Participant Information Sheet

Study Title: Safety and efficacy of thalamotomy by ultrasound for Parkinson's disease (SUNRISE)

Chief Investigator: Dr Tom Gilbertson

We're inviting you to take part in a research study

Before you choose whether or not to take part, we want you to understand why we are doing the study. We also want to tell you what it will involve if you agree to take part. Please take time to read this information sheet carefully. You can ask us any questions and talk to other people about it if you want. We'll answer your questions and give you any additional information you ask for. You don't have to decide straight away.

Why are we doing this study?

Around 145,000 people in the UK live with Parkinson's Disease. The disease develops when cells in the brain stop working properly. This happens gradually and symptoms get worse over time. Symptoms include tremor, slowness of movement and stiffness. While medicines can help, for some people medicines do not prevent the tremor and this has a severe detrimental effect on their quality of life.

This study is aiming to investigate the safety and effectiveness of a new treatment for tremor in Parkinson's disease. This treatment is currently used to treat tremor caused by conditions other than Parkinson's disease and is used to treat Parkinson's disease tremor in other countries such as the USA but is not yet recommended for use in the UK by The National Institute of Health and Care Excellence (NICE). The device that we will use is called an Exablate Neuro 4000 type 1.0 and type 1.1. This device is CE marked (3902589CE01).

The treatment is called MRI guided Focused Ultrasound (MRgFUS) thalamotomy. Ultrasound beams are guided by MRI (Magnetic Resonance Imaging) so that they target a region of the brain called the thalamus, which contains the brain circuits that cause tremor. Once the beams are targeted to the correct site in the brain, they heat the brain tissue and permanently destroy the brain cells that are causing the tremor.

Why have I been asked?

We're contacting you because you have Parkinson's disease with tremor that is not controlled by medication. With your permission, you will be referred to the research team in Dundee, led by Dr Tom Gilbertson, a consultant neurologist who is Chief Investigator of this study. You can contact the research team on the details provided on page 11 of this information sheet. Or you can complete the response page of the invitation letter you received from your care team and an appointment will be arranged for you.

Do I have to take part?

No. Taking part in this study is entirely your choice. If you choose to take part, you can withdraw from the study at any time. You don't have to give a reason for not taking part or for stopping. If you don't want to take part or want to stop the study, the medical care you get and your relationship with the medical or nursing staff looking after you won't be affected. If you decide to withdraw from the study, data already collected will be kept and used in the study. If you choose to stop taking part in the study, we would like to keep collecting information about your health from your hospital records for 6 months after your treatment. If you don't want this to happen, tell us and we'll stop.

What will happen to me if I take part?

ONLINE/TELEPHONE APPOINTMENT – Approx. 1 hour

You attend an online (video) research consultation with clinical staff from the Neurology/MRgFUS clinic in NHS Tayside. They will tell you about the study and ask you some preliminary questions, including about your health, medical history and medication history to find out whether you may be suitable for the study and whether you would like to consider taking part.

IN PERSON VISIT- FURTHER SCREENING AND BASELINE ASSESSMENT – 1 day

You attend outpatient Neurology/MRgFUS clinic at Ninewells Hospital in NHS Tayside for a neurological and neuropsychiatric assessment. All the details of the study will be discussed with you and all of your questions will be answered. After this, if you are happy to take part, you will be asked for your written consent to be enrolled into the study. You will then have a number of assessments to make sure you are suitable for the study:

Physical and neurological examination. This will include assessment of your blood pressure and where necessary examination of your heart and lungs. The neurological examination will focus on the assessment of tremor severity and other physical signs of Parkinson's disease including your balance. This will be used to score the severity of each aspect of your Parkinson's disease using Unified Parkinson's Disease Rating Scale (UPDRS). The impact of your Parkinson's Disease on your Quality of Life will be assessed using the PDQ-39 questionnaire. Mood and anxiety and memory will be assessed with standardised questionnaires including the The Addenbrookes Cognitive Examination (ACE-R). The clinical team will also ask about your past medical history and about the medication you are taking.

If your neuropsychiatric assessment indicates that you are suitable for ultrasound treatment you will have a CT scan to measure your skull size and anatomy, and an MRI scan to pinpoint the location of the thalamus that will be targeted by the ultrasound. You may need to have a pre-MRI X-ray

of your skull if there is a possibility that you have a metal fragment in your skull.

If your assessments indicate that you are not suitable for the ultrasound treatment we will retain your basic data as part of the study dataset unless you ask us to remove this data.

If you consent, a video of your appointment may be recorded so that it can be reviewed by other expert clinicians from hospitals within the UK. This is to obtain the opinion of other experts in this field who form a Clinical Oversight Group to ensure this treatment is safe and suitable for you. You will not be identified in the video.

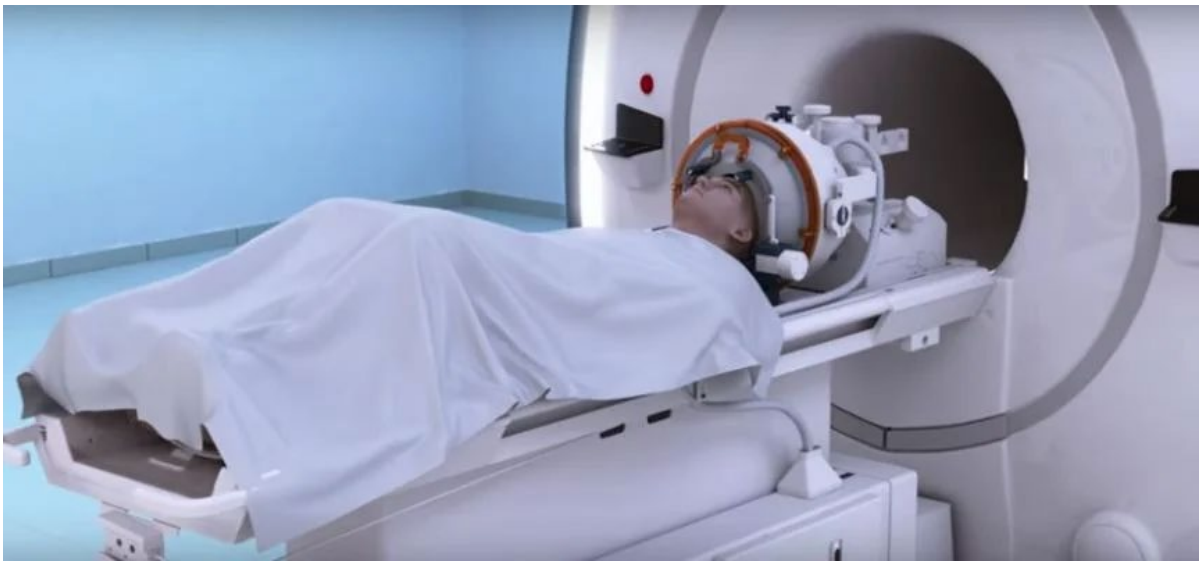
IN PERSON VISIT 2- SURGICAL CONSENT FOR TREATMENT AND BASELINE BLOODS – 1-2 hours

You attend the Neurology/MRgFUS clinic so that detailed surgical consent for MRgFUS thalamotomy can be obtained as per standard NHS care. Specifically at this appointment we will explain what will happen on the day of treatment and re-discuss the side effects, risks and what you should expect from the treatment and procedure. You will have blood taken for baseline assessment of your blood counts, liver & kidney function plus blood clotting. These blood tests will be used to ensure that the treatment can be safely performed. The clinical team will review the blood test results and confirm whether you are fit enough to undergo the ultrasound procedure. It is possible that the results may show you are not fit enough to undergo the ultrasound treatment at that time. In this case the clinical team will get in touch with you to discuss the results and the next steps.

IN PERSON VIST 3 – TREATMENT – 1 day plus overnight stay in hospital

You attend the Neurology ward for treatment. Your head will be entirely shaved to stop your scalp getting too hot from the ultrasound beam. If the head is not shaved there is a risk of burning the scalp as the ultrasound passes through the skull. The surgeon will attach a metal frame to your head under local anaesthetic and you will wear this throughout the treatment. This ensures that your head is held still during the treatment as

the frame is fixed to the MRI scanner table, within the MRI machine. You will not be able to move.



The treatment will take 1-3 hours and you will be awake during the procedure. You will be able to have a relative or friend with you. They may be present for the whole procedure but you will not be able to see them. You can talk to them for reassurance if you want.

During the procedure ultrasound treatments lasting around 10 seconds will be delivered. Typically, these are repeated between 5-15 times. These will have short lasting effects on your tremor and any side effects can be assessed. The intensity of the ultrasound is gradually increased until permanent tremor relief is reached.

During the treatments it is common to feel heating and discomfort around the headframe. You may also feel dizzy and/or nauseous. This is most common towards the end of the procedure when the ultrasound intensities necessary to create permanent tremor relief. The clinical team will be able to provide you with pain relief, anti-sickness medication or mild sedation during the treatment. After the ultrasound treatment is complete a neurologist will assess you and review the MRI scan taken of your brain.

After the treatment you will be taken back to the neurology ward where you will be monitored over night for as a precautionary measure. The following day you will have another MRI scan and then you will be able to go home.

IN-PERSON VISITS AT 6 MONTHS AFTER TREATMENT

You attend the Neurology/MRgFUS outpatient clinic to have another MRI scan and document your tremor response to treatment, monitor any unexpected signs of memory or mood disturbance and record any side effects of the treatment. The UPDRS and PDQ-39 questionnaires will be repeated at this visit.

A flowchart of the study visits is on the last page of this information sheet.

All in-person visits will be subject to the COVID regulations that are in place at that time.

We will reimburse reasonable travel expenses.

Will taking part in the study affect my usual care?

No, you'll continue to receive your usual medical care.

What are the possible benefits of taking part?

The aim of the thalamotomy surgery is to reduce the tremor on one side of your body by around 50%. Typically your dominant side will be treated.

What are the possible disadvantages and risks of taking part?

MRgFUS thalamotomy can only be used to treat one side of your body. Tremor in Parkinson's disease is often worse on one side of the body. Thalamotomy is also safest when performed on one side. Therefore, patients treated in this study will receive a single treatment to one side of the brain to treat tremor in the opposite limb. The procedure is unlikely to improve head or voice tremor.

Sensory disturbance (e.g. numbness or tingling of the limbs or face) affects 1 in 3 people (coloured figures in the illustration, first 6 on the top row). In half of the people affected (green figures, first 3) this resolves within weeks or months of the treatment but in half of affected people (blue, second 3) this can be permanent.

Balance disturbance (e.g. unsteadiness when walking) affects 1 in 3 people (coloured figures in the illustration, first 6 on the top row). In two thirds of the people affected (green, first 4) this resolves within weeks or months of treatment but it can be permanent in the other one third of affected people (blue, second 2).

Speech disturbance (e.g. slurring of speech) is generally a short term complication that lasts weeks to months and affects around 1 in 20 people.

A computed tomography head examination will be performed. It may also be necessary to have an orbital eye x-ray as part of the pre-MRI screening process. This will not be the case for most patients and only in instances

where there is reason to believe metal may be present in your skull. These procedures use ionising radiation to form images of your body and provide your doctor with clinical information. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to you are the same whether you take part in this study or not. Due to the CT scan and potential x-ray there is an increased risk of 0.01% of this exposure causing cancer. For comparison the natural lifetime cancer incidence in the general population is about 50%.

We will discuss possible severe side effects with you before you consent to take part. These include; headache during sonication, burning scalp sensation, pin site pain, transient dizziness, vertigo and nausea during sonications. Short term or persistent weakness or inability to move one side of the body. Short term or persistent lip, scalp and eyelid burning or prickling sensations. Taste disturbance, gait disturbance. Coordination disturbance, difficulty speaking, blood clots, lack of energy and strength, vocal change, neck, back or shoulder pain, decline in mental status, swelling around the eyes and spots in your visual field. There may be other risks we cannot predict. For more information about the risks, please speak with your doctor.

In the unlikely event that brain scans performed during the study identify an abnormality that is unexpected, you may need to declare this on future applications for travel and life insurance.

Who is organising and funding this research?

The study is organised by Dr Tom Gilbertson The study is being sponsored by the University of Dundee. The study is being funded by Insightec Ltd.

How have patients and the public been involved in the study?

The Chief Investigator, Dr Tom Gilbertson, has links with various patient support groups and has discussed this study with them.

Independent Contact: Prof Miratul Muqit, m.muqit@dundee.ac.uk

If you wish to discuss this study or thalamotomy further, you can contact Prof Miratul Muqit by email. Prof Muqit is a clinical neurologist with over 15

years experience in the field. Prof Muqit is not involved in this study and can offer you independent, impartial advice.

What COVID-19 precautions will be in place when I come for my visits?

The current Government COVID-19 guidelines for the country you are in will be in place when you come for your visits. This may include wearing facemasks, handwashing, social distancing when appropriate, checking your temperature and asking about any recent COVID-19 symptoms.

Staff will wear face masks and other personal protective equipment (PPE) when appropriate.

What will happen with the information collected about me?

Identifiable information and the information collected about you during the study will be stored by the NHS Tayside research team. Only authorised members of the research team will be able to see this information.

People who don't need to know who you are won't be able to see your name or contact details. Your data will have a code number instead. Only authorised members of your local research team will have the link between your code number and your personal information.

Information collected about you during the study is called "study information". Your study information will be securely stored on password-protected databases in the University of Dundee.

Your study information will be kept securely for 5 years after the end of the study. After 5 years, your identifiable information held locally will be deleted, and the rest of the information will be kept for research purposes. If you'd like to be informed about future studies that you might be interested in taking part in, we'll ask your permission for us to hold your contact details.

We'll ask your permission to tell your GP that you are taking part in this study.

Information which identifies you won't be published or shared.

Your anonymised study information may be shared with other researchers.

What if something goes wrong?

If you are concerned about your participation in the study you have the right to discuss your concern with a researcher involved in the study or a doctor involved in your care.

If you have a complaint about your participation first of all please talk to the researcher.

If you are not satisfied, you can make a formal complaint to a senior member of the research team or to the Complaints Officer for NHS Tayside.

Complaints and Feedback Team

NHS Tayside

Ninewells Hospital

Dundee DD1 9SY

Freephone: 0800 027 5507

Email: TAY.feedback@nhs.scot

If you think you have come to harm due to taking part in the study there are no automatic arrangements to get financial compensation.

Insurance

The University of Dundee is sponsoring the study.

The University of Dundee has a policy of public liability insurance which provides legal liability to cover damages, costs and expenses of claims.

Who has reviewed this study?

This study has been reviewed and received a favourable ethical opinion from South East Scotland REC 02 Ethics Committee who are responsible for reviewing research which is carried out in humans. The Research Ethics Committee doesn't have any objections to this study going ahead.

Data Protection Privacy Notice

How will we use information about you?

We'll need to use information from you and your medical records for this research project.

This information will include NHS number, name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

When we have finished the study, we will keep 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.

If you consent to receive them, at the end of the study we will provide you with the results of the study.

What are your choices about how your information is used?

- You can stop participating in the study at any time, without giving a reason, but we'll keep information about you that we have already collected.
- If you choose to stop taking part in the study, we would like to keep collecting information about your health from your hospital records for 6 months after your treatment. If you don't want this to happen, tell us and we'll stop.
- We need to manage your records in controlled and tightly regulated 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.

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/
- http://www.ahspartnership.org.uk/tasc/for-the-public/how-we-use-your-information
- https://www.dundee.ac.uk/information-governance/dataprotection/
- http://www.nhstayside.scot.nhs.uk/YourRights/PROD_298457/index.htm
- or by contacting Research Governance, Tayside Medical Science Centre (TASC), 01382 383900, email tascgovernance@dundee.ac.uk

Contact details for further information

Thank you for taking the time to read this Participant Information Sheet and for considering taking part in this study.

If you want to take part in this study or if you'd like more information or want to ask questions about the study, please contact the research team directly using the contact details below. Alternatively, please speak to your own Parkinson's doctor if you want to take part and they can refer you to the research team.

Chief Investigator: Dr Tom Gilbertson

Phone: 01382 383617

Email: t.gilbertson@dundee.ac.uk

Research Nurse: TBC

Phone: TBC

Email: TBC

You can contact us Monday – Friday between 09:00-17:00.

Outside of those hours, if you need advice, you can contact your out-of-hours GP service/NHS24 via 111.

VIRTUAL CLINIC

PRE-SCREENING

You attend a NearMe (video) outpatient research consultation in the Neurology/MRgFUS clinic in NHS Tayside. Further discussion of the study and initial study suitability screening.

VISIT 1

FURTHER SCREENING AND BASELINE ASSESSMENT

- Attend an outpatient Neurology/MRgFUS clinic in NHS Tayside.
- Provide informed consent to take part in the study
- Recorded neurological and neuropsychiatric assessment
- Pre-surgical MRI and CT scan
- Pre-MRI x-ray (if required)

TELEPHONE CALL

- All results provided by telephone call

VISIT 2

SURGICAL CONSENT FOR TREATMENT AND BASELINE BLOODS

- You attend at the neurology outpatient clinic to:
  - Provide informed surgical consent for the MRgFUS thalamotomy procedure
  - Bloods taken to assess suitability and safety

VISIT 3

TREATMENT

- You attend at the neurology outpatient clinic to:
  - Receive MRgFUS thalamotomy treatment
  - Post-treatment MRI
- You will be observed overnight after treatment, on the neurology ward at Ninewells Hospital
- Further MRI and assessment the following day

VISIT 4

6 MONTHS POST-TREATMENT

- You attend at the neurology outpatient clinic for follow-up assessment
  - MRI
  - PDQ-39 questionnaire
  - Clinical Rating Scale for Tremor
  - Adverse events and medication update