feel back to their usual selves about 6-8 hours after taking psilocybin. Sometimes it takes up to 12 hours. We know that psilocybin has completely left the body after 24 hours. Psilocybin is not known to be toxic to the body. The most common after-effects of psilocybin are a feeling of mental 'exhaustion' and a headache. You should get plenty of rest after you have received the treatment. You can take simple painkillers like paracetamol for the headache if it is troublesome. Psilocybin is not known to stop you from sleeping.

What are the possible benefits of taking part?

1. You will be helping with clinical research, which may help others in the future.
2. The treatment may induce positive feelings.
3. The treatment may help you to feel better from your depression.

What are the possible risks of taking part?

1. Most people who volunteer for this study will, for one reason or another, turn out not to be eligible. Your eligibility for this trial will not be confirmed until shortly before the day of treatment and the study team reserve the right not to give you the treatment if they think it is not in your best interests. It could be very disappointing and frustrating for you and your loved ones if you volunteer for this study and then are excluded shortly before treatment. This could make your depression worse. This does not happen often, but please consider this possibility before deciding whether to take part in this study.
2. The treatment may not work, may make you feel worse, or may result in other symptoms that you did not have before.
3. Some people who take psilocybin-containing mushrooms in a recreational setting report ongoing disturbance in their vision and unpleasant sensations, emotions or charged memories long after

the drug has left the body. We do not know if this will happen when psilocybin is given in a clinical trial setting, however it has not happened to anyone in modern trials yet.

4. We will ask you questions about your life history and current circumstances. This can include personal questions about traumatic events that may be distressing.
5. Because the trial is randomised, you may not get the treatment you want, even though we have asked you to stop taking your existing treatments for depression. You may feel frustrated and disappointed by this.
6. We will ask you to have blood tests, which may be painful and could lead to bruising or infection where the needle enters your skin.

Safety Database

We want to increase understanding of psilocybin's safety profile. To do this, we are working with a company called COMPASS Pathways, who manufacture the psilocybin and are seeking to collect a consolidated database of safety data from different studies. To do this, safety data we collect as part of the trial will be transferred for storage in a secure central database with restricted access, managed by COMPASS Pathways (and their contractor Worldwide Clinical Trials). All data in the database will be anonymised, which means your name will not be associated with it. The data may contain information about your medical history (but only if it is relevant to the safety event that is recorded). The data may be held in this database indefinitely, but you will be able to request to see any data stored in the database relating to your study participation and request for it to be removed.

What happens when the research study finishes?

We will keep in touch with you to let you know the results of the study if you wish and we will organise events to help raise awareness about the results of the study. We will ask for your consent to contact you about other studies in depression or with psilocybin that might interest you.

What about media interest?

Because psilocybin has a colourful history, it is quite likely that the media will be interested in the trial. We will never tell the media that you are involved in the study. However, if the media approach you then please do not talk to them. Refer them to the Principal Investigator of the study, who is Dr. James Rucker.

Isn't psilocybin Illegal?

This study has received all required government approvals. It is legal for you to be given psilocybin in this trial. No one who receives psilocybin in this trial will be committing a criminal offence.

Will this study affect my medical insurance?

We suggest checking with your medical insurance provider, if you have this. You should tell them that this is government approved medical research using a single dose of psilocybin or placebo that has been manufactured to 'good manufacturing practice' standards. There is no ongoing medication.

What if there is a problem?

Any complaint about your experience within the study will be responded to and we will try to address any concerns you have as best we can. Detailed information is given in Part 2 of this document. Please contact Dr. James Rucker if you have any complaints about the study. You can also talk to an independent body, such as the Sponsor's Patient Advice and Liaison Service (PALS). Contact PALS on freephone 0800 731 2864 (Option 2) or by email at pals@slam.nhs.uk.

In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against King's College London and/or SLaM NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). King's College London has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

Can the study team stop me from participating in the study?

Yes. The study team and the sponsor of the study can stop your involvement at any time. For example, this may happen because we are concerned for your safety if you continue in the study.

PART 2

What if relevant new information becomes available?

It is possible that whilst performing normal medical checks we may identify a significant problem that you didn't know you had. If this occurs, we will inform you.

Sometimes during a research project, new information becomes available about the treatment that is being studied. Although unlikely, if this happens, a member of the research team will tell you about it and discuss whether you want to continue in the study. If you decide to continue in the study, you may be asked to sign an updated consent form. If the study is stopped for any other reason, we will tell you why.

What will happen if I don't want to carry on with the study?

If you withdraw from the study, your usual care and treatment will continue as before. We will retain and continue to use any data collected before you withdrew.

How do I get help if I am concerned about anything?

If you have a concern about any part of this study, you should ask to speak with a member of the study team, who will do their best to address your concerns. You should report any adverse events or medical occurrences that you experience whilst in the study to a member of the study team. If you have any medical concerns that cannot wait until you can talk to a member of the team you should dial 111 to talk to NHS direct (24 hours a day), or speak to your GP or secondary mental health care professional using the information in this sheet to tell them about your participation in the study. In an emergency, you should visit A&E or dial 999.

If you have any questions about the study, if you want to know your rights as a research volunteer, if you want to tell us about any side effects, or if you want to make a complaint please contact us at psilocybin@kcl.ac.uk or 07931251093

This trial is co-sponsored by King's College London and the South London and Maudsley NHS Foundation Trust. The co-sponsors will at all times maintain adequate insurance in relation to the study. Kings College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient. Participation in this study does not affect your normal rights to complain about any aspect of your treatment and care. If you need to discuss this, freephone 0800 731 2864 or by email at pals@slam.nhs.uk. Finally, if you have private medical insurance you should consult with your insurer before agreeing to take part.

Will my participation in this study be kept confidential?

Yes, however we need to tell other professionals involved with your care, for example your GP, that you are a part of this study and if any serious concerns arise. Similarly, we will ask them whether they have any concerns about you being in the study. They are bound by the same legal duty of confidentiality as the study team. We will always try to ask for your approval before contacting your GP or other health professional if we have concerns about your safety or welfare. However, it we think that your safety and welfare is seriously at risk then we may not seek your consent beforehand if we think this would introduce unnecessary delay or cause unnecessary risk to yourself or others.

For this study you will need to give us the contact details of a trusted friend or relative who you are happy for us to speak to about your participation in the trial. We will speak to this person if we need more information about you, or if we are worried about your safety. We recommend that this person accompany you home after the treatment.

How will we use information about you?

We will need to use information from you, from your medical records, from your named carer or relative and from your GP for this study. This information will include your name, initials, date of birth, contact details and NHS number. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. At the beginning of the study, you will be allocated a code number that will be used to identify all the research data we keep about you. Your name, address and other identifiable information will be kept in a separate, secure place, with the code number. This means that it will not be possible to identify you from any research data stored about you.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. Research data collected on paper will be stored securely in files in a locked cupboard, or in a locked office. Electronic research data and audio-visual data will be stored on secure computer servers located in the same country as the study itself. Only members of the clinical or research team or representatives from the Sponsor will have access to your data.

King's College London and the South London and Maudsley NHS Foundation Trust are the co-Sponsors for this study, based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The Sponsor organisation will keep identifiable information about you for 15 years after the study has finished or until it is no longer needed for research. After this it will be destroyed, either by shredding (paper) or secure deletion (electronic data).

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. You can find out more about how we use your information at:

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to King's College London Data Protection Officer Mr Albert Chan info-compliance@kcl.ac.uk or via https://www.slam.nhs.uk/about-us/privacy-and-gdpr
- by ringing us on **0800 731 2864**

What will happen to the results of the research study?

The results of the study will be published in academic peer-reviewed journals, presented at conferences and discussed at other public events. We will also produce a newsletter summarising the findings of the study which we will send to you and your clinical team. You will not be identified in any report or publication.

Who is organising and funding the research?

The study is organised by the Institute of Psychiatry, Psychology & Neuroscience, King's College London. The sponsors of the study are King's College London and the South London and Maudsley NHS Foundation Trust. Funding is provided by the National Institute for Health Research, Clinician Scientist Fellowship programme. The psilocybin drug substance is manufactured by Compass Pathways, Ltd. The researchers involved in conducting this study do not receive any financial incentives for including you in this study and do not benefit financially from this study.

Who has reviewed the study?

This research has been notified to the Medicines and Healthcare products Regulatory Agency (MHRA) and reviewed by the Health Research Authority and an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study was given a favourable ethical opinion for conduct in the NHS by the London – Brent Research Ethics Committee (20/LO/0206).

Names of the study team

Chief Investigator: Professor Allan Young

Principal Investigator: Dr James Rucker

Research Assistant: Tim Mantingh

Contact us

Email: psilocybin@kcl.ac.uk OR telephone: 07931251093