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Centre Name: Centre for Psychedelic Research
Study Protocol number: 175297
REC Reference: 26/LO/0001

Study Title: PsilOpioid: A proof of concept randomised controlled trial to investigate psilocybin therapy and brain reward mechanisms in opioid use disorder (OUD).

Participant Information Sheet

You are being invited to take part in a research study. Before you decide whether to participate, it is important to understand why the research is being done and what it will involve. Please read this information carefully, and feel free to talk it over with others. If you have any questions, you can ask us at any time.

This sheet has two parts. The first part explains the study and what will happen if you decide to join. The second part gives you more details about the study.

Part 1: Study Summary

What is the purpose of the study?

This study is investigating whether psilocybin, a substance found in 'magic mushrooms', combined with supportive therapy sessions, could help people who have recently completed detox from opioids (e.g. heroin) and/or opioid substitution therapy such as methadone or buprenorphine (e.g. Buvidal/Espranor/Subutex). This treatment, known as 'psilocybin therapy', has shown promise in treating conditions such as depression, smoking addiction and alcohol use disorder (alcohol addiction). In other studies, for some people psilocybin therapy has been shown to reduce consumption of alcohol or cigarettes (depending on the study), improve quality of life, and help people explore thoughts and emotions linked to their addiction. We will investigate if psilocybin therapy can be helpful in treating people recovering from opioid use disorder (opioid addiction) and how it might work. We want to see if it can also reduce drug use and improve mood, craving, and quality of life in people with opioid use disorder. As part of the study, we will conduct brain scans to help understand how psilocybin therapy works in the brain.

Who are we looking for?
We are looking for people who:

- have a history of opioid use disorder
- have completed detox in the last 90 days
- are not currently using any opioids, including opioid substitution therapy such as methadone or buprenorphine (Buvidal/Espranor/Subutex).
- are able to read, comprehend and record information written in English

We believe that you meet these criteria, or soon will do, and as a result may be eligible to take part in the trial.

Do I have to take part?
No, taking part is voluntary. You can choose to leave the study at any time without giving a reason. Your decision will not affect your current or future care in any way.

What will happen to me if I take part?
See Figure 1 on page 4 for an overview diagram of the study. We will start with a screening process to check your health and ensure it's safe for you to take part in the study. If you are eligible and decide you would like to take part, you'll visit Hammersmith Hospital at least 5 times, with 2 overnight stays (free of charge), and participate in supportive therapy sessions. If staying overnight is not practical for you, please do let the study team know and they can discuss alternative arrangements. The study has the following parts:

Preparation
A week before the psilocybin session, you will meet with two guides from the therapy team in a remote call. They will be with you throughout the process, starting with this 'preparation' session. The day before you receive psilocybin, you will come to our clinic where you will have a brain scan (magnetic resonance imaging, MRI). During this 'preparation' visit, you'll meet your guides in person. They will support you in getting ready for the psilocybin experience, helping you feel comfortable and prepared for the dosing session. You will then stay overnight in the accommodation provided for you.

Dosing day
On this day, you will meet your therapy team to ensure that you are ready for the psilocybin experience. You will be given a low to high dose of psilocybin in the form of capsules, and your guides will stay with you throughout the session, which lasts up to 6 hours. You will be provided with an eye mask and there will be music playing through headphones and speakers. A medical doctor (study medic) will always be nearby. It is important that you have not used opioids for 3 days before this session. Afterward, you'll stay overnight at the accommodation provided and have a follow-up the next day to discuss your experience.

After dosing
The next day, you will come back to the centre for a two hour integration session, followed by two hours of questionnaires. A week later, you'll return for another 'integration' session and a brain scan. There will be another integration session two weeks later, which can be done in-person or remotely. For the next 10 weeks, there will be shorter integration sessions every two weeks which will be remote and last up to 1 hour. All integration sessions provide supportive therapy to help you

understand and apply your psilocybin experience to your daily life. At the end of this period, you will visit the clinic for a final follow-up where the study team will ask you about your quality of life, craving, drug use and wellbeing. We will also take a hair sample to assess drug use.

Other information

If you wish to take part in the study, we require a commitment that you will attend all follow up visits, complete all scans and questionnaires, and will remain contactable for follow up. It's important to be aware that at some visits there are multiple questionnaires to complete, which may take some time, but we will ensure you have breaks if you find this too much. This trial is open to both smokers and non-smokers. If you do smoke, you should be able to go for several hours without a cigarette, but you can use nicotine replacement. You should not be dependent on any other drugs or alcohol. If you have questions regarding this, please do speak to the study team.

There are certain medications which you cannot take as part of this trial. This will be discussed with you at screening if you decide to take part. You should continue to take your usual medication as prescribed and should not make any changes to your medication without the guidance of the prescriber or your GP.

You should not be enrolled in any other studies of new medications at the same time as this trial.

Second point of contact

We will ask you to share a second point of contact during the study where possible. This could be a friend, family member or sponsor. If we cannot get in touch with you during the follow up period, we may contact them to ask for updated contact details. We ask that you tell the contact about the study and explain that you have given their contact details to the study team for this purpose. We will not share any information about your participation with this individual.

Will I be paid for taking part in the study?

Participants who complete all 12 study visits will be compensated for your time. The details of payments for each visit are provided in section 2. All travel will be reimbursed, and accommodation will be provided when overnight stays are required.

Further questions

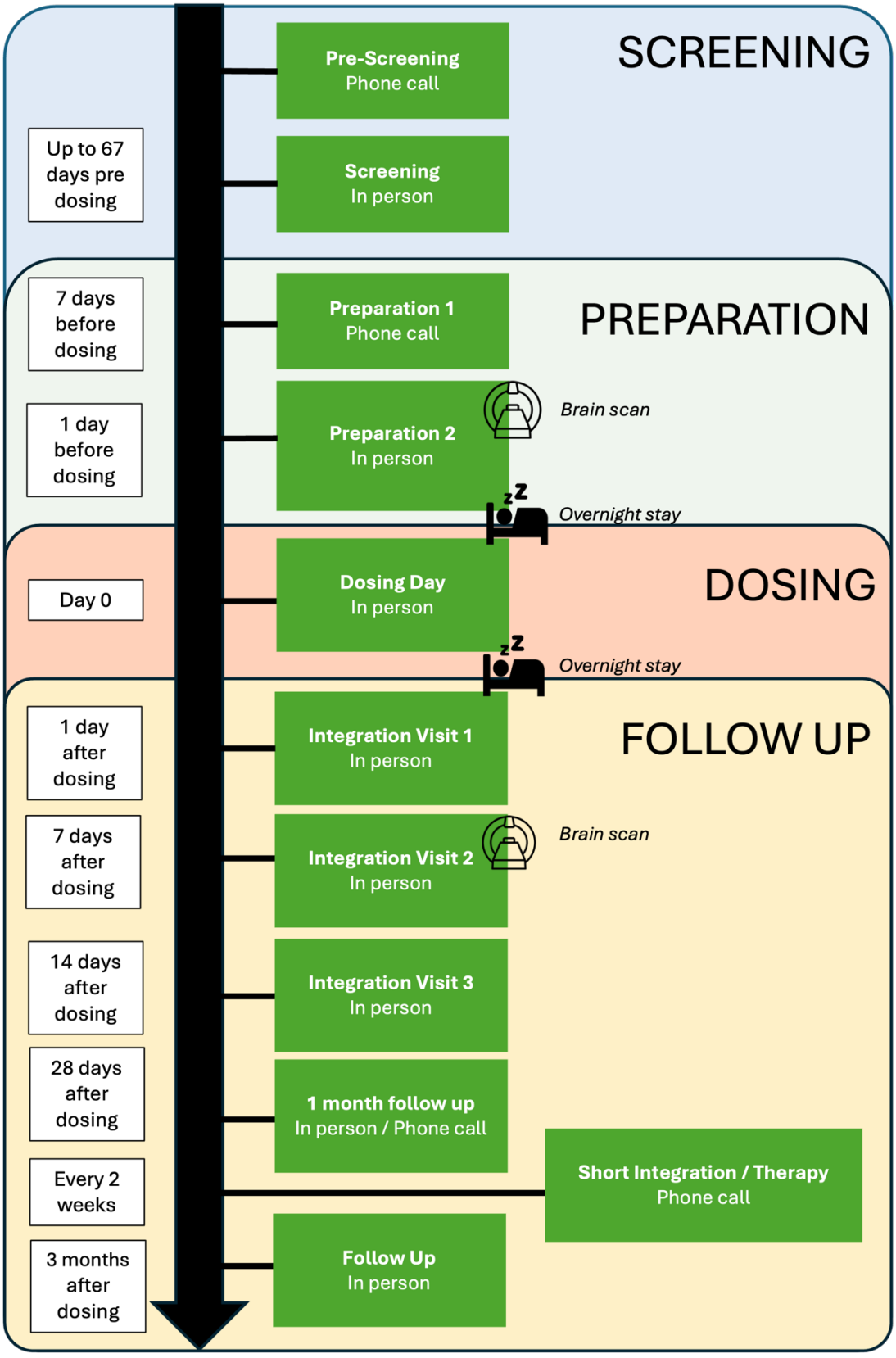
If you have any further questions or would like more information about the study, please contact the study team using the following details

Email: psilopioid@imperial.ac.uk
Telephone: 07442791857

Thank you for considering taking part in this study

Figure 1. Study overview diagram

The diagram below outlines the study visits.



Part 2: Detailed information on the conduct of the study

What is the main purpose of the study?
This study will compare a range of doses of psilocybin capsules from a low to a high dose, which may or may not have a psychedelic effect. This will allow us to compare the different doses and understand the effect of psilocybin therapy. You will receive only one dose of psilocybin, which will be chosen at random, so neither you nor the study team will be able to choose which dose you receive. This study is double blind. This means that neither you nor your doctor will know which dose you have received (although, if your doctor needs to find out they can do so).

What is the drug being investigated?
We are investigating the compound psilocybin. It is the main active ingredient in "magic mushrooms". Recent studies have shown that psilocybin may help to manage conditions including depression, alcohol use disorder, tobacco use disorder and obsessive-compulsive disorder. It does this by working on the serotonin system in the brain, which is linked to several important functions in our body, including regulation of mood, sleep, and thinking processes.

The team at Imperial College is one of the most experienced groups in the world at delivering psilocybin therapy and have used this compound in previous and ongoing studies in healthy volunteers and multiple other conditions.

What are the effects of psilocybin?
Most people find the effects of psilocybin quite pleasant; others can get anxious or have difficult experiences so we will prepare you for this. Psilocybin can have many different effects, which can be different for each person. Some of the common effects include:

-a feeling of euphoria, energy or excitement.
-changes to how things look - for example sizes or shapes of things can change.
-some people may see shapes and colours, or the room may appear to get bigger or brighter.

The effects of psilocybin can last about 5-6 hours. You will be encouraged to close your eyes during the experience. Some people report that they see shapes or colours, and sometimes liken it to dreaming. Such dream-like experiences can sometimes feel more real than a normal dream. Time may appear to pass slower than usual, and as a result some people find it may be hard to judge how much time has passed. People sometimes report a difference in perception, feel their emotions are magnified or changes to how they think.

It is not uncommon for people to have visions of their pasts; for example, they might feel as if they are remembering or even reliving events from their childhood. However, these could equally be more 'symbolic' in nature, similar to dreaming rather than recollections of true events that happened in the past. Sometimes it's difficult to know either way. The therapy team will support you if this were to happen.

Some people also may have difficulty putting their experience into words (ineffable). Whatever experience you have, you will be invited and supported by the study guides to approach it with a mindset of curiosity and openness. Your guides will be there to support you in making sense of your experience.

Will I be able to take psilocybin again after the study has ended?
No. Psilocybin is a Schedule 1 Controlled Drug in the UK. This means that it cannot be prescribed outside the study.

Will I be paid for taking part in the study?
The cost of travel expenses will be covered, as will overnight accommodation around the dosing day when required. You will be paid for completing key visits, either by bank transfer or voucher, depending on your preference. You can request payment after each visit. While vouchers can typically be arranged within a few weeks, bank transfers may take up to three months to process. The study team can advise on current payment timelines. If you take part in all study visits and complete both MRI scans, you would be eligible for a payment of up to £450.

What will be expected of me if I take part in the study?
- Turn up for all visits on time
- Plan the dates and times of your visits in advance
- Do not use alcohol within 24 hours of each study visit
- Inform the study coordinator if any events happen that may affect your participation in the study
- Complete questionnaires when asked to do so
- Complete two brain (MRI) scans, lasting up to 90 minutes each.
- Use an adequate form of contraception from enrolment and for 28 days after receiving psilocybin.

What sort of people are we looking for?
We are looking for people over the age of 18, who have a diagnosis of opioid use disorder, in remission, and are not on any opioid substitution therapy (e.g. methadone or buprenorphine). That means you will have been using opioids in the past, but not currently be using them, or have reduced your dose of opioid substitution therapy to zero.

You will need to undergo a screening with a study medic (doctor) to see if you can take part. We will also need to contact your GP, detox provider, mental health team or keyworker to tell them you are taking part in the study. We may also need to ask them to provide information about your medical history.

What if I am on other medication?
There are some medications that you cannot take whilst you are taking part in the trial. This is because they affect how the study drug works, which may not be safe. The study medic will talk to you about your medications as part of the screening process.

For example, regular use of the following medications which would mean you could not take part in the study:

-Some antidepressants (e.g. mirtazapine, trazadone)
-Some painkillers (e.g. tramadol, tapentadol)
-Some mood stabilisers or antiepileptics (e.g. lithium, carbamazepine)
-Monoamine oxidase inhibitors (e.g. selegiline, moclobemide or phenelzine)

-Some antipsychotics (e.g. risperidone, olanzapine, quetiapine)
- Alcohol dehydrogenase inhibitors and aldehyde dehydrogenase inhibitors (e.g. disulfiram (Antabuse) and UDG modulators

Please note this is **not** a complete list – please contact the study team if you have any questions or would like to discuss your medication with them.

Alcohol and other drug use
It is recommended that in early recovery you do not use any mind-altering substances including alcohol or other illicit drugs.

We will ask you to tell us how much alcohol and/or illicit substances you consume each week. It is important that you are open and honest about this. This is because alcohol and other drugs can affect the results of the trial, and we need to make sure that it is safe for you to take part as some drugs may affect the way that psilocybin works. You should not drink any alcohol 24 hours before each study visit. A breathalyser test will be done when you visit the study centre. To ensure your safety, the study team will perform a urine drugs test to check for any drugs in your body. If you have a positive urine drugs test, then we will share the results with you, and discuss if you are able to take part in the study. We may have to reschedule that study visit.

Contraception
All people of childbearing potential must agree to use adequate contraception from the point of enrolment until 28 days after the day you receive psilocybin. For participants assigned female at birth, this includes hormonal contraceptives (such as the combined pill or implant), intrauterine devices (IUDs), permanent contraceptive procedures and sexual abstinence. For participants assigned male at birth, this includes condoms or sexual abstinence. You will need to discuss and confirm your chosen method of contraception with the study team before you can take part in the study.

You should not be pregnant or attempting to conceive while taking part in this trial. You must inform the study team if you or your partner become pregnant within 28 days of the dose of psilocybin.

The study team will ask you to perform a urine pregnancy test at the screening visit, on the day of dosing and before the MRI scans, if applicable.

Where will the study take place?
All in-person study visits will take place at the National Institute for Health Research/Wellcome Trust Clinical Research Facility (CRF) at the Hammersmith Hospital on Du Cane Road, West London.

All MRI scanning visits will take place in the Burlington Danes Building on the Hammersmith Hospital campus. Scans are completed by Perceptive (previously called Invicro), a partner of Imperial College London. A map has been included at the bottom of this document, on the last page.

What are the disadvantages of taking part in the study?
Taking part in this study could have some disadvantages, including:
- Multiple visits to the study centre.
- Large number of questionnaires to complete, which may be burdensome at times.

- Short term anxiety around taking the psilocybin (the study drug).
- Revisiting challenging or upsetting themes or experiences during the study.
- Potential triggering questions, images/videos related to opioid use or interventions.

The clinical interview will focus on your upbringing, family life and experience of life as well as your substance use and recovery plans. This may bring up sensitive issues – but they are relevant to any study of drug dependence. We will be able to provide support and guidance, which will help reduce any worries you may experience.

As part of the study, you will take part in two brain scans (fMRI). These scans are safe, non-invasive, and commonly used in research. Each scan lasts up to 90 minutes and involves lying still in the scanner while your brain activity is measured during a series of simple tasks. A trained researcher will accompany and support you throughout.

The purpose of these scans is to help us understand how psilocybin therapy may affect brain processes related to opioid dependence and recovery.

One of the tasks involves viewing short video clips designed to explore how the brain responds to emotional and motivational cues. These include everyday scenes such as household chores, playing music, social interactions, and nature. Some clips will also contain drug-related content, such as people using opioids.

> *"I can see why it might be difficult, but you need to see how someone's brain is reacting when they see drugs… it will show if people are able to move on from it or get stuck. I think it is a good idea though, I'd love to see what my brain does when I watch someone using gear in a film or on the telly."*
>
> **Feedback from person with 40 years lived experience of heroin use**

You can speak with the study guides after the cue-reactivity task if you are having any challenging feelings or a desire to use drugs. You will be given the telephone number for the study medical team, who you can call if you are feeling cravings in the day after the cue reactivity tasks. You will also have access to support after and can contact the study medics at any point during the study.

If you currently have private medical insurance, please check with your provider before agreeing to take part in the study, to confirm that it does not affect your current medical insurance. We do not expect to uncover any medical condition you may be unaware of, but if we do, you will be informed immediately, and the next steps will be discussed with you. Any unexpected findings could increase future insurance premiums or make it more difficult to obtain insurance.

What are the advantages of taking part in the study?

Taking part in this study has some advantages, including:

-Opportunity to take part in one of the first trials of psilocybin therapy in opioid dependence in modern times.
-This study drug may be helpful to you.
-You will receive supportive therapy sessions that may be helpful to you.
-You will help advance our understanding of how psychedelic drugs work and if they may be helpful in treating opioid use disorder.

We cannot promise that the study will help you, but the information that we get will help us to learn whether psilocybin therapy could be a useful treatment and improve our understanding and treatment of people with opioid use disorder.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, the study medic will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information, the study medical team might consider it to be in your best interests to withdraw you from the study. Your doctor will explain the reasons and can signpost you to treatment providers.

What if the researchers find something medically important during the study?
If a medically important issue is identified during the study, the trial doctor will inform you and, with your consent, share relevant information with your GP or your treatment provider (treating drug/alcohol team), if applicable.

All information, including personal information, obtained in the interviews, questionnaires, visits will be treated as confidential and not be disclosed without the participant's consent, unless required by safeguarding.

What will the study involve?
If you take part in the study, you will have **12 visits** in total. These visits will be a combination of in person (at the clinic) and remote (either via phone or video call).

As part of these visits, you will have two MRI brain scans, several urine drug screens, and a hair sample taken which will require a small section of hair. You will also be asked to complete questionnaires and talk about your recovery journey and your experience of psilocybin therapy.

Pre-screening: phone or video call – what will it involve?
You will have a telephone or video call with a member of the study team, when we will discuss the study with you and see if you are interested in taking part. This will see if you are interested in taking part in the study. It will also check you are eligible to take part in the study. You will be asked some questions about your health, substance use and to see if it is safe for you to take part, and to have an MRI (brain) scan.

The study team will ask for your consent to request a copy of your summary care record (SCR) or medical records from your GP.

Visit 1: Screening visit – *in-person*
This visit will take place at the Clinical Research Facility at Hammersmith Hospital. The visit should take no longer than 5 hours. You will meet with members of the research team for the first time face to face. We will talk to you about the study and check you understand everything that is involved. This is a good time to ask questions about the study. If you are sure you would like to take part, and

the team think you understand everything and have weighed up your decision, you will be asked to sign a consent form. Even if you sign the consent form, if you change your mind, you can still withdraw (leave) the trial at any time. This will not affect your care in any way.

We usually start with the most important assessments first. This is because if you do not meet the criteria to take part in the study, then we do not waste your time. We know that this can be disappointing for people. If you are not eligible (you are not able to participate) then we will let you know in a considerate way. It is important that you do not withhold (in other words hold back) information because it may mean you can't take part in the trial. This may put yourself at risk of harm.

If you are sure you would like to take part, and the team think you understand everything, you will be asked to sign a consent form. Even if you sign the consent form, if you change your mind, you can still withdraw (leave) the trial at any time. This will not affect your care in any way.

At the screening visit, a study medic will review your medical record, to confirm that there is nothing which would rule you out of taking part in the study. They will also perform a physical examination and routine tests. This will include an ECG (electrocardiogram, a measure of the heart's electrical activity). We may need to request blood tests from your doctor or other health care provider. If the results of your blood tests or your ECG are not normal, you may not be able to take part in the trial.

There is increasing awareness and evidence that hormonal fluctuations related to the menstrual cycle affect psychedelic experiences. If you are someone who has periods, we will therefore ask you to let us know the start date and length of your last period, and if you are experiencing any symptoms related to your period (such as premenstrual syndrome, or PMS). We may also ask you questions about your menstrual cycle at other visits.

You're allowed to bring personal devices (e.g. mobile phone) with you to all visits. However, we ask participants to refrain from using their mobile phone during the dosing session.

If you complete this visit, you will be paid £25.

If I am considered eligible for the trial, what happens next?

Visit 2: Preparatory Session 1 - *phone or video call*

This visit will take up to 2 hours and will take place one week before you attend the centre for dosing (where you are given psilocybin). You will have a phone or video call with the study team. It will give you the chance to ask any questions or tell us if you are worried about anything. We will help prepare you for your dosing session. This will be with one or more members of the study team who will be with you during your dosing session, giving you the opportunity to get to know your guides better. The study team will also ask you some questions about your recovery and beliefs about your addiction.

Visit 3: Preparatory Session 2 & Baseline Assessments – *in-person*

This visit will take place at the Clinical Research Facility at Hammersmith Hospital. The visit will take around 7-8 hours and will take place one day before you have your dose of psilocybin. There will be opportunity for breaks, as well as refreshments (drinks and snacks) and a lunch. This will give you the chance to meet the study team again, ask any questions and tell us if you are worried about

anything. We will show you where you will have your dosing session and explain more about it. You will get to spend more time with the two guides who will be with you during your dosing session, and they will help prepare you for the dosing. The guides will discuss means of supporting you during the dosing, including the possibility of supportive touch, such as a hand hold, if that is something you potentially wish to request from them if the experience becomes challenging. They will go through with you in detail what this could be like, and ultimately it is entirely your decision if you wish to explore this with them.

This will take about 2 hours with breaks. You will have an MRI (magnetic resonance imaging) brain scan. The scanning procedure takes approximately 3 hours, including getting ready for the scan, familiarisation with the process and getting into the scanner. The actual scan itself will take about 90 minutes. You will be asked to complete a series of tasks (like games) during the scan. We will also ask you complete more questionnaires and interviews.

If you complete this visit, you will be paid up to £70, made up of £30 for completing questionnaires, £35 for the brain scan and up to £5 as a prize for one of the scanner tasks. As you will be visiting the centre the next day, we will provide you with accommodation for the night free of charge.

Visit 4: Dosing Session – *in-person*
This visit will last between 8 – 9 hours. We will ask you to arrive at the Clinical Research Facility in the morning. On dosing day, you will be asked to provide a urine sample and take a breathalyser test to make sure that it is safe for you to take psilocybin in the trial. We will also check your blood pressure, heart rate and oxygen saturation.

Members of the study team, which include the researchers, study medic and the two study guides, will spend some time talking to you to prepare you for having a dose of psilocybin. The guides will talk more to you about how best to manage the effects of the drug and relaxation techniques, as well as how they will support you during the dosing.

We will help prepare you for the experience by asking you to lie down. We will dim the lights and play relaxing music. We will use guided imagery to help you to relax. This involves the study team talking to you about a pleasant place for you to imagine. Once you are relaxed, we will give you the dose of psilocybin to take.

After you have taken the psilocybin, it will only be the guides present with you in the room, who will sit either side of you or nearby. The other researchers and study medic will always be nearby to help if needed. We will not speak to you for a bit, and we would encourage you not to speak to us. But if you do want to speak to us, then that is fine too. We will “check-in” with you regularly. In other words, we will ask you how you are feeling regularly.

The effects of psilocybin usually start about 45 minutes after you have taken it. It typically is most intense in the first 2-3 hours. The experience can last about 5-6 hours, and your guides will be present throughout to support you. You can eat a light lunch and fruit if you would like. About 5 hours later, we will talk to you about your experience. We will ask you to complete a short interview and do some more questionnaires to rate your experience.

Sometimes people can find difficult feelings come up during the dosing session. In other studies, we have found that going through difficulty can help you overall. For example, if a memory of a bad experience comes up during the session, the person can feel less bothered by it and more "at peace" with the experience. Sometimes, on rare occasions people can feel very anxious. When this happens, you can talk to the study guides to help you with relaxation techniques to reduce the anxiety. If this doesn't help, or the study medics are concerned for your safety, a single dose of a fast-acting anti-anxiety medication (called a benzodiazepine) can be prescribed by the doctors and administered, which will alleviate any anxiety or emotional distress. It is very rare for a medication to be used – relaxation techniques are usually sufficient.

Psilocybin is a safe drug for your body. So even if you feel strange, your body won't be in danger. We will have gone through your medical and psychiatric history to make sure it is safe for you. Several hundred people have had similar doses of psilocybin in studies over the last 10 years.

The study guides will be with you for the entire duration of your experience. As the day draws to a close, you will be assessed by a study medic to make sure you are ready to leave the centre. Before you leave, you will be asked to complete some questionnaires about your experience. We ask that you remain for the duration of the day in the research facility, until around 4:30-5:30pm, when the medic will check you are comfortable and safe to leave. You will be provided with a contact card (similar to a credit card) with details of emergency contact details to carry with you. A member of the study team will take you to the overnight accommodation which has been provided for you to stay overnight in. We will also provide you with an evening meal. We suggest you have a relaxing evening in the accommodation and advise against driving and tasks requiring fine motor skills.

If you complete this visit and the questionnaires, you will be paid £50.

Visit 5: Integration Session 1 – (Day +1) – *in-person*
The day after your dosing session, you will come back to the research facility. This visit will take about 4 hours in total and there will be opportunity for breaks, as well as refreshments (drinks and snacks). We will ask you to complete follow up questionnaires and take part in the integration session with your study guides. We will ask you about how you felt about your experiences during the dosing session, how you slept and how you feel now. This session will help you to understand how best to make use of the session. If you complete this visit, you will be eligible for a payment of £70. After completing your visit, you should be able to drive and perform tasks requiring fine motor skills. However, if you feel impaired in any way, we recommend refraining from these activities until you feel fully capable.

Visit 6: Integration Session 2 – (Day +7) – *in-person*
This visit is very similar to visit 5 (integration 1) and happens 7 days after your dosing session, in the clinic. It will last approximately 7-8 hours and there will be opportunity for breaks, as well as refreshments (drinks and snacks) and a lunch. You will take part in an interview and integration session with your study guides and we will ask you to complete some questionnaires and an interview. After this, you will have another brain scan which will be the same as the one you had at your first visit. This scan itself will take about 90 minutes.

If you complete this visit, you will be eligible for a payment of up to £80, made up of £40 for completing the questionnaires and £35 for the brain scan, as well as a potential £5 voucher reward for the MRI task.

Visit 7: Integration Session 3 (Day +14) **-** *This visit can take place either in-person or remotely.* This visit is very similar to the two earlier integration visits. This will happen 14 days after your dosing session and will take about 2 hours.

Visit 8: Follow Up and mini integration – 1 month (Day +28) - *remote*
This session will last 3 hours and there will be opportunity for breaks. First, there will be an integration session, lasting up to 1 hour. This will then be followed by two hours for questionnaires. If you complete these visits, then you will be paid £55.

Visits 9-11: Remote follow-up and mini integration sessions (Day +42, +56, +70) - *remote*
There will be follow up visits every two weeks. These are smaller (up to 1 hour) integration sessions, with the study guides. These will take place over the phone.

Visit 12: Final Study Visit (3 months) – *in-person*
This will be an in-person visit at 3 months at the clinic at Hammersmith Hospital and will take 4 hours. There will be opportunity for breaks, as well as refreshments (drinks and snacks). During this visit, you will meet with your study guides and we will ask you about your mood, wellbeing, quality of life and craving. We will ask you how you are feeling and whether you have experienced any adverse (unexpected) events. We will also discuss with you your drug use since we last spoke. It is important to be open and honest about this, so that we can understand the effects of the psilocybin therapy. During this visit, we will also collect a hair sample from your head. This will allow us to measure if you have used any drugs in the previous 3 months. We will keep this hair sample until it's analysed by the Toxicology Unit, after which it will be destroyed. We will ask you to complete more interviews and questionnaires. Only authorised staff will have access to the hair sample. If you complete this visit, you will be paid £100.

Out of Study Follow-Up
There will be a further and final follow up session at 6 months. This will take place via telephone.

If at any point during or after the study you feel like your wellbeing has worsened, you can get in touch with us to talk about this. You will be able to contact the study guides at any time outside of the arranged follow up appointments. If you do not feel well enough to contact us yourself, then you could ask a friend or family member to get in touch with us instead.

What happens when the research study stops?
At the end of the study, we will provide information of groups for people who have also taken place in clinical studies, which you may be interested in joining. This is optional.

After the end of the trial, a summary of findings from the trial will be prepared and published on the ISRCTN website, usually within 1 year. This will include no personally identifiable information. The ISRCTN registry is a database that records clinical research studies and can be searched by members of the public and other researchers. This can be accessed from

https://www.isrctn.com/ISRCTN10232579. We will also ask you whether you would like the findings shared with you directly.

Video and audio recording
For the safeguarding of yourself and the research team, and for research purposes, we will have audio recording as part of this trial. For added detail, there is the option to have a video recording. These recordings would include you talking about your expectations, response to the study drug and surrounding experience in the trial. This may be useful in understanding how your experience progressed and whether anything you do or say can be used to explain and/or predict how you respond to the treatment. This would happen by using a discrete camera and microphone. If you are nervous about this and would prefer not to be video recorded, then we will not do this.

Any recorded material would be securely stored and only accessible to members of the study team. A member of the research team will transcribe the interviews using the recorded material. If we wished to present a recording of you in a scientific presentation or for public engagement, for example, we would ask your permission for this and you would have the right to refuse this. If we were to use a quote from you in a scientific presentation or publication, this would be anonymised. The recorded material will be stored for 3 years but can be destroyed (via deletion of digital files) at any time upon your request.

What happens if something goes wrong?
There are doctors at the research clinic at all times who will provide emergency medical cover if required. You will be given a contact card (similar to a credit card) with details of the study, and emergency contact details to carry with you.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study, then you should immediately inform the Investigator (Dr David Erritzoe, d.erritzoe@imperial.ac.uk). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team.

Who has reviewed the study?
This study has been approved by London – Fulham, a research ethics committee and the Medicines Health Research Authority (MHRA). The study will follow the principles of Good Clinical Practice.

Who is organising and funding the research?
This research will be conducted by the Centre for Psychedelic Research at Imperial College London and National Institute for Health and Care Research (NIHR).

What will happen next?

If you choose to take part, we will contact you after you have received and read this information sheet and a time will be arranged for a screening visit. We would also like to contact your doctor or mental health practitioners involved in your care to establish your background history and confirm whether you are appropriate to enter the study. If you could provide their details, then we can contact them straight away and delays to your entry in the trial will be minimised. We will give you directions to the study centres where screening and scanning sessions will take place. More time can be given if you have not yet had a chance to read through the information sheet.

Contact for further information

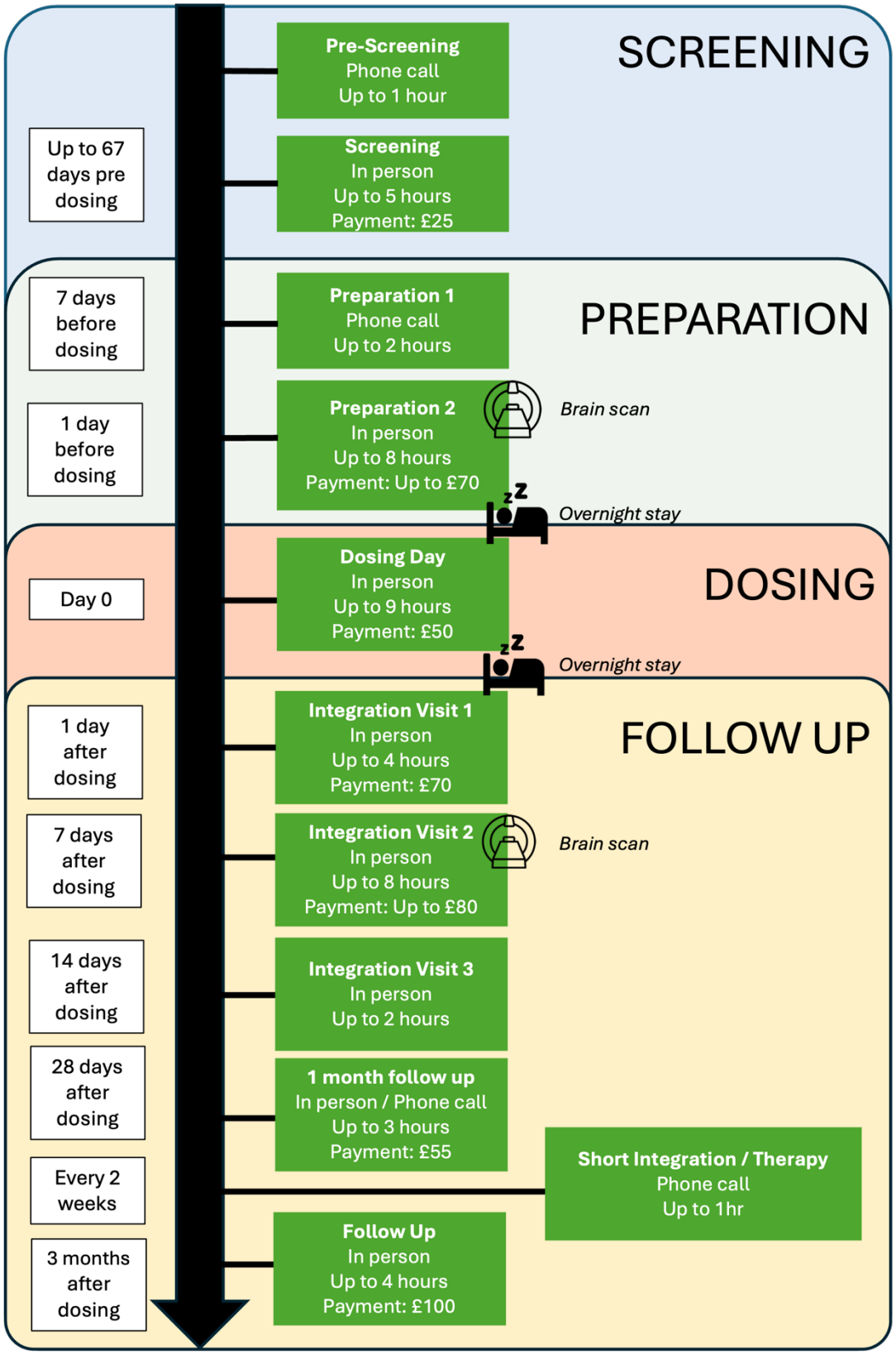
If you have any further questions or would like more information about the study, please contact the study team using the following details

Email: psilopioid@imperial.ac.uk
Telephone: 07442791857

Thank you for reading this sheet, and your interest in taking part in our study.

Figure 2. Study overview diagram

The diagram below outlines the study visits, durations and the amount you could be paid if you complete the visit.



Further Information: MRI Scanning

What is an MRI scan?



An MRI (Magnetic Resonance Imaging) scan is a routine procedure in medical practice and has not been found to be harmful. It involves lying in a "tunnel" and staying still for the duration of the scan. During two of the study visits you will have an MRI brain scan at the imaging facility (approx. 5 minute walk away from the clinic). A researcher will accompany you and stay with you during the scan. The scan will take about 90mins, and we will ask you to complete some tasks while you are in the scanner. The MRI scanner will take structural pictures of your brain, and images of your brain while you are performing certain tasks. These tasks are essentially short games.

The MRI scanner uses powerful magnets. This means that it is not safe for everyone. You must not have a scan if you have a heart pacemaker, metal injuries to the eye, implant, shrapnel, a shotgun injury or metallic objects (e.g. pins, clips) inside your body near to your head. You will be asked to change into a hospital scrubs and remove any metal objects from your body such as keys or coins.

The MRI uses radiofrequency waves to do the scan. This can cause your head and body to warm up slightly. Most people do not notice this. We keep the scanner room cool so you will be comfortable and provide blankets for warmth if needed. If you feel uncomfortable during your scan, you can tell us immediately and we will stop the scan. The scanner may damage credit cards and some watches so we will provide you with a secure place to leave valuables. The MRI operator will check possible risks with you before you go into the scanner.

The MRI scanner is noisy. This is normal and the scanner cannot hurt you in any way. You will be provided with ear plugs and headphones to minimise any discomfort. There is a microphone inside the MRI scanner so that you can talk to us at any time. It is common to feel slightly anxious when you are first placed in the MRI scanner, but this normally passes. You will be free to leave the MRI scanner at any time should you wish to stop the scan. You may not be able to take part in this study if you are claustrophobic (nervous in small spaces). Please make sure you discuss this with the study team before deciding if you would like to take part.

Are there any risks from having an MRI scan?

MRI scans involve minimal risk. There are no serious side effects of being in an MRI scanner - millions of scans are carried out across the world each year. Some people have reported minor side effects. These have included feeling dizzy, feeling claustrophobic or nauseous. These effects disappear after leaving the scanner.

What happens if you find something unusual on my MRI scan?

Sometimes we find unexpected things on your MRI scan. If this happens, we will tell you. After looking at your scan, if the MRI operator or study team thinks that it is appropriate, we can forward your scan to a radiologist (a doctor who specialises in scans) or your GP for further investigation or

referral if this is appropriate. Early detection of problems may have the benefit of earlier treatment for any abnormality. In a small number of cases, it can have implications, so it may affect future employment or insurance.

Further Information: Psilocybin

There is great variability in the effects people can experience, e.g. in our first depression study, 3 out of 20 patients did not experience any subjective effects from a high dose of psilocybin (25mg), and we could not always be sure why this was the case. Some people have reported experiencing psychological insights on psilocybin that provide a useful new perspective on the potential causes of their illness. Research suggests that psilocybin may be effective as an aid to psychotherapy or 'talking' therapies

Psilocybin may increase how suggestible people are. This can increase both the inherent power difference between guides and participants, and the meaning given to their psychedelic experience. Establishing and nurturing a trusting relationship with your guides is an important part of the treatment process, to create a safe space for you to discuss with them whatever comes up, without fear of judgement. The guides themselves will also be noticing what comes up for them during their process of guiding for you, and they will be exploring it in supervision with other members of the therapy team to consider how best to support you. Your guides will be there to support you in making sense of your experience.

Are there any risks associated with taking psilocybin?
There are risks when putting any drug in your body. However, psilocybin is a relatively safe compound, and it has limited risks when used in a clinical trial. Psilocybin is not considered to be addictive. In the 1950s and 1960s, thousands of patients were treated with it. Hundreds of people have taken psilocybin in modern scientific studies – with over 250 people having taken it as part of studies run by our group. This means we have some of the best experience and data to help us to understand the effects and side effects of using psilocybin.

On dosing day (the day you take psilocybin) you will be fully supported by a therapy team. This includes a psychotherapist and/or psychiatrist as well as other members of the research team. They are all able to help with any problems that may come up. The research clinic is in a hospital. This means we have access to further help and support if needed. Our priority is to make sure you are always safe and ensure you get the best possible care.

The most common physical undesirable effects of psilocybin use include mildly increased heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes, dizziness/light-headedness, weakness, sometimes nausea (feeling sick), and rarely vomiting. This will be checked by a doctor before you leave us for the day.

Anxiety that can be associated with psilocybin is normally short lived and helped by support and guidance from the therapy guides. We know that developing a trusting relationship with your guides and research team is important in decreasing the chance of you developing anxiety or paranoia. It is also important that you feel content in your surroundings and you will be able to visit the research facility for your screening visit so you can can become more familiar with it. We will try and make you feel as comfortable and relaxed as possible for your psilocybin experience. If you do feel anxious, we will always be there for you, and you can always talk it through with us.

Psilocybin can in some people result in longer-lasting changes of their 'worldview', or their understanding of reality and their place in it. While this can be positive and meaningful, for some this can be challenging, confusing and possibly frightening. If this were to happen, you would be supported by the guides in working through these difficult feelings or experiences, to make sense of them and potentially learn from them in a positive way that benefits your mental wellbeing.

You should not feel bad if you do feel anxious or afraid. It is better not to fight the anxiety or the bad feelings. We will talk to you about trying to accept it, let it go and allow the feelings to unfold naturally. There is some evidence that "facing up" to your fears and anxieties when you have taken psilocybin can have positive future effects.

In our previous study where we used psilocybin in patients with depression, the main side effects reported by patients who took two doses of psilocybin (10mg and then 25mg of psilocybin one week later) were anxiety surrounding the experience of taking psilocybin itself (over 50% of people) and headaches that lasted up to 1-2 days after the experience (40% of people). 25% of people reported some nausea. Further details on side effects are provided below.

Summary of the side-effects of psilocybin:

Common (over 50%)

1. Nausea
2. Visual hallucinations, feeling of unreality and changed sense of time
3. Increased short term anxiety after taking the drug, which usually reduces over several hours
4. Increased heart rate and/or blood pressure

Less common (about 10-40%):

1. Dizziness, blurred vision, drowsiness and sleepiness
2. Headache
3. A 'bad trip' i.e. negative thoughts and mood during the short-term drug effects. In other psilocybin studies, good preparation, support during the experience and integration helped mitigate negative impacts of this. With support, challenging content can be worked through and contribute to a psychological 'breakthrough' on the part of the patient. Recent evidence indicates that challenging psychological experiences in supportive environments can produce therapeutic benefits, improving psychological well-being in the long-term.
4. Temporary suspiciousness, which is usually short-lived.

Rare:

1. Estimated <1% of psychedelic users overall: Flashbacks or persisting visual changes lasting beyond the acute drug effects, which are considered distressing. It may be more common to experience some visual changes that last after the acute drug effects, such as intensified colours and lingering visual images, but very rarely are these considered distressing, and there are no known cases reported in participants of previous psychedelic clinical trials.
2. Worsening of your mental state after the drug experience. This is rare, but there is growing research as to what can support people to feel better again if there are enduring difficulties

after a psychedelic experience. If you would like to know more about the published scientific literature on psilocybin, then please ask a member of the research team).

Data Protection

HOW WILL WE USE INFORMATION ABOUT YOU?
Imperial College London is the sponsor for 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 appropriately. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.
- 3 years after the study has completed in relation to recorded material.

Perceptive archive data in relation to the neuroimaging (MRI scans) for 25 years after the study has finished.

The study is expected to finish in June 2027.

For more information / confirmation regarding the end date please contact the study team, see **'WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED'** for contact information.

We will need to use information from you and your medical records for this research project. This information will include your initials / NHS number/ name and contact details.

People within the College and study team (see section sharing your information with others) will use this information to do the research or to check your records to make sure that research is being done properly and the information held (such as contact details) is accurate.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Some of your information will be shared in pseudonymised (this means that your name has been replaced with an identifier) form with external collaborators who may be in other countries. They must follow our rules about keeping these data safe. 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.

As a university we use personally-identifiable information to conduct research to improve health care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

• Imperial College London - "performance of a task carried out in the public interest"; Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

Where special category personal information is involved (most commonly health data, biometric

data and genetic data, racial and ethnic data etc.), Imperial College London relies on "scientific or historical research purposes or statistical purposes".

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the United Kingdom (for example, to a research partner, either within the European Economic Area (EEA) or to other countries outside the EEA. Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a UK adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient research partner that incorporates UK approved standard contractual clauses or utilise another transfer mechanism that safeguards how your personal data is processed.

SHARING YOUR INFORMATION WITH OTHERS

We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

- Other Imperial College London employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.), Imperial College London agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.
- The following Research Collaborators / Partners in the study
  - Third Party Company – explain what data and why it will be shared
    Perceptive (previously Invicro LLC) – this company will be responsible for the brain scanning part of this study and as a result will require some of your personal details, including your name, address, date of birth and medical history.
  - Filament Health – this company supplies the drug which will be used in the study. At the end of the study, we will provide a full report on the outcome of the study, looking at the drug's effectiveness and a review of the study. All information will be provided in a pseudonymised form, so that they will not be able to identify individual subjects from the data that we share.
  - No identity of study subjects will be disclosed without prior written / expressed consent, unless required to by law, NHS Confidentiality Code of Practice (November 2003), unless in relation to a claim or proceeding brought by the Study Subject in connection with the Study

POTENTIAL USE OF STUDY DATA FOR FUTURE RESEARCH

When you agree to take part in a research study, the information collected either as part of the study or in preparation for the study (such as contact details) may, if you consent, be provided to researchers running other research studies at Imperial College London and in other organisations which may be universities or organisations involved in research in this country or abroad. Your information will only be used to conduct research in accordance with legislation including the GDPR and the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you, used against you or used to make decisions about you.

COMMERCIALISATION

Data from the study may also be provided to organisations not named in this participant information sheet, e.g. commercial organisations or non-commercial organisations for the purposes of undertaking the current study, future research studies or commercial purposes such as development by a company of a new test, product or treatment. We will ensure your name and any identifying details will NOT be given to these third parties, instead you will be identified by a unique study number with any sample / data analysis having the potential to generate 'personal data'.

Aggregated (combined) or anonymised data sets (all identifying information is removed) may also be created using your data (in a way which does not identify you individually) and be used for such research or commercial purposes where the purposes align to relevant legislation (including the GDPR) and wider aims of the study. Your data will not be shared with a commercial organisation for marketing purposes.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

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 because some research using your data may have already taken place and this cannot be undone.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you if this could affect the wider study or the accuracy of data collected.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from the study team.
- by asking one of the research team
- by sending an email to psilopioid@imperial.ac.uk, or
- by ringing us on 07442791857.
- https://www.imperial.ac.uk/psychedelic-research-centre/

COMPLAINT

If you wish to raise a complaint about how we have handled your personal data, please contact the research team first by sending an email to psilopioid@imperial.ac.uk, or by ringing us on 07442791857.

Following our response, if you are not satisfied please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk / imperial.dpo@nhs.net via telephone on 020 7594 3502 / 020331304001 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ./8th Floor of Salton House, ICT Division, St Mary's Hospital, Praed Street, London, W2 1NY

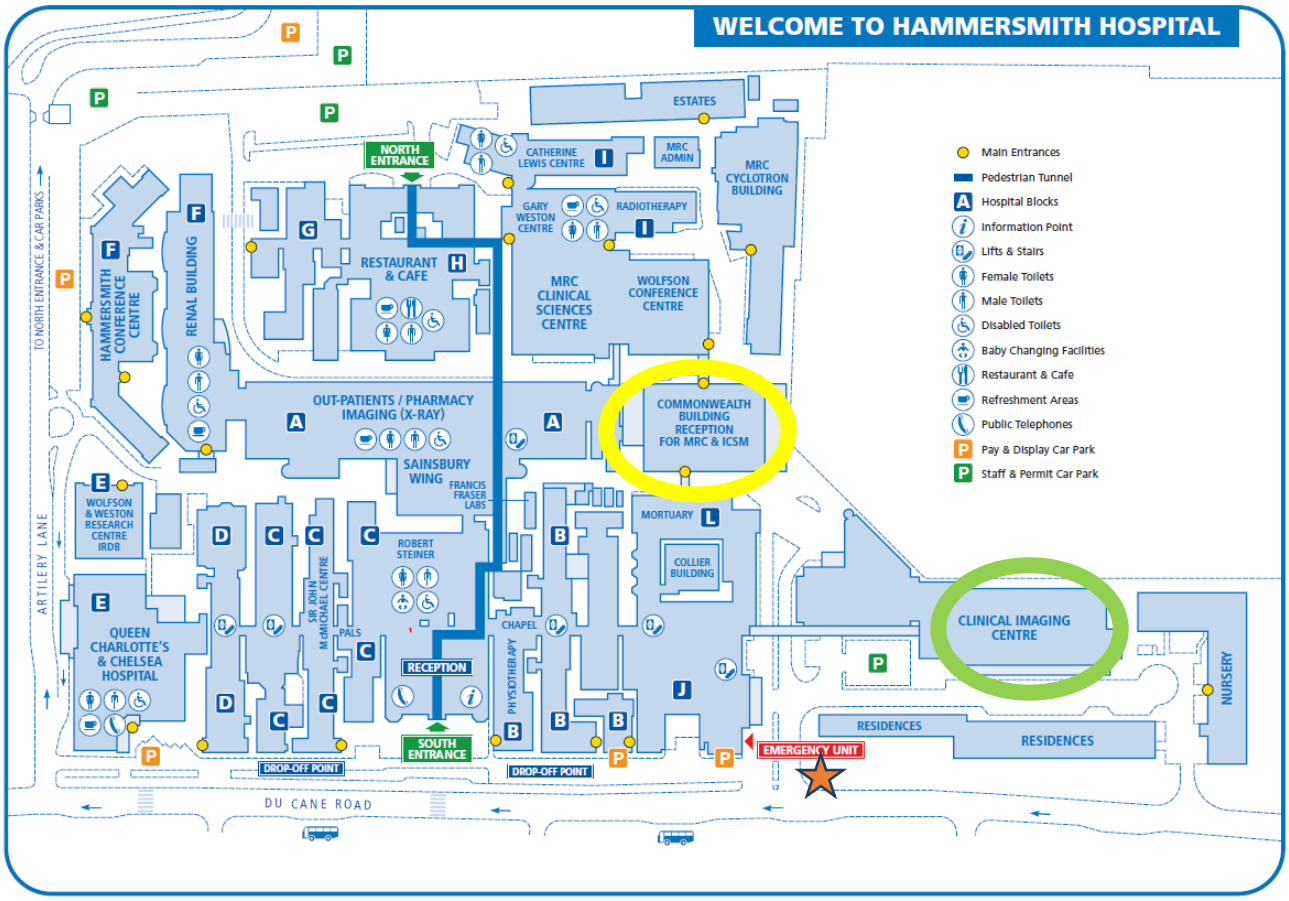
If you remain unsatisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO)- via www.ico.org.uk. Please note the ICO does recommend that you seek to resolve matters with the data controller (us) first before involving them.

Appendix: How to find us

How to find us

Nearest underground stations White City (Central Line), East Acton (Central Line) or Wood Lane (Hammersmith and City, Circle Line). The Hammersmith campus is well connected with buses including the 7, 70, 72, 272 and 283. Please check Transport for London for up-to-date travel information.

From White City underground station, it takes about 15 minutes to walk to us. Turn right on exiting the station; this road is called 'Wood Lane'. Walk along Wood Lane, past the BBC buildings, under the Westway flyover and turn left at Du Cane Rd. Walk past the playing fields and turn right at Costcutter. The CRF is a large silver and black building with some yellow framing. The entrance to the CRF is a revolving door with a large yellow frame around it. The Burlington Danes Building (a large silver building with a glass front) contains the scan centre called 'Perceptive'.



See the **CRF** circled in **yellow** – where screening will take place. On Du Cane Rd, turn right at Costcutter shown as an orange star on the map. The CRF is a large black, yellow and silver building ahead and to the left (see the photo below, the CRF is on the ground floor of this building).

The **Burlington Danes** building (which contains the scanning centre 'Perceptive') is to the right of the CRF (we'll show you this when you come in for your screening), connected by a bridge or walkway (see photo below).



The CRF is on the ground floor of this building. Go through the yellow-framed revolving door. This is where you will come for your first visit.



This is the Burlington Danes Building. The entrance is the large glass-fronted area.

Screening & Study Location
NIHR/Wellcome Trust Imperial CRF,
Hammersmith Hospital
160 Du Cane Rd,
London,
W12 0NN
020 3313 8070

Scanning Location
Perceptive
Burlington Danes Building,
160 Du Cane Rd,
London
W12 0NN
0208 008 6218.