FULL/LONG TITLE OF THE TRIAL

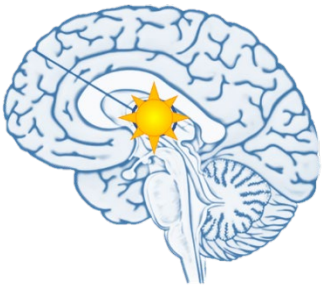
Pilot study of Safety and efficacy of Unilateral MR guided Focused Ultrasound thalamotomy in Tremor Dominant Parkinson's Disease

SHORT TRIAL TITLE / ACRONYM

SUNRISE

PROTOCOL VERSION NUMBER AND DATE

Version 1 10th November 2022



SUNRISE

Safety and efficacy of thalamotomy by Ultrasound for Parkinson's disease

This protocol has regard for the HRA guidance and order of content Version 1.2 March 2016

RESEARCH REFERENCE NUMBERS

IRAS Number:	311871
Registry Number:	TBC
SPONSORS Number:	2-025-22
FUNDERS Number:	

SPONSOR

University of Dundee

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

…..... ……..

Name (please print):

…..

Chief Investigator:

Signature: Date:

…..... .....

Name: (please print):

Dr Tom Gilbertson

Position:

Clinical Senior Lecturer/Honorary consultant,
Imaging Science and Technology,
School of Medicine

KEY TRIAL CONTACTS

Chief Investigator	Dr Tom Gilbertson Division of Neuroscience University of Dundee Ninewells Hospital & Medical School Dundee DD1 9SY t.gilbertson@dundee.ac.uk
Study Coordinator	Dr Sarah Inglis Senior Trial Manager, Tayside Clinical Trials Unit s.k.inlgis@dundee.ac.uk
Sponsor	University of Dundee
Funder(s)	Insightec
Clinical Trials Unit	Tayside Clinical Trials Unit tctu@dundee.ac.uk
Key Protocol Contributors	Dr Tom Gilbertson (Chief Investigator) t.gilbertson@dundee.ac.uk Dr Sarah Inglis (TCTU senior trial manager) s.k.inglis@dundee.ac.uk Mr Lewis Beer (TCTU clinical trial manager) l.j.z.beer@dundee.ac.uk
Statistician	TBC, will be a member of the CI's team
Chair of Clinical Oversight Group	TBC

I. LIST OF CONTENTS

II. LIST OF ABBREVIATIONS

AE	Adverse Event
ACE	Addenbrookes Cognitive Examination
AR	Adverse Reaction
BOLD	Blood oxygenation level dependent
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Insurance Scheme
COG	Clinical Oversight Group
CRF	Case Report Form
CRST	Clinical Rating Scale for Tremor
CT	Computed Tomography
CTU	Clinical Trials Unit
DBS	Deep Brain Stimulation
DMC	Data Monitoring Committee
ET	Essential Tremor
EudraCT	European Clinical Trials Database
fMRI	Functional magnetic resonance imaging
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ISF	Investigator Site File (This forms part of the TMF)
MRgFUS	Magnetic resonance guided focused ultrasound
NHS R&D	National Health Service Research & Development
NICE	The National Institute for Health and Care Excellence
PDQ	Parkinson's Disease questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
TDPD	Tremor dominant Parkinson's Disease
UPDRS	Unified Parkinson's Disease Rating Scale
Vim	Ventral intermediate nucleus

III. TRIAL SUMMARY

Trial Title	Pilot study of Safety and efficacy of Unilateral MR guided Focused Ultrasound thalamotomy in Tremor Dominant Parkinson's Disease	
Internal ref. no. (or short title)	SUNRISE: Safety and efficacy of thalamotomy by ultrasound for Parkinson's disease	
Clinical Phase	Pilot	
Trial Design	This is a Non-CTIMP feasibility study exploring the safety and efficacy of MR guided focused ultrasound thalamotomy in Parkinson's Disease	
Trial Participants	Patients with Tremor Dominant Parkinson's disease that is unreceptive to medication	
Planned Sample Size	10	
Treatment duration	1 day	
Follow up duration	6 months	
Planned Trial Period	3 years	
	Objectives	Outcome Measures
Primary	Assess the effects of MRgFUS thalamotomy on TDPD	Clinical rating scale for tremor (CRST)
Secondary	Effect of MRgFUS thalamotomy on patient	CRST
		PDQ-39/UDPRS III

	health immediately after the intervention, 1 day later and during the 6 months following the intervention	Structural MRI
		Medication collection
		Adverse events

IV. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
Insightec Ltd.	

V. ROLE OF TRIAL SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder are detailed in the Clinical Research Agreement of XXX.

VI. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The CI will be responsible for the conduct of the trial. A trial-specific Delegation Log will be prepared for the trial site, detailing the duties of each member of staff working on the trial.

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from an appropriate NHS REC. NHS Tayside R&D permission will be obtained prior to commencement of the trial.

The trial will be coordinated by a Trial Management Group, consisting of the CI and trial manager with other appropriate individuals being invited. Details of membership of the TMG and TMG meetings will be held in the TMF.

A Clinical Oversight Group (COG) consisting of NHS consultant neurologists and Neurosurgeons will meet regularly to review patients selected in a virtual Multi-disciplinary meeting. The purpose of the COG will be to provide additional clinical feedback to the CI on patient selection, particularly where patients may be suitable for treatments that are part of standard NHS care including DBS. The COG will also review patient safety data, which may include AEs, SAEs and 6 month assessments. This will be detailed in the COG charter.

VII. PROTOCOL CONTRIBUTORS

Chief Investigator, Dr Tom Gilbertson: Review and final approval

Senior Trial Manager, Dr Sarah Inglis: Initial draft and review

Trial Manager, Mr Lewis Beer: Initial draft and review

VIII. KEY WORDS: Parkinson's disease, Tremor, Thalamotomy.

IX. TRIAL FLOW CHART

Patient with Parkinson's disease receives patient information sheet (PIS) and invite letter from their current neurologist or care of the elderly physician on behalf of the CI.

Patient confirms interest in taking part by responding by telephone or email via the contact details provided or by completing a response form to indicate they are happy to be referred to the research team.

↓

VIRTUAL CLINIC PRE-SCREENING

Patient attends 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

Patient attends outpatient Neurology/MRgFUS clinic in NHS Tayside. Patient will be asked for their written consent to be enrolled into the study by the CI. Patient will then have a neurological and neuropsychiatric assessment. This assessment visit will be recorded to further clinically assess the participant. The video of this assessment may be shared with the COG if the CI deems it necessary. This video will be retained to compare to the assessment video at 6 months.

Patient receives pre-surgical MRI and CT scanning plus pre-MRI skull X Ray if clinically required.

↓

TELEPHONE CALL

Patient receives results of all tests by telephone.

↓

VISIT 2- SURGICAL CONSENT FOR TREATMENT AND BASELINE BLOODS

Patient attends outpatient Neurology/MRgFUS clinic in NHS Tayside so that detailed surgical consent for MRgFUS thalamotomy can be obtained as per standard NHS care. The patient has blood taken for baseline preassessment FBC, LFT, U+E and clotting at this appointment.

↓

VISIT 3- TREATMENT

Patient attends for MRgFUS thalamotomy.

Patient observed overnight following treatment on the Neurology ward, Ninewells Hospital

MRI following intervention. Further MRI and assessment the next day (Day 1).

↓

VISIT 4- FOLLOW UP

Patient attends outpatient Neurology/MRgFUS clinic in NHS Tayside for follow-up assessments at 6 months; MRI, PDQ-39/UDPRS III, CRST, AEs and medication collection. This assessment will be recorded and compared to the baseline assessment video.

1. BACKGROUND

Parkinson's disease is a progressive neurodegenerative disease characterised by gradually worsening tremor, muscle rigidity and difficulties with starting and stopping movements. The tremor in Parkinson's disease occurs at rest and becomes less prominent with voluntary movement. It typically occurs first in the distal upper extremities then moves proximally and spreads to affect other parts of the body over time [1].

Treatment for Parkinson's disease include supportive therapies and medications such as levodopa, dopamine agonists and monoamine oxidase B inhibitors. Surgery may be considered in people whose condition has not responded adequately to best medical therapy. Surgical treatments include deep brain stimulation (DBS) and radiofrequency thalamotomy [2].

Transcranial Magnetic Resonance guided focused ultrasound (MRgFUS) is a technology which allows permanent modification of brain function and relief of symptoms including tremor. MRgFUS thalamotomy, where focused ultrasound is targeted at the Ventral intermediate nucleus (Vim) of the thalamus, has been adopted world-wide as a minimally invasive alternative to established techniques such as Deep Brain Stimulation (DBS) in patients with medication resistant Essential Tremor (ET). Clinicians based at Ninewells hospital performed the first MRgFUS thalamotomy in Scotland in June 2021 and are the second unit in the UK able to deliver this therapy.

The therapeutic effect of MRgFUS relies upon the permanent lesioning of the Vim by thermal coagulation necrosis caused by ultrasound induced heating of the nucleus. Effective lesioning requires a 3 hour awake procedure during which patients receive repeated High Intensity Focused Ultrasound (HIFU) treatments. The intensity of each treatment is gradually increased to achieve thermal heating of the treatment target region to >50°C at which permanent lesioning and tremor suppression is achieved. HIFU involves the delivery of short (10-20 second) continuous ultrasound at intensities (~150-200W) necessary to produce the thermal effects.

The potential benefits of unilateral MRI-guided focused ultrasound thalamotomy are that it: is less invasive than the other existing procedures; results in a faster recovery time; and allows for testing of the effects of sub-lethal doses before ablation. However, unlike deep brain stimulation, it can only be done on 1 side.

The National Institute for Health and Care Excellence (NICE) has considered the current evidence on the safety and efficacy of unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease. They have recommended that the available evidence is inadequate in quantity and quality, and that the procedure should be used only in the context of research [3].

2. RATIONALE

The aim of this feasibility study is to investigate the impact of MRgFUS thalamotomy in patients with treatment-resistant Parkinson's disease in reducing tremor, tolerability of the intervention and the safety profile of the intervention both immediately following intervention and over the subsequent 6 month period [4].

The follow up will run in conjunction with A Post-Approval Registry for Exablate 4000 Type 1.0 and Type 1.1 for Unilateral Thalamotomy for the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease. Known as PD012. Protocol version 2 dated June 7, 2022 (IRAS number 311870. Clinicaltrials.gov number NCT04991831). This is a long-term registry funded and sponsored by Insightec Ltd. Data collected in the SUNRISE study will be used and shared with the PD012 registry (see section 11.2 Data Transfer). A PIS for PD012 will be provided by mail or email after the participant has been deemed eligible for treatment or in person at Visit 1. Consent for PD012 will then be taken at the same time as surgery consent. Participants are not required to consent to both studies and are free to decline joining the registry.

MRgFUS thalamotomy is part of standard NHS care for patients with Essential Tremor [5] but there is limited experience of this treatment in Parkinson's disease patients .This study will add to the current available evidence of the effectiveness and safety of the procedure and enable NICE to review their recommendations on the use of the procedure in the NHS [6]. Parkinson's disease patients with medication resistant tremor that is significantly impacting on day-to-day function will be considered for treatment.

2.1. Assessment and Management of Risk

The NICE interventional procedure overview details potential benefits of MRgFUS thalamotomy in 62 people with Parkinson's disease [6]. It reports improvements in tremor in 4 case studies [7-9]. Improvements were also seen in a randomised control trial (RCT) with 20 patients receiving MRgFUS thalamotomy showing significant improvements in tremor when compared to patients (n=7) receiving sham treatment [3]. The overview also describes improvements in functional activities of daily living and quality of life measured in some of the studies. While length of follow-up in the studies reviewed by NICE varied between studies, the longest reported follow-up period was around 7 months. Some recurrence of tremor was reported in some patients during follow-up but the data on recurrence were sparse. While the numbers of patients reported in the case studies and RCT are small, they show sufficient improvements for NICE to recommend that the procedure continue to be used for research purposes. With the equipment and expertise at Ninewells Hospital, we are in a good position to add to the evidence of the effects of the intervention, both in the acute phase and during long term follow-up.

The NICE interventional procedure overview also details the safety summary of the case studies and RCT reported above [6]. As for efficacy reported above, it is difficult to distinguish the relative impact of safety risks due to the small number of patients in each study. Headache during the sonication was reported in up to 60% of patients. Burning scalp sensation and pin site pain were also reported. Transient dizziness, vertigo and nausea during sonications were reported in up to half of patients. One study reports that these symptoms resolved within seconds to minutes. Hemiparesis was reported in 2 studies, with the symptoms being persistent in three individuals and transient in 2 other individuals. Lip, scalp and eyelid paraesthesia were reported in relatively small numbers of patients in 3 of the case studies and the RCT. In some individuals this was transient while it persisted in others. Two case studies reported taste disturbance in just over 10% of patients while gait disturbance was also reported in 2 case studies and the RCT at similar rates. Other reported side effects were hand ataxia, dysarthria,

haematoma, asthenia, vocal change, neck, back or shoulder pain, decline in mental status, periorbital swelling, spot in visual field. The overview also reported the anecdotal adverse event of sensation of spinning, and they considered theoretical adverse events may include intracranial haemorrhage, stroke, increased intracranial pressure, the effect wearing off over a longer time period and permanent unintended neurological complications.

Participants will go through a robust screening process to ensure that MRgFUS treatment is a procedure they are suitable for and can undergo safely. Participant safety will be reviewed throughout the study and the CI will regularly discuss participant safety with the COG. There are several stages where participants can fail screening (Near Me consultation followed by in person physical assessment). High levels of screen failure are expected in order to enrol 10 suitable participants.

Participants will have adequate time from their initial local clinical visit where they are provided with study information, through to the first in person assessment where informed consent is obtained to decide to not take part in this study.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Hypothesis

MRgFUS thalamotomy is a safe, and tolerable treatment of tremor in patients with Parkinson's disease.

Treatment of patients with Parkinson's disease with MRgFUS thalamotomy will significantly improve their tremor immediately, and some improvement over baseline will be maintained during a 6 month follow-up period.

3.1. Primary objective

The overall objective of the study is to demonstrate tolerability and safety of using MRgFUS thalamotomy to treat tremor in patients with Parkinson's disease.

3.2. Secondary objectives

See Section 3.7

3.3. Outcome measures/endpoints

See Section 3.7

3.4. Primary endpoint/outcome

See Section 3.7

3.5. Secondary endpoints/outcomes

See Section 3.7

3.6. Exploratory endpoints/outcomes

See Section 3.7

3.7. Table of endpoints/outcomes

Primary Objective	Outcome Measures	Timepoint(s)
Assess the effects, safety and tolerability of MRgFUS thalamotomy on TDPD	Clinical rating scale for tremor (CRST parts A+B)	During MRgFUS Thalamotomy
Secondary Objectives	**Outcome Measures**	
Effect of MRgFUS thalamotomy on patient health during the 6 months following the intervention. Lesion location as a prediction of outcome.	CRST rating scale	Day 1, Month 6.
	UPDRS part III motor exam	Day 1, Month 6.
	PQD-39	Day 1, Month 6.
	Adverse events	Day 1, Month 6.
	Medication collection	Day 1, Month 6.
	MRI	Day 1, Month 6.

4. TRIAL DESIGN

This is a pilot study aimed to investigate the effect of MRgFUS thalamotomy on tremor in up to 10 participants with Parkinson's disease with follow-up lasting 6 months

5. TRIAL SETTING

Following confirmation of interest by the participant, the initial research appointment to discuss the study with patients will be done remotely, using Near Me. Near Me is a video consulting service that enables people to attend appointments from home or wherever is convenient. The service is already widely used across NHS Scotland for health and care appointments with around 20,000 consultation being held every week. All you need is a device for making video calls like a smartphone and an internet connection. Near Me is a secure form of video consulting approved for use by the Scottish Government and NHS Scotland. (https://www.nearme.scot/)

All outpatient clinic research assessments will occur either in the MRgFUS thalamotomy clinic, or at the Clinical Research Centre (CRC) both in Ninewell's Hospital & Medical School, Dundee. Pre-treatment imaging assessment and MRgFUS thalamotomy will be performed in the Clinical Imaging Research Facility (CRIF), University of Dundee/ NHS Tayside (Clinical Research Centre). Current regulations required for COVID safety will be followed.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

- Men and women age 30 years or older.
- Subjects who are able and willing to give consent and able to attend all study visits.
- An established diagnosis of Parkinson's Disease as confirmed from clinical history based upon UK Brain Bank criteria.
- Tremor refractory to adequate trials of at least two medications, including levodopa equivalent dosage of 800mg (total daily dose). An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
- Tremor dominant PD defined by the UPDRS tremor scores (items 16,20,21) to the mean UPDRS postural instability/gait disorder scores (items 13-15,29,30) was ≥ 1.5
- Vim nucleus of thalamus can be target by the MRgFUS device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
- Able to communicate sensations during the treatment.
- Postural or resting tremor severity score of grade 3 or 4 in the most affected hand/arm as measured by the CRST (part A) rating scale while stable on medication (items 1-9).
- Significant disability due to Parkinson's tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])

6.2. Exclusion criteria

- Subjects with unstable cardiac status including:
    - Unstable angina pectoris on medication
    - Subjects with documented myocardial infarction within six months of protocol entry
    - Significant congestive heart failure
    - Subjects with unstable ventricular arrhythmias
    - Subjects with atrial arrhythmias that are not rate-controlled
- Severe hypertension (diastolic BP > 100 on medication)
- Significant speech impairment that would prevent communication during procedure.
- Unsteadiness when walking or turning and or instability on tandem walking during formal examination.
- Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
- Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium).
- Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m2 (or per local standards should that be more restrictive) and/or who is on dialysis.
- History of abnormal bleeding and/or coagulopathy
- Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or haemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
- History of immunocompromise including those who are HIV positive.
- History of intracranial haemorrhage
- Cerebrovascular disease (multiple CVA or CVA within 6 months)
- Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).

- Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment (can be up to 4 hrs of total table time.)
- Significant claustrophobia that cannot be managed with mild medication.
- Subjects unable to communicate with the investigator and staff.
- Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
- Presence of significant cognitive impairment as determined with a score ≤ 85 on the ACE-R.
- Diagnosis of Dementia including Parkinson's Disease Dementia (PDD).
- Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
- Subjects with a history of seizures within the past year.
- Subjects with a history of psychosis will be excluded. Subjects with a history of self-harm/personality disorder, bipolar disorder, or moderately severe depressive illness will be excluded. For the purpose of this study, we consider moderately severe depressive illness to include any subject who:
    - has an IDS-SR score > 26
    - is currently under the care of a psychiatrist
- Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimetre, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
- Subjects with brain tumours
- Any illness that in the investigator's opinion preclude participation in this study.
- Pregnancy or lactation.
- Legal incapacity or limited legal capacity.
- Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
- Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
- Subjects who have an Overall Skull Density Ratio of 0.3 or less as calculated from the screening CT.

7. TRIAL PROCEDURES

7.1. Recruitment

7.1.1. Participant identification

Potential candidates for this treatment will be identified across Scotland by their consultant neurologist or Care of the Elderly Physician in their local Scottish Health Board as having Parkinson's disease with tremor that is unresponsive to standard medical therapy, they will receive the PIS and an invite letter on behalf of the CI from their current care team. The potential participant can then contact the research team if they wish to take part in the study. Alternatively, the participant completes a response form to confirm their permission to be referred to the CI at the MRgFUS-Thalamotomy clinic at Ninewells Hospital. The response form will be included with the patient referral. This is the same referral pathway that currently exists

for patients with essential tremor (ET) and who are assessed in the MRgFUS Thalamotomy clinic as part of standard NHS care for ET patients.

In NHS Tayside, the potential participant's primary care team is the research team.

7.1.2. Screening

On receipt of their referral for assessment patients will be sent an appointment for a research NearMe video consultation to discuss any questions about the study and to assess the potential participants' suitability for the study.

In the event that the patient agrees to proceed to be enrolled in the study they will be given an appointment to attend the MRgFUS-Thalamotomy outpatient clinic at Ninewells Hospital, Dundee (VISIT 1). Informed consent will be taken from the patient at this appointment and then screening against the clinical inclusion and exclusion criteria will be performed by the study CI. If the patient meets the clinical eligibility criteria, they will undergo both MRI and CT brain imaging on the same day of this appointment. If the screening process indicates a participant may potentially have metal in their skull, a confirmatory X-ray will be performed to ensure they can safely proceed with the MRI and CT scans. Radiological screening criteria (e.g Skull density ratio) will be determined following reporting of the CT and MRI scans by a consultant neuroradiologist. The results of these tests will be fed back to the patient at a telephone consultation approximately 6 weeks following the initial in person assessment (**Telephone Consultation**).

In the event that they are deemed unsuitable for MRgFUS they will be referred to the appropriate clinical care pathway.

Patients who are deemed appropriate will have a further appointment with a consultant neurosurgeon to obtain their consent for MRgFUS Thalamotomy **(VISIT 2)**.

7.1.3. Ineligible participants

If a patient does not fulfil the screening criteria for the study, they will be informed of this and the reasons for this at either a face to face consultation or telephone consultation.

Data on the reasons for ineligibility together with basic demographic information (age, sex) will be collected to inform the design and eligibility criteria of future studies.

7.2. Payment

Participants will be reimbursed for reasonable travel expenses, including an overnight stay as required.

7.3. Consent

Patients attending **VISIT 1** will be offered the opportunity to ask any further questions about the study. They will then provide written consent to be enrolled into the study at this consultation. Clinical assessment and screening for eligibility base upon inclusion and exclusion criteria will then be performed following consent being obtained. Patients who are enrolled into the study

and are found to be eligible for MRgFUS thalamotomy will be consented for this treatment by a consultant Neurosurgeon at **VISIT 2**.

7.4. Baseline data

- CRST via video assessment
- PDQ-39
- UPDRS III
- Demographics
- Medical History
- Addenbrookes Cognitive Examination ACE
- Depression score (IDS)
- Medication/Dosage
- MRI/CT

7.5. Trial assessments

Clinical Rating Scale for Tremor (CRST) – scale used to assess the severity of tremor. Scores range from 0 to 4 per component assessed and higher scores indicate more severe tremor. Assessments are videoed to enable referral to the COG and for comparison of baseline and 6 month assessment.

Unified Parkinson Disease Rating Scale (UPDRS) – scale used to assess symptoms associated with Parkinson's disease. Part III is the motor examination and assesses various motor functions.

Quality of life scale (PDQ-39) – assesses how often people with Parkinson's experience difficulties across 8 dimensions of daily living including relationships, social situations and communication. It also assesses the impact of Parkinson's on specific dimensions of functioning and wellbeing.

Skull X-Ray – If the screening process indicates a participant may potentially have metal in their skull, a confirmatory X-ray will be performed to ensure they can safely proceed with the MRI and CT scans

MRI brain imaging - Patients will undergo standard pre-surgical MRI (3T, Seimans) for surgical planning and identification of the thalamotomy target. Patients will also undergo MRI scanning duringthe thalamotomy, 1 day after the thalamotomy and six months after thalamotomy to determine lesion localisation.

CT brain scanning - Patients will undergo pre-surgical CT scanning to estimate the patient's Skull Density Ratio (SDR).

Safety bloods pre surgery - FBC, LFT, U+E and clotting. These blood samples will follow the usual NHS laboratory pathway for clinical samples.

'Inventory of Depressive Symptomatology' (IDS) – standard tool used to assess the mood and anxiety symptoms of patients at baseline

Addenbrookes Cognitive Examination (ACE),- tool used to assess cognitive function at baseline

7.6. Long term follow-up assessments

All patients will be followed up in the MRgFUS clinic in person at 6 months. The CRST, UPDRS-III and PDQ-39 assessments will be repeated at this visit. In addition patients will have an MRI scan, physical and neurology examination and adverse outcomes will be documented.

7.7. Qualitative assessments

None

7.8. Withdrawal criteria

Participants are free to withdraw at any time and are not obliged to give reason(s). It will be clearly stated in the PIS that the participant is free to withdraw from the study at any time for any reason without prejudice to future care. The CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights. Following a request to withdraw from the study this will be acted on immediately by the local study team and communicated to the CI.

The investigator may withdraw a participant at any time if it is in the best interest of the participant and continuation would be detrimental to the participant's well-being. A full explanation will be provided.

If a participant withdraws or is withdrawn from the study, the research team will retain any data and samples obtained up until the time of the point of withdrawal for use in the study analysis. No further data or samples will be collected after withdrawal.

7.9. Storage and analysis of clinical samples

7.10. Safety bloods will be processed by NHS laboratories and be reported and treated as clinical samples. MRI imaging data will be exported as anonymised DICOM imaging files and stored on the University of Dundee secure server and accessed on a University of Dundee work station. End of trial

The end of trial is defined as completion of 6 month assessments for last participant. The Sponsor and/or CI have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, REC, NHS R&D Office(s) within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

8. TRIAL INTERVENTION

MRgFUS Thalamotomy is performed in awake patients using an integrated system which combine multiple-channel phased-array focused ultrasound transducer (MRgFUS, Insightec) and Magnetic Resonance Imaging (Siemens, T3 Prisma). Patients will receive thalamotomy targeted at Ventral-intermediate nucleus (Vim). The thalamus contralateral to the limb with the most marked tremor will be treated. A stereotactic frame will be attached to the patient's head

with local anaesthetic at four pin sites. The frame facilitates targeting of the Vim as its position is aligned to pre-operative patient MRI imaging. It also ensures that the patients head is in a fixed position during the treatment as the headframe is locked into the ultrasound transducer array attached to the MRI scanner table. Clinical examination and imaging feedback are used during the treatment to identify the optimal thalamotomy target. Typical ultrasound treatments last between 10-20 seconds and are associated with varying levels of pressure at the head frame pin sites, vertigo sensation and side effects relating to the effects of the ultrasound on the Vim and surrounding brain structures. These include sensory symptoms such as numbness. These are transient and are used by the treating team to re-direct the focus of the treatment area before delivering high power ultrasound treatment which create permanent symptomatic relief. Detailed assessment of limb tremor after each ultrasound treatment allows the treating team to identify the optimal target of the intervention based upon clinical feedback. Typically between 5-15 ultrasound treatments are delivered with increasing intensity during the course of the 1-3 hour procedure. The aim of MRgFUS is to create a permanent lesion of the thalamus by harnessing the thermal effects of focused ultrasound.

The patients will be observed overnight following treatment on the Neurology ward (23a), Ninewells Hospital & Medical School. Patients are discharged with a 5 day course of dexamethasone (2mg twice a day) to reduce peri-lesional oedema and side effects relating to this.

9. SAFETY

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence
Serious Adverse Event (SAE)	A SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.2. Operational definitions for (S)AEs

Each AE will be assessed for its cause and defined as follows:

- Parkinson’s Disease Related Events: Events that are commonly associated with worsening -Parkinson’s Disease.
    - On/off freezing
    - Falls
    - Medication related Dyskinesia
    - Postural Hypotension
    - Hallucination or acute confusion state
- Procedure Related Adverse Events: Events that are expected procedure findings, for example drug or contrast media reaction
    - Nausea/vomiting/ dizziness during ultrasound treatment delivery
    - pain related to ultrasound treatment delivery
    - Claustrophobia / Anxiety
- Thalamotomy Related Adverse Event: Events that are commonly associated with ablation and/or DBS
    - Gait disturbance
    - Sensory loss (numbness or tinging)
    - Speech disturbance (dysarthria)
    - Change in taste (dysgeusia)
- Device Related Adverse Events: Events are caused specifically by the MRgFUS Neuro
    - Haematoma around head frame pin sites
    - Skin burns to scalp
- Unrelated Adverse Events: These are events that are captured and determined by the CI or PI
- Investigator(s) to be unrelated to the treatment device or procedure such as colds, ear infections, and miscellaneous musculoskeletal events.
- Unknown Relationship: Unknown or inadequate data for determination

9.3. Recording and reporting of AEs

All AEs will be recorded on the AE Log in the case report form (CRF) and will be assessed for severity by the CI or PI. AEs will be recorded from the time a participant consents to join the study until the participant's last study visit. An AE may be classified as a SAE. SAEs will be followed up until recovered/recovered with sequelae/death/30 days after participant's last visit - whichever is the soonest.

SAEs which are both unexpected and related to study participation will be submitted on an HRA non-CTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office

9.4. Responsibilities

Chief Investigator (CI) / delegate:

Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.

Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.

Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

This is a pilot study which is aimed at testing the feasibility of performing MRgFUS Thalamotomy and assessing the effects of this both clinically (through clinical rating outcome scales) and structural imaging. The data from this study will inform subsequent estimate of the effect size of MRgFUS Thalamotomy and determine the appropriate study sample size for future investigations.

10.2. Planned recruitment rate

We aim to recruit 10 patients over 3 years.

10.3. Statistical analysis plan

Since this is a feasibility study the statistics will mainly be descriptive. A statistical analysis plan detailing the planned analysis will be finalised prior to database lock.

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

Medical records will be used as source data. The medical record will be flagged to state that the patient is participating in the SUNRISE study.

The PI or delegate will maintain source documents for each participant in the study, consisting of hospital medical records containing demographic and medical information.

A paper case report form (CRF) will be developed to collect the data required by the protocol. The CRF will not collect more information than is required to meet the aims of the study and to ensure the eligibility and safety of the participant.

Baseline and 6-month assessments may be video recorded and shared with the COG for additional expert clinical input into suitability for the study, and to compare baseline and 6month assessments. The videos are performed on the neurology department ipad which is encrypted and password protected. They are stored on an encrypted (password protected) external HD and then deleted at 1 year follow up if treated. Patients who are not selected for treatment videos are deleted after the meeting or before if they are not deemed suitable for the MDT. The videos may be presented at a Teams (NHS account) meeting with the COG.

The PI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Delegated study staff will enter the data required by the protocol into the CRFs following training in the definitions and methods used in completing the CRF. Any queries will be resolved by the CI or delegated member of the study team. On completion of data collection, the PI must certify that the data entered into the CRFs is complete and accurate.

An electronic data management system reflecting the CRF will be developed in Microsoft Excel as per the relevant TASC SOP.

Data preservation and sharing will be in accordance with established procedures at the University of Dundee. All electronic data will be stored on secure University of Dundee or cloud-based servers which have restricted access and have disaster recovery systems in place.

11.2. Data Transfer

Participants enrolled in the SUNRISE study will be invited to join the Insightec PD012 registry study. If a SUNRISE participant enrols in the PD012 registry study, some data will be shared with this study. The data that will be shared are:

At baseline; Demographics, Concomitant medication check, UPDRS and CRST

At 6 months; AEs, Concomitant medication check, UPDRS and CRST.

An agreement enabling these data to be shared with Insightec will be put in place by TASC legal team. No participant identifiable data will be shared with Insightec.

11.3. Access to Data

The CI, PIs and all institutions involved in the study will permit study-related monitoring, audits, and REC review. In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or REC direct access to all trial records and source documentation.

11.4. Archiving

Essential documents will be archived for 5 years post end of study. The research dataset will be archived by the University of Dundee according to local policy. Medical case notes will be maintained in compliance with local NHS Policy on Retention of Medical Case notes.

12. MONITORING, AUDIT & INSPECTION

12.1. Monitoring

The study may be selected for audit and/or monitoring by the Sponsor.

12.2. Clinical Oversight Group

The clinical oversight group (COG) will comprise UK clinical experts and will include the chief investigator and the NHS Tayside neurosurgeon. They may review the baseline screening assessments of potential participants to ensure that the treatment is offered only to the correct patients. The COG will also review patient safety data including a review of AEs and SAEs. The remit of the COG will be described in the COG charter.

12.3. Data Monitoring Committee

13. THIS IS A PILOT STUDY WITH A SMALL NUMBER OF PARTICIPANTS BEING RECRUITED AT A SLOW RATE. THE REVIEW OF SAFETY DATA WILL BE DONE BY THE CLINICAL OVERSIGHT GROUP (SEE ABOVE) AS PART OF THEIR ROLE TO MAINTAIN CLINICAL OVERSIGHT OF THE PARTICIPANTS. AN ADDITIONAL DMC IS THEREFORE NOT REQUIRED.ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a UK REC for the trial protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

A copy of all REC reports will be submitted to the Sponsor.

13.2. Public and Patient Involvement

The study documents and design are subject to ongoing review by members of the Dundee Research Interest Group (DRIG).

13.3. Regulatory Compliance

Before any site can enrol participants into the trial, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the trial delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

13.4. Protocol compliance

The CI will not implement any breach of the protocol except where necessary to eliminate an immediate hazard to study participants. In the event that there is a breach of the protocol, the nature of and reasons for the breach will be recorded in the study Breach Log.

It is Sponsor policy that waivers to the Protocol will not be approved.

13.5. Notification of Serious Breaches to GCP and/or the protocol

If a breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the TASC Breach Reporting Form and documented in the study Breach Log.

If a breach necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, and NHS R&D for review and approvals as appropriate..

13.6. Data protection and participant confidentiality

The CI and study staff will comply with the requirements of the Data Protection Act 2018 and UK General Data Protection Regulation (UK GDPR) or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal information and will uphold the Directive’s core principles.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate study staff only. Computers used to collate data will have limited access measures via usernames and passwords.

Personal clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee or regulatory authorities.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to the CI and appropriate delegated study staff.

Where data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

13.7. Financial and other competing interests for the Chief Investigator, PIs at each site and committee members for the overall trial management

The CI declares no competing interests in relation to the SUNRISE study.

13.8. Indemnity

The University of Dundee is Sponsoring the study.

Insurance. – The University of Dundee will obtain and hold Professional Negligence Clinical Trials Insurance cover for legal liabilities arising from the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Sponsor does not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

13.9. Amendments

The CI will seek Sponsor approval for any amendments to the Protocol or other approved study documents. Amendments to the protocol or other study documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC and NHS R&D Office(s).

13.10. Post-trial care

Participants will be cared for as per their local Parkinson's Disease clinical service.

13.11. Access to the final trial dataset

The CI will have access to the final dataset. Any access to the final dataset granted to others will be authorised by the CI.

14. DISSEMINATION POLICY

14.1. Dissemination policy

Trial investigators have the right to publish orally or in writing the results of the trial. The criteria for authorship will follow the criteria of the International Committee of Medical Journal Editors.

Publications will be reviewed according to the agreed contractual terms but will not restrict the general rights outlined above for the Investigators to publish the results of the trial.

15. REFERENCES

1. Postuma, R.B., et al., *MDS clinical diagnostic criteria for Parkinson's disease.* Mov Disord, 2015. **30**(12): p. 1591-601.
2. Ferreira, J.J., et al., *Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease.* Eur J Neurol, 2013. **20**(1): p. 5-15.
3. Bond, A.E., et al., *Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial.* JAMA Neurol, 2017. **74**(12): p. 1412-1418.
4. NHS. *Transcranial magnetic resonance guided focused ultrasound thalamotomy for treatment of medication-refractory essential tremor*. 2021; Available from: https://www.england.nhs.uk/publication/transcranial-magnetic-resonance-guided-focused-ultrasound-thalamotomy-for-treatment-of-medication-refractory-essential-tremor/.
5. NICE. *NICE Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease interventional procedure overview [IP1692]* 2017; Available from: https://www.nice.org.uk/guidance/ipg606/evidence/overview-pdf-4778656525.
6. NICE. *NICE Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in interventional procedures guidance Parkinson's disease [IPG606]* 2018; Available from: https://www.nice.org.uk/guidance/ipg606/chapter/1-Recommendations.
7. Schlesinger, I., et al., *MRI Guided Focused Ultrasound Thalamotomy for Moderate-to-Severe Tremor in Parkinson's Disease.* Parkinsons Dis, 2015. **2015**: p. 219149.
8. Zaaroor, M., et al., *Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases.* J Neurosurg, 2018. **128**(1): p. 202-210.
9. Yamamoto, K., et al., *Focused Ultrasound Thalamotomy for Tremor-dominant Parkinson's Disease: A Prospective 1-year Follow-up Study.* Neurol Med Chir (Tokyo), 2021. **61**(7): p. 414-421.

APPENDICIES

15.1. Appendix 1 – Schedule of Procedures

	VIRTUAL Clinic Pre-Screening	**VISIT 1** Screening Baseline	**VISIT 2** Surgical Consent	**VISIT 3** Treatment (overnight stay)	**VISIT 4*** 6 month follow up
NearMe Video consult	X				
Study informed consent		X			
Surgical consent			X		
Eligibility		X			
Demographics		X			
Medical history		X			
Physical and neurological examination		X			X
Concomitant medication check		X		X	X
Vital signs		X			
UPDRS part III motor exam		X			X
Clinical Rating Scale for Tremor (CRST) on meds		X		X	X
PDQ-39		X			X
IDS		X			
ACE		X			
Neuropsychiatric rating scale		X			
Bloods for LFT (ALT/ALP); FBC (WBC, Hb, platelets); U+E (Urea, Sodium, Potassium); Clotting (prothrombin time, thromboplastin time, PTT,aPTT, INR)			X		
Safety X-ray (if required)		X			
MRI		X		X	X
CT scan		X			
MRgFUS **treatment**				X	
Adverse event review and report			X	X	X

*6 month study visit window: ± 21 days