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Randomised controlled trial of deep brain stimulation for chronic post-stroke pain

PATIENT INFORMATION SHEET

V 1

Date: 17/09/2019

REC REFERENCE:

We would like to invite you to take part in our research study. Before you decide it is important that you understand why the research is being done and what it would involve. Please take time to consider the following information carefully. Talk to others about the study if you wish such as your GP. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Pain is common after stroke, affecting up to 1 in 5 patients. This can be difficult to treat with medicines, leaving some sufferers disabled by pain. Deep brain stimulation surgery is a treatment that has been used in the treatment of pain. It involves placing electrical wires into a part(s) of the brain and stimulating that area with electricity from an electrical device placed under the skin of the chest. Although some patients have reported improvement in pain after this type of surgery, the quality of the evidence that this form of surgery works reliably for pain is not good enough to justify its routine use in the NHS. We would like to study if this form of surgery is useful in post-stroke pain using a randomised controlled trial design. The purpose of this would be to provide high quality evidence for the use of this form of surgery in post-stroke pain. Equally, if this surgery is not useful, this will provide evidence that this form of surgery should be excluded as a treatment.

Why have I been invited?

You are an adult who has suffered a stroke in the past, and have pain caused by the stroke. This may have been described as neuropathic pain by your physicians. You have suffered pain for at least 2 years and your pain has not responded to medicines, specifically opiates (such as codeine), antiepileptics such as gabapentin and antidepressants such as amitriptyline in combination. Your physicians may have described this as medically refractory pain, meaning it has not responded to treatment. You have indicated you would like to know more about a trial of surgery for your pain, so you have contacted us to ask for a clinic appointment.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. There is no obligation to take part as part of your normal treatment from the team treating you for pain. If you do not take part it will have no effect on your usual treatment.

Before you take part in the study, we will describe the study and go through this information sheet in person. If you agree to take part, we will then ask you to sign a consent form. **You are free to withdraw at any time, without giving any reason and with no effect on your usual care**.

What will happen to me if I take part?

Visit 1 (Preoperative assessment)

We invite you to meet the study team before any study procedures are planned. You meet the surgeon who can talk in detail about the surgery, a nurse specialist who is your main point of contact during the trial who you can contact at any time in working hours, and the assessor. The assessor monitors your response to treatment mainly by filling in questionnaires based on your answers. The assessor is not involved in your clinical care, so we ask you not to reveal any information to the assessor about your surgery or treatment, simply to answer the questions they ask you directly.

If you agree after meeting the team, you are asked to complete a consent form for the research. At this stage we access your medical letter from your doctor/GP once you have given consent for this. You undergo tests, namely neuropsychology, MRI and the assessor's questionnaires. These research assessments are an intimate part of the study, since we do not know for certain the effect of the surgery.

If you are suitable to continue, your surgery is scheduled. Details of circumstances preventing you from taking part in the study are written in the next section. You are admitted to hospital for surgery. You meet the surgeon again before the operation who asks you to complete a NHS consent form, having talked to you about the risks and potential benefits of the surgery. The surgery is called deep brain stimulation surgery, which involves placing wires in your brain attached to a rechargeable pacemaker in your chest, all under the skin. This delivers electrical stimulation to parts of your brain with the goal of treating your pain symptoms.

Visit 2 (surgery)

The first stage of the surgery is performed with you awake under local anaesthetic, because the surgeon needs to assess your response to treatment directly during the operation. You are transferred to the theatre anaesthetic room from the ward and the surgeon is present with you and often an assistant. A metal ring is fixed to your head. This involves putting an injection of local anaesthetic in your scalp and adjusting the pins to securely attach the metal ring to your head. Local anaesthetic numbs the local area of the injection, it does not make you fall asleep. Next a fiducial frame (a frame made of carbon rods) is placed on the metal ring, and you are transferred to neuroradiology for a CT head scan on a trolley. Theatre assistants help you to transfer onto the CT scanner and your head with metal ring and fiducial frame are taped to the CT scanner patient bed to avoid movement of your head. The scanner patient bed moves you into the scanner apparatus which is a wide shallow doughnut shape. The scan takes 3-5mins, then you are transferred back to the theatre trolley. This CT scan is essential to the operation, as part of the process to insert the electrical wire into the correct part of your brain.

After the CT scan you are transferred to the theatre proper, whilst the surgeon leaves to plan your operation using the CT scan in the neurosurgical offices. Present are the theatre staff and the anaesthetic staff. Occasionally medical students are present, but you are specifically asked permission for this. The surgeon rejoins you in theatre once the surgical plan has been made. You are prepared for surgery by fixing the metal ring (and thereby your head) to the operating table adjusted to be comfortable to you, sterilising your scalp with alcoholic solution and putting surgical drapes around the sterilised area. There may be a requirement to shave a small amount of hair at the site where the wires will be inserted but we do not require very much to be removed. The surgeon

prepares for surgery by washing, putting on a sterile gown and sterile gloves. Once ready, the surgeon configures the apparatus (stereotactic frame) used to insert the wires that will be inserted into your brain and attaches this to the metal frame. The surgeon puts more local anaethetic into your scalp at the place where a cut in your scalp is required. The local anaesthetic sometimes hurts for a minute or so before having a numbing effect, it does not make you fall asleep.

The surgeon checks the area has gone numb and makes an incision (surgical cut) in your scalp. Next two small holes are made in your skull with a hand operated twist drill to allow the wires to be passed to the targets in your brain. You may hear noises associated with drilling, but this will not hurt, since the bone of the skull has no sensation. You may notice when this goes through the lining of your brain (dura mater) but this sensation is short. The stereotactic frame is used to judge exactly where these holes should be made. Next the electrical wires are passed to the target parts of your brain, the sensory thalamus and periaqueductal grey matter, which are important regions deep in the core of the brain involved in relaying and controlling information including pain coming from and going to the body. The team including your nurse specialist delivers electricity through the wires and assesses if you are getting any sensation like warmth or numbness in the area of pain from the stimulation and any side effects. The surgeon may adjust the position of the wires at this stage until the sensations cover your affected pain area. It may be that you do not have an effect with stimulation, in which case the wires are removed and you do not continue to the next stage, your operation finishes and you do not continue in the trial. This is unlikely but a risk of the procedure.

If you do have an effect and the surgeon and nurse specialist are satisfied, the wires are buried under your scalp, and you are transferred for another CT scan. This procedure is as described above. The second CT scan is then analysed by the surgeon in the neurosurgical office to check the position of the electrical wires is as planned and that there are no complications such as bleeding.

After this stage, you are transferred back to the theatre anaesthetic room for a general anaesthesia, where you will be made to sleep. The surgeon then fits a pacemaker device (internal pulse generator) to the wires, the pacemaker device being located on your chest, under the skin, connected to the wires in your head under the skin. You recover from the anaesthetic and are transferred back to the ward. You may go home the next day, the pacemaker is off. The surgeon and nurse specialist see you after the operation and before discharge and can answer any questions you have.

After the surgery (0 to 2 months post-operatively)

After your operation your pacemaker device will be off for 2 months. This is to allow healing related to the surgery and to allow the physical effect of placing the wires to wear off before the pacemaker device is switched on. Each team member – the surgeon, nurse specialist and the assessor will assess you in the first 2 months. This is to see how the surgery has affected you.

Visit 3, 4, 5 & 6 (3 – 5 months)

After all three have assessed you, at visit 3 you are randomised to have your pacemaker switched ON or OFF. This means that by a computer based programme you are randomly allocated to have your device switched on or off by the nurse specialist. The assessor contacts you 3 times over the

next 3 months to assess how your pain is, but does not know if your pacemaker is on or off. We ask you not to volunteer information to the assessor except to answer only the questions they ask. If you do have other questions or comments, the nurse specialist is available to help with these. The assessor and nurse specialist will contact you by telephone twice, but on one occasion (visit 6) they will ask you to attend the hospital. You will see the nurse specialist on this day too.

Visit 7, 8 & 9 (6 to 8 months)

6 months post-surgery 'cross over' will occur, that means if your pacemaker was ON it is switched OFF, and vice versa, if your pacemaker was OFF it is switched ON. This is done by the nurse specialist. The assessor and nurse specialist sees you three times again, as described above – once in person with the nurse specialist, twice by telephone.

Visits 10 &11 (9- 14 months)

After you complete randomisation and cohort stages, your pacemaker is switched ON (or kept ON) and you are assessed by the assessor twice (who still does not know your stimulation details), surgeon, neuropsychologist and nurse specialist, all in person. The nurse specialist is always available to you between the scheduled appointments.

You have complete autonomy during this trial. If you do not want stimulation, we can discontinue your participation in the trial and we will remove the pacemaker and wires. Equally if you do not want us to switch OFF the pacemaker during the randomisation stage, we will accommodate that. We will ask you to come to clinic to understand your choice, as it may uncover reasons to change your treatment, change the study or discontinue the study. We will keep data about you generated in the trial up to the point you leave unless you ask us to destroy this.

Your involvement in the trial ends 14 months after your surgery. At this point you can opt to have the device removed, or continue treatment. If you choose to have the device removed you do not continue any follow up treatment with us. If you continue to have treatment with this device we (the surgeon and nurse specialist) continue to care for you thereafter, including regular clinical follow up. We propose to use rechargeable pacemakers (PINS G102R) in this study. This means like a mobile phone you will have to charge the battery periodically, once or twice a week usually for an hour. This involves placing an induction coil over the area of the pacemaker connected to a transformer. It does not involve any needles or other invasive measures. Sometimes you may experience heating with this. We propose to use these because they have a much longer life spans than non-rechargeable, therefore we can continue treatment long term, depending on your stimulation parameters ranging from 15 to 20 years

Contraindications to surgery and participation in the trial

In the process of deciding if you can take part in the trial, we may come across reasons that you are not able to have surgery safely, or identify procedures in the trial you are not happy with but are essential for the trial. The possible problems are:

- **You are unable or unwilling to stop anticoagulation (e.g. aspirin, vigabatrin) in the week before and week after surgery.** One of the main risks of surgery to the brain is bleeding, which can cause symptoms like your previous stroke or in the worst case can require emergency surgery and can cause death. Anticoagulation increases the risk of bleeding in the brain even without surgery, but especially during surgery. However

anticoagulation is an important part of prevention of further strokes in many patients who have had a stroke. Since we would need to stop your anticoagulation for 5 days before the operation and 5 days after (perhaps longer if we need to test your blood before proceeding) we want to make sure this is safe in your case. If it is not safe or the risk is not acceptable to you, we would not offer surgery and you would not join the trial.

- **Mental illness diagnosed by previous doctors, neuropsychologist or test battery.** The neuropsychologist will assess you in detail before any surgery. Severe mental illness and cognitive problems like dementia mean this form of surgery is not safe. In the event these are uncovered by the neuropsychologist, we will be unable to offer you surgery. See below for more details (**What are the possible disadvantages and risks of taking part?)**

- **Stimulation during the operation is not effective.** We test the effect of stimulation during the surgery (stage 1) to see if the procedure is likely to be effective or not. If we do not get an adequate response to test stimulation during the procedure, we remove the wire and do you do not continue in the trial.
- **Rechargeable pacemaker not suitable/acceptable to you.** We will implant rechargeable pacemaker to allow us to treat you with stimulation long term if you find stimulation useful. These require recharging usually once or twice per week. This often takes an hour and involves placing an induction coil (like a satchel strap) over the device connected to a power source. These have a long life span (although not indefinite) allowing prolonged treatment, after the end of the trial.
- **Study follow-up or procedures such as randomisation are not acceptable to you.** Our goal is to get good quality information about this form of surgery (deep brain stimulation) for chronic post stroke pain. Critical to this are to have a randomisation phase (that involves the device being off for a period of time) for all participants, and assess patients' pain repeatedly before and after surgery. Since all participants will undergo surgery, we will offer all participants a period on stimulation, and minimise the off period to 5 months of the 14 months of the trial. Unfortunately, the surgery is not available on the NHS and will only be performed as part of the study to assess its effectiveness. Therefore we cannot offer the surgery if the trial procedures are unacceptable to you.

What are the possible disadvantages and risks of taking part?

The main risks of the study are those related to surgery, those related to study investigations and those related to stimulation or the device itself.

- Surgery:

The main risk of the study is the requirement for brain surgery (neurosurgery). The procedure involved inserting metal wires in to your brain. Although it is uncommon to come to harm from this procedure nonetheless there is the risk of bleeding/scarring at the operation sites, bleeding in the brain which can result in symptoms like stroke, worsening stroke symptoms and a risk of death. Further emergency surgery and treatment may be required. There is also a risk of infection, haematoma (blood clot) or seroma (fluid) formation related to the device that often requires further surgery including device removal and antibiotic treatment. Other risks include damage to the device implanted which can result in surgery to repair the damage. The device is likely to run out of charge after implantation, usually 15 to 20 years after the surgery, but this does vary from individual to individual depending on programme requirements, i.e. if you require a programme to get pain relief requiring a higher than average charge, your device will not last as long as someone who requires a lower charge. You will require further surgery to continue stimulation beyond this.

- Stimulation

Stimulating the brain can carry some risks. These include unwanted sensations in the body such as tingling or abnormal sensations. The areas stimulated in this study are parts of the central pain network, areas of the brain that process pain signals, but stimulation may cause changes in other functions of the brain. These include but are not limited to cognitive (thinking, including psychiatric functions) and movement function. You will be monitored for these by the nurse specialist and should they occur we may have to adjust or switch stimulation off to prevent these symptoms in which case you would not continue in the trial.

- CT scans

If you take part in this study you will have CT Head exams. All of these will be extra to those that you would have if you did not take part in the trial. These procedures use ionising radiation to form images of your body. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous.

We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 50% to 50.02%

The main reasons that wold prevent you having the scans are if you do not consent to the scans, in which case we would not be able to continue with surgery, or if you have a skin-borne infectious disease transmissible to others. This would contraindicate surgery also.

- MRI scans

MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. For example, if you suffer from claustrophobia, you could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think you may be pregnant you should not take part in this study. As some of the scans are noisy, we would give you earplugs, head padding or headphones to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your ears. In preparation for your scan and for your comfort and safety we may ask you to change into pocketless and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on, but we would ask ladies to remove underwired bras. If you have a suitable sports type bra you may wear this instead. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing.

- Neuropsychology

This takes place pre and post operatively by a clinical psychologist. The purpose of these assessments is to assess for major psychiatric comorbidities that contraindicate surgery (pre-operative), and assess whether stimulation has altered personality in any way including affecting patients' attitudes to stimulation. This process may involve consultation with patients' relatives. There is the risk we uncover an illness that requires further treatment or investigation, or

adjustment/removal of the device. In this case the most appropriate specialist advice will be sought by letter with your permission, or of the surgeon/nurse specialist if the problem is device-related.

- Test battery

The assessor will do multiple assessments during the period of the study. This will not form part of your medical notes, and will not be analysed during the trial. However, the questionaires could reveal an undiagnosed medical health issue. In this case the most appropriate specialist advice will be sought by letter with your permission, or of the surgeon/nurse specialist if the problem is device-related.

Will my GP be informed of my participation?

We will inform your GP of your participation in the study.

What if we find something unexpected?

In the course of assessing you for surgery and afterwards we may find new unexpected medical problems that require further investigation and may prevent you from having surgery. The main areas would be findings on radiology scans we perform or during tests run by the neuropsychologist or assessor. If this happens we will tell you that we have found something that in our opinion requires further testing by a specialist and make arrangements for you to be assessed by a relevant specialist. The specialist may require further tests before they see you which could include further scans and blood tests.

It is important to note that we do not carry out MRI scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

What if I have some feedback about my participation?

If you wish, you can provide us with feedback on the study. Tell us what we did well, what we can improve upon, and tell us if you'd recommend us to a friend. This allows you to help us improve our processes to make the testing as pleasant as possible.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

We will be using information from you and your medical notes in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 3 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 5 years after the end of the study.

Your medical notes will be kept for longer by the Oxford University Hospital trust according to NHS guidelines as these will be important for your continuing routine care if you opt to continue DBS treatment after the end of your participation in the research study itself. Consent forms for your participation in the study will be kept in your medical notes and the trial master file. Your consent forms will have your name only on the form. Other personally identifiable information will form part of you medical record rather than your study information and be only accessible to medical members of the study team and any other health care professionals directly involved in your medical care.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/]

You can find out more about how we use your information by contacting the study team.
Prof Tipu Aziz
Department of Neurosurgery
West Wing
John Radcliffe Hospital
Oxford
OX3 9DU.

What are the possible benefits of taking part?

Our previous research on this type of surgery is promising, in that this technique can improve pain symptoms. Therefore, the potential benefit of participating in the trial is to experience pain relief.

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

You are free to withdraw at any time, without giving a reason. Your clinical care will continue as normal. If you withdraw from the study, unless you state otherwise, any data e.g. assessments which have been collected whilst you have been in the study will be used for research as detailed in this participant information sheet. You are free to request that your data that can still be identified as yours are destroyed at any time during or after the study.

What if there is a problem?

The *University of Oxford*, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.
If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Prof Tipu Aziz (contact details on page 1 of form) or you may contact:

University of Oxford Clinical Trials and Research Governance (CTRG) office
01865 616480,
Or the head of CTRG
Email ctrg@admin.ox.ac.uk

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study.
If you wish to contact the PALS team please contact:
Patient Advice and Liaison Service (PALS)
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU
Tel: 01865 221473
Email: PALSJR@ouh.nhs.uk
PALS website http://www.ouh.nhs.uk/patient-guide/pals.aspx

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Once you agree to take part, you will be given a patient identification number that will be used on all paperwork and computer files to do with the study. We do not use any information that can identify you, although we may use details like which surgery you have had or what medication you take in publications or presentations to help clarify results. These details will not be able to identify you personally. Any information about you which leaves the research unit will not have any details that can identify you personally (except for by a secure code held by the research team), such as your name, address, etc. so that you cannot be recognised from it.
Responsible members of the University of Oxford or the Oxford University Hospitals NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

Will I be reimbursed for taking part?

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

What will happen to the results of the research study?

The results of this study are likely to be published in scientific journals and presented at academic meetings. You may request a copy of the published results if you wish. No personally identifiable information will be published but de-identified images may be used in publications and presentations.

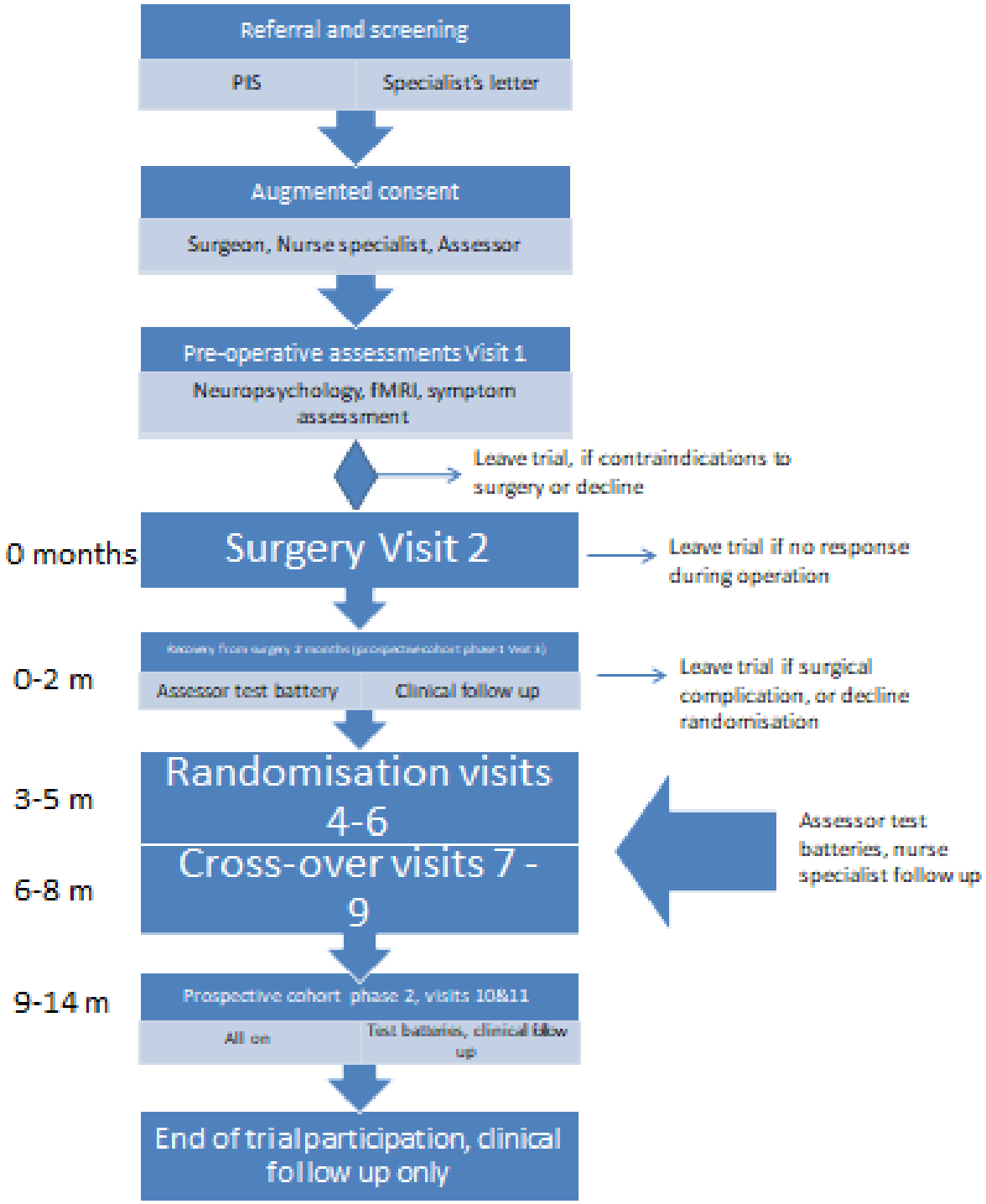
Who is organising and funding the research?

This study is funded by the Jon Moulton Charity Trust (Registered in Guernsey)

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by _____Research Ethics Committee.

Study Flowchart


Referral and screening
PIS
Specialist's letter
Augmented consent
Surgeon, Nurse specialist, Assessor
Pre-operative assessments Visit 1
Neuropsychology, fMRI, symptom assessment
Leave trial, if contraindications to surgery or decline
0 months
Surgery Visit 2
Leave trial if no response during operation
0-2 m
Assessor test battery
Clinical follow up
Leave trial if surgical complication, or decline randomisation
3-5 m
Randomisation visits 4-6
6-8 m
Cross-over visits 7 - 9
Assessor test batteries, nurse specialist follow up
9-14 m
Prospective cohort phase 2, visits 10&11
All on
Test batteries, clinical follow up
End of trial participation, clinical follow up only