Professor Valerie Voon
Department of Psychiatry
Addenbrookes Hospital,
Level E4, Box 189
Cambridge, CB2 0QQ
Tel: 01223 761327
vv247@cam.ac.uk

PARTICIPANT INFORMATION SHEET

Project Title: Deep brain stimulation for disorders of addiction: mechanisms and a pilot blinded randomized cross-over placebo controlled trial
IRAS ID: 316169

You are being invited to take part in a research trial. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the trial if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this trial and what will happen to you if you take part.
Section 2 gives you more detailed information about the conduct of the trial.

PART 1

1. ***What is the purpose of this study?***

We are running this study to ask if a brain pacemaker known as deep brain stimulation (DBS) works for addiction. This study will compare treatment on and off DBS in a randomized control study in 12 patients to assess its effects on alcohol and opioid addiction.

This study involves a brain pacemaker, DBS, a surgical procedure in which small electrodes are placed into specific brain areas that will be then stimulated to control symptoms of severe addiction that has not responded to other treatments.

DBS works well for severe Parkinson's disease and for obsessive compulsive disorder which have not responded to medications. DBS has been approved for Parkinson's disease since 2002 and for obsessive compulsive disorder since 2009. Over 250,000 people world-wide have DBS electrodes for treatment of their disorder showing that it is safe in the long term. Multiple studies using DBS have been run in the world for obsessive compulsive disorder and depression. Small open label studies for DBS for addiction show that it works for heroin and alcohol addiction. A recent German study published a randomized controlled trial in 12 alcohol use disorder patients with several ongoing studies in the world using DBS for addiction including in the United States, Canada, China and other countries in Europe. A figure of the device is shown in Figure 1.

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In this study we will also record brain activity from deep brain structures using DBS. We ask how the brain uses information when seeing alcohol or opioid images or emotional images that might be involved in symptoms of craving and addiction. We then ask how we can make stimulation better by using this brain activity to start stimulation or teach you to train yourself to control your own brain waves to assess the effect on craving. We will do a magnetic resonance imaging (MRI) brain scan to assess how your brain might process this information. We will also ask you to complete questionnaires related to the addiction, depression, anxiety, function and quality of life.

We will adjust DBS stimulation to treat symptoms of craving or urges over a 6 month period. The DBS stimulation should decrease the amount of alcohol or opioids you use. After this time we will conduct a randomized controlled trial study over a 4 month period to assess the effect of DBS on addiction. This trial involves either turning on the stimulation for two regions, or one of the regions for a month each time or turning off the stimulation for a month. You and the clinician assessing your symptoms will not know whether the stimulation is on or off. The trial is a total of 10 months.

2. What is the device being tested?

DBS is a neurosurgical procedure that involves a small electrode placed into specific brain areas and a pacemaker that is implanted under the chest fat pad similar to a cardiac pacemaker. The device and how it is placed in the brain and chest wall is shown in Figure 1.

Figure 1. Deep brain stimulation

The figure shows an image of the implanted deep brain stimulation electrode and pacemaker (left). The pacemaker is similar to a cardiac pacemaker. An image of the DBS electrodes which are the size of a spaghetti strand (middle) and the pacemaker (right) similar to a cardiac pacemaker is shown.

3. Why have I been invited?

You have been invited to participate in this trial because you have alcohol use disorder or opioid use disorder and we believe deep brain stimulation may be a suitable treatment.

We plan to include 6 participants with alcohol use disorder and 6 participants with opioid use disorder from hospitals across the UK.

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4. Do I have to take part?

Participating in this trial is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the trial at any time without giving a reason. If you chose not to participate or to leave the trial, your future medical treatment and normal standard of care will not be affected in any way.

5. What will happen to me if I decide to take part?

If you agree to participate in the trial, you will sign the Informed Consent Form at the end of this document and be given a copy of this to take away and refer to later.

The study total duration of 10 months. An example of the Study Flow and Timeline is shown in Figure 2.

i. Screening assessment:
Duration: 4-6 hours

This study will involve screening at the Herchel Smith Building, University of Cambridge or at Kings College Hospital to assess your appropriateness for the study. All follow up will also take place at these places. This screening may take several hours. You will also be assessed by a group independent of this study to ensure you have consented for the study.

ii. Baseline tests: outpatient

If you agree to take part in the study, you will undergo a 60 minute magnetic resonance imaging (MRI) brain scan which will be used to plan the surgery. The MRI will take place at the Wolfson Brain Imaging Centre at Addenbrookes Hospital in Cambridge.

MRI takes high-resolution pictures of your brain to measure certain structures in your brain. We can also use this same equipment to collect images of the parts of your brain that are active during certain tasks or when responding to different images. It does this by measuring the changes in the magnetic properties of your brain as the blood flow changes. The scanner is entirely safe but can be quite confined and noisy. In order to protect you from the noise we will provide earplugs.

Before surgery, you will be tested on computer-based tests and questionnaires. You will be seen by a neurosurgeon, an anaesthetist and a psychiatrist before surgery. Blood work will be done before surgery to ensure that you are healthy which will be collected and analyzed by the laboratory at Addenbrookes Hospital.

There is a chance that you might sign up for the study but you may not be able to take part in the study.

iii. Inpatient hospitalization: surgery
Duration in hospital: 7-10 days

You will stay on the same medications throughout the hospitalization and study including opioid substitutes such as methadone and buprenorphine.

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During the first surgery, you will be under general anaesthesia during which the DBS is implanted. The DBS device is a small electrode inserted into your brain through a small hole in your skull and a pacemaker will be placed under the chest wall which allows control of the stimulation. The hair around the two burr holes will be shaved for the surgery. The DBS is connected to the pacemaker through a connector under the skin. The device, pacemaker and how the device is implanted is shown in Figure 1.

During the inpatient stay we will then record brain wave activity while you are playing computer games or seeing emotional images or alcohol or opioid images. We will then stimulate your brain based on your brain activity and also train you to control your own brain activity. This testing will take place over a 4 day period at Addenbrookes Hospital at the University of Cambridge or a 6 day period at Kings College Hospital. On the 5^{th} or 7^{th} postoperative day, a second surgery will connect the DBS and pacemaker.
During this 7 to 10 day stay in hospital, you will not have access to alcohol or opioids. If you experience withdrawal symptoms you will be seen by our addiction liaison psychiatrists who are part of the study team and deal with inpatients in hospital for other medical reasons who experience withdrawal. We might consider using medications to manage your withdrawal symptoms or to turn on the stimulator to treat your withdrawal symptoms.

The stimulator will be turned on at the first post-operative month. The DBS team including the neurosurgeon and a psychiatrist will see you during the hospital stay and just before discharge.

iv. <u>Outpatient assessment</u>
<u>Duration: 6 months</u>

The DBS team and psychiatrist will see you in the first week after discharge, then every 2 weeks for the first 2 months or more or less frequently as needed to adjust the stimulator. After that we will see you once per month as needed to adjust the stimulator. The assessments to adjust the stimulator will take 1-2 hours.

During week 2, months 1, 3 and 6, we will measure brain activity and other physiological activity such as eye movement tracking, heart rate, skin conductance and electrodes placed on your scalp to record electrical activity while you play computerized games. The assessments during week 2, months 1, 3 and 6 will take between 2 to 4 hours per visit.

We will ask you to monitor the amount of alcohol or opioids you use along with symptoms of craving or withdrawal using a specially designed App. The App can be downloaded to your mobile phone and all information collected will be kept confidential. No personal information will be collected on the App. The information on the App will include the amount of alcohol or opioids or other substances used, and ratings of craving, mood, anxiety, sleep and stress. The App is designed and owned by the research team (University of Cambridge CAM:IDE) and only used for research purposes with data stored on a secure platform (REDCap). Only the study researchers will have access to the anonymized information on the App.

We will also test for alcohol and substance use during the visits which will involve a breathalyser, urine and hair sample test. The research team will collect the breathalyzer and urine tests for drug and alcohol use and analyze them immediately. The hair sample will be sent to an external lab for testing and will not be identifiable. The urine and hair samples will be discarded following analysis.

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Additional recordings of physiology during cognitive tasks of recordings from DBS electrodes, surface electroencephalography (EEG), heart rate variability, pupillometry and skin conductance. For the recordings from the DBS electrodes, we will record brain activity while you play computer games. You should not feel any side effects from the recordings but might find that paying attention to the computer games might be associated with fatigue. We might test stimulating the DBS and will use either the same clinical parameters used to treat your addiction or different parameters. For the EEG we will use dry electrodes on the surface of the scalp; we will ensure the cap is comfortable and EEG should not be associated with side effects. Heart rate variability will be recorded through an electrode on the chest wall skin surface; this can be rarely associated with local irritation from the sticky gel on the electrode. For pupillometry, you will sit in front of a computer screen with an eye movement tracker that will track the size of your pupil and eye movements and should not be associated with side effects. The skin conductance recordings are conducted through a band around a finger and should not be associated with side effects.

We will also ask you to wear a watch in the daytime and nighttime to monitor your heart rate and skin conductance (EmpaticaPlus) for the first 6 months after surgery. The anonymized data is stored on the secure and password protected Empatica Cloud.

For the first 3 months after surgery, we will provide you with a number to be able to contact us 24 hours a day in the case any major issues arise.

v. Test: outpatient trial
Duration: 4 months

After this 6 month time, you will take part in a randomized controlled trial study over a 4 month period to assess the effect of DBS on addiction. This is a cross-over trial which means that each person will be given a different treatment in turn. This trial involves either turning on the stimulation for two regions for one month, or turning on stimulation for one of the regions for a month each time or turning off the stimulation for a month. You and the clinician assessing your symptoms will not know whether the stimulation is on or off. You will be assessed at the beginning of the trial, and at the end of each month for a total of 4 months.

We will test for alcohol and substance use during the visits which will involve a breathalyser, urine and hair sample test. The research team will collect the breathalyzer and urine tests for drug and alcohol use and analyze them immediately. The hair sample will be sent to an external lab for testing. The urine and hair samples will be discarded following analysis.

Any medications you are on prior to the study will remain the same throughout the course of the 10 month study unless it is causing side effects or if it might not be further needed if stimulation works for your addiction symptoms.

Figure 2. Study flow and timeline

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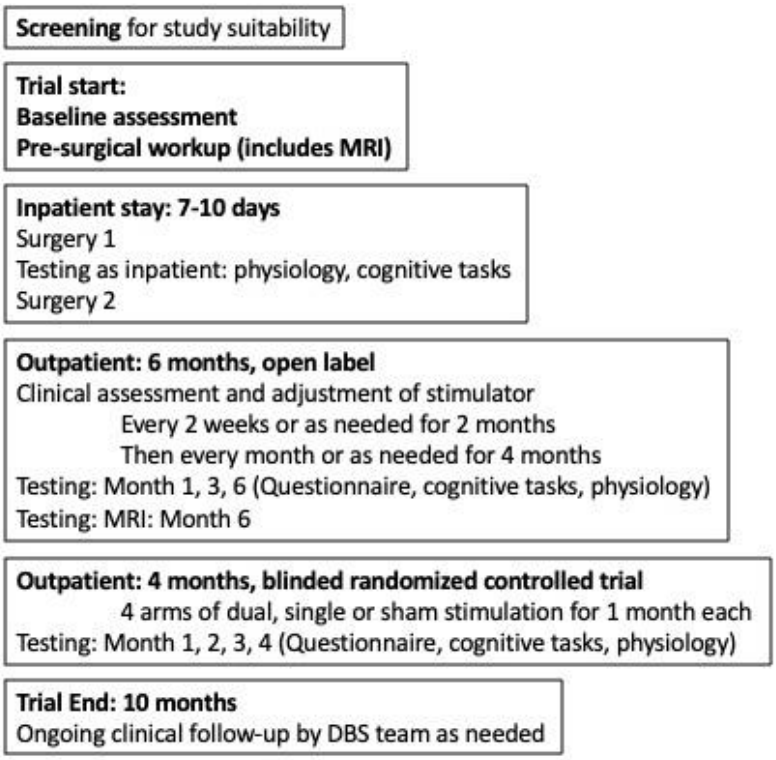

6. What will we do if we notice something abnormal?

Although unlikely, it is possible that whilst performing normal medical checks or the brain scan we may identify a clinically significant illness or abnormality that you didn't realise you had. If this occurs the doctor will discuss the illness or abnormality with you immediately.

7. What are the possible risks in taking part?

The main neurosurgical risk is that of infection, bleeding or a reaction to the anaesthetic. You will be seen by a neurosurgeon and anaesthetist prior to the surgery to ensure you are not at increased risk for bleeding or anaesthetic complications. The likelihood of a serious risk requiring hospitalization is uncommon and has been assessed systematically at Kings College Hospital and reported at 0.1% (the median in the United Kingdom is 1%). The neurosurgical team is very experienced with DBS (more than 40 per year and 500 DBS procedures total have been conducted at Kings College Hospital) including much more complex neurosurgical procedures. In the event the DBS is not effective, the DBS device can be removed with the risk of any complications associated with removal at less than 1%. Occasionally patients can have mild discomfort around the battery site or the connection cables.

The DBS stimulation may be associated with hypomania (elated mood, decreased sleep, fast speech, increased rewarding behaviours) reported between 4 to 30% in patients. If this occurs, it is early between the first to third month after surgery. Extensive education for you, your care giver and your GP will be provided on what to look out for and we will also contact you and see you regularly after surgery and ask about these behaviours specifically. We ask that you report any of these symptoms to us as soon as possible. The hypomania can be

managed by decreasing or changing the stimulation or decreasing medication doses that might be contributing. An improvement in mood is expected as part of the treatment.

The DBS stimulation itself will not cause addiction relapse and is safe to use if you continue to actively use alcohol or opioids. If you have a relapse or slip, we will adjust the stimulator settings to target the addiction symptoms. Relapse can also occur as part of your illness and you will also be seen by your regular addiction therapy team along with the DBS team.

If you experience any distress from filling out questionnaires, you may choose to take a break or fill out at a different time. If you experience an addiction relapse or any symptoms of hypomania, the DBS team is available on call 24 hours 7 days per week for the first 3 months after surgery. We will arrange to see you in person as soon as possible for outpatient assessment and to adjust stimulation. If the symptoms are urgent, you can also attend the A&E department. The DBS team and psychiatrists work closely with the A&E department at Addenbrookes Hospital in Cambridge and at Kings College Hospital in London. With your permission we will also liaise with the A&E department at your local hospital if needed.

For the MRI scan, because the scanner is built around a large magnet, you will have to remove all metal from your body, including all jewellery. MRI scanning is a routine procedure in medical practice, and has not been found to be harmful in anyway. If you experience any negative effects from the study, a psychiatrist will be available for you to talk to.

8. What are the possible benefits of taking part?

The DBS stimulation may decrease your addiction behaviours and craving symptoms. Addiction is associated with high mortality and comorbid physical and mental illnesses, interferes with work, family, relationships and associated with poor quality of life. The secondary benefits of improving addiction symptom control will include an improvement on these outcomes.

9. What will happen after the study is over?

Your involvement in the study is over after the randomized controlled trial is completed. The total period is 10 months. The DBS team including the psychiatrist will continue to monitor and see you for stimulation adjustments as needed for as long as you have the DBS device in place. On average the battery life lasts 3 years. If the DBS is not effective, the device can be turned off. The DBS device remains in your body. You may also choose to remove the device. This can be discussed with the DBS team and may include removal of just the pacemaker and connector. The DBS device can also be removed and may be associated with neurosurgical risks of bleeding of less than 1%.

If the DBS is effective, a trial of turning off DBS can be considered if stable long term abstinence is achieved on discussion with the DBS team. If DBS stimulation is required you will be followed by the DBS team and a psychiatrist. If the battery requires replacement this will be discussed with the DBS team and the surgery and the battery replacement should be covered by the National Health Service.

10. Expenses and payments

We will reimburse you for any travel and accommodation expenses along with £500 in cash on completion of the study to compensate you for your time.

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11. Will my taking part in the study be kept confidential?

All the information about your participation in this study including the results of the drug screen and breathalyser will be kept confidential. If the drug or alcohol screening is positive, we will inform you but will keep all results confidential. We will not contact any friends or family unless you advise us to do so. The details are included in Part 2. If we access any medical notes, this will only be accessed by your health care team involved in the study. Your GP will be informed that you are involved in the study. We encourage you to inform and have your addictions therapy team be aware of your involvement in the study.

PART 2

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

You are free to come off this trial at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, no further tests will be performed on you and no further research samples will be collected. Any data already collected or results from tests already performed on you or your samples will continue to be used in the trial analysis.

The trial doctor may also choose to withdraw you from the trial if they feel it is in your best interests or if you have been unable to comply with the requirements of the trial. Reasons for trial withdrawal could include:

- You have experienced a serious side effect
- You are unable to complete the visits, medication or trial documentation as required
- You become pregnant or plan to become pregnant
- The trial doctor feels you no longer appear to benefit from the treatment.

If you withdraw from the study, we will switch off the stimulator if you request us to do so but you may also choose to keep the stimulator on. The DBS team will continue to monitor and see you for stimulation adjustments as needed for as long as you have the DBS device in place.

If you withdraw from the study, you may choose to remove the device. This can be discussed with the DBS team and may include removal of just the pacemaker and connector. The DBS device can also be removed and may be associated with neurosurgical risks of bleeding of less than 1%.

If you withdraw from the study and the DBS is effective, a trial of turning off DBS can be considered if stable long term abstinence is achieved on discussion with the DBS team. If DBS stimulation is required you will be followed by the DBS team and a psychiatrist. If the battery requires replacement this will be discussed with the DBS team and the surgery and the battery replacement should be covered by the National Health Service.

13. What if there is a problem?

Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this trial you should speak to your trial doctor who will do their best to answer your questions.

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In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this trial, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact PALS 01223 216 756 (Cambridge University Hospital) for any questions or complaints. If you remain unhappy and wish to complain formally, you can do this with the Department of Psychiatry (01223 768509). If taking part in this research project harms you, there are no special compensation arrangements, but if you are harmed by someone else's negligence, then you may have grounds for legal action and you are free to complain.

14. Will my taking part in the study be kept confidential?

Cambridge University Hospitals NHS Foundation Trust (CUHNFT) and the University of Cambridge are joint sponsors for this study based in the United Kingdom. CUHNFT and the University of Cambridge will be using information from you in order to undertake this study and will act as joint data controllers. This means that both organisations are responsible for looking after your information and using it properly. The University of Cambridge will keep identifiable information about you for 5 years after the study has finished. CUHNFT will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information using the following links:
For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: cuh.gdpr@nhs.net
For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance/, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk

We will need to inform your GP of your participation in this trial so that any medical decisions made by your GP account for any treatment you are receiving as part of this trial.

15. What will happen to my samples?

The urine samples will be tested immediately then discarded. The hair samples will be anonymized and sent to an external lab for testing then discarded. The blood work for pre-operative work up will be tested by the laboratory at Addenbrookes Hospital then discarded. The anonymized data from the App for craving and mood changes will be stored in the online secure NHS-compatible REDCap website managed by the

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University of Cambridge and removed 5 years after the study is completed. The anonymized data from heart rate and skin conductance from the watch wearable will be stored on the secure Empatica cloud and removed when downloaded by the researcher to secure password protected computers. The data will be removed 5 years after the study is completed.

16. What will happen to the results of the research study?

The results of the trial will be anonymous and you will not be able to be identified from any of the data produced. When the results of this trial are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. They will also be published on the EU Clinical Trials Register website, a central registry for all clinical trials conducted in the EU.

Anonymous datasets from the trial may also be made available to other researchers in line with national and international data transparency initiatives.

If you would like to obtain a copy of the published results please contact your trial doctor directly who will be able to arrange this for you.

If you choose to do so, the publication from the study will be made available to you up to 5 years after the study is completed. We will remove any contact details 5 years after the study is completed.

17. Who has funded this study?

This study is funded by a grant from the Medical Research Council.

18. Who has reviewed the study?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given favourable opinion by Yorkshire and The Humber – Sheffield Research Ethics Committee.

19. If you would like more information

Dr. David Christmas, at Cambridge, is the Associate investigator responsible for the conduct of the study in Cambridge and Dr. David Okai is the Associate investigator responsible for the conduct of the study at South London and Maudsley NHS Foundation Trust. They will be happy to answer any questions you may have and are available for details and information about the study 02078365454 david.okai@slam.nhs.uk; 01223 746058 david.christmas@cpft.nhs.uk

Professor Valerie Voon, at Cambridge, is the Chief investigator responsible for the conduct of the study. She will be happy to answer any questions you may have and are available for details and information about the study on 01223 768015 during working hours or email: vv247@cam.ac.uk.

If you decide to take part in the study you will be asked to sign a consent form. Before you sign the consent form, you should ask questions about anything that you do not understand. If you do not feel happy about signing this you do not have to take part in the study. If you want to pull out of the study once it has started you are also free to do so. You do not have to give a reason, although it will be helpful for us to know what the reason is. A copy of this information sheet and consent form will be given to you to keep.

For your own well being please be honest about the information you tell the investigator.

Thank you for taking the time to read and consider this information sheet.

HQ Elizabeth House, Fulbourn Hospital, Cambridge CB21 5EF.
T 01223 726789 **F** 01480 398501 **www.cpft.nhs.uk**