University of Sheffield | Clinical Trials Research Unit
School of Health & Related Research

TRanscutaneous lImb reCovEry Post-Stroke

TRICEPS Protocol (Redacted version for blinding purposes)

An efficacy and mechanism evaluation of transcutaneous vagal nerve stimulation for upper limb recovery post-stroke – a randomised, controlled, multi-arm, multi-stage, adaptive design trial.

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Sheffield Clinical Trials Research Unit (CTRU)

An efficacy and mechanism evaluation of transcutaneous vagal nerve stimulation for upper limb recovery post-stroke – a
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TRICEPS: TRanscutaneous l**I**mb re**C**ov**E**ry **P**ost-**S**troke

This document describes a clinical trial, and provides information about procedures for entering participants.

Contents

Abbreviations

Definition of terms

ACh	Acetylcholine
ADL	Activities of Daily Living
ADE	Adverse Device Effect
AE	Adverse Event
ARC	Assessment and Rehabilitation Centre
ARSAC	Administration of Radioactive Substances Advisory Committee
ASADE	Anticipated Serious Adverse Device Effect
BDNF	Brain-derived Neurotrophic Factor
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CIs	Confidence Intervals
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CST	Consent Support Tool
CTRU	Clinical Trials Research Unit
DD	Device Deficiency
DPA	Data Protection Act
DMEC	Data Monitoring and Ethics Committee
EDI	Equality, Diversity and Inclusion
EME	Efficacy and Mechanism Evaluation
fMRI	Functional Magnetic Resonance Imaging
GAD-7	General Anxiety Disorder Assessment
GCP	Good Clinical Practice
GLM	General Linear Model
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISDN	Integrated Stroke Delivery Networks
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
LPLV	Last Participant Last Visit
MAS	Modified Ashworth Scale
MCID	Minimum Clinically Important Difference
mITT	Modified intention-to-treat
MRC	Medical Research council
MRI	Magnetic Resonance Imaging
mNIHSS	Modified National Institute of Health Stroke Scale
mRS	Modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NIHSS	National Institute of Health Stroke Scale
NFI-Stroke	Neurological Fatigue Index for stroke
NEADL	Nottingham Extended Activities of Daily Living
PET	Positron Emission Tomography
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per Protocol
RRT	Repetitive Task Training

QoL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SIG	Sheffield Stroke and Aphasia Group
SIV	Site Initiation Visit
SMP	Site Monitoring Plan
SOP	Standard Operating Procedure
SSI	Site Specific Information
SSNAP	Sentinel Stroke National Audit Programme
SS-QOL	Stroke-Specific Quality of Life
SUVR	Standard Uptake Value Ratio
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TVNS	Transcutaneous Vagus Nerve Stimulation
ULFM	Upper Limb Fugl-Meyer
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
VN	Vagus Nerve
VNS	Vagus Nerve Stimulation
WMFT	Wolf Motor Function Test

1. General information

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments

Protocol amendments since version 1.0

Section 7.2 updated to confirm that participants in the Group A (control) will not be offered the opportunity to use the active TVNS device after the trial has ended.

Protocol amendments since version 2.0

Trial Summary and sections 5.1.2, 9.1 and 9.1.4 (Table 2) have been updated to remove the exclusion criteria relating to the ECG and requirement to conduct an ECG at baseline.

Section 1.2 has been corrected to state that participants will be asked about AEs at all treatment review contacts.

Section 6.4 has been updated to state that participants will receive automated text messages every 2 weeks to remind them to complete their rehabilitation therapy.

Section 9 has been updated to state that the baseline, 3-month and 6-month follow-up appointments can take place either in the clinical setting or at the participant's home, if applicable.

Protocol amendments since version 3.0

Trial Summary and section 3.2 have been updated to clarifiy the wording for Hypothesis 2.

Trial Summary and section 5.1 have been updated to clarify that 'Severe spasticity' as an exclusion criteria will be identified, for example, by the ULFM assessment.

Figure 1. updated to clarify that the ULFM score taken at screening will be used for eligibility confirmation and as the baseline score. The two additional outcome measures have also been added.

Figure 2. updated to include the two additional outcome measures.

Section 7 updated to clarify that site will be a stratification factor in the minimisation.

Section 7.1 has been updated to confirm that members of the Data Management team will be unblind to participant allocation.

Section 8.2 clarification of secondary outcomes and how summary measures will be calculated from instruments.

Section 11.1, Table 5 has had a footer added for clarity.

Section 11.2.2, included wording on how ordinal outcomes will be analysed.

Section 11.2.4 the sub-group analysis categories for the mNIHSS have been corrected.

Protocol amendments since version 4.0

Section 6.5 Minor modification to device set-up for participants allocated to groups B & C, as the level of stimulation tolerance is likely to change for participants from day to day.

Section 8.2.2 Ordinal outcomes – Clarification added for assessment of abduction or extension added for each joint.

Section 10 Safety reporting - updated to include definitions, plus the recording and reporting requirements for ADEs, SADEs, USADEs, ASADEs and DDs.

The time-frame for identification of AEs and SAEs has been updated to 'participant randomisation to 6-months', to exclude non-trial related events.

Asking the participant if they have experienced bradyarrhythmia (slow heart rate) or an irregular heartbeat is considered adequate for identification of this Adverse Event.

The requirement to check participant medical notes for evidence of bradyarrhythmia has been removed from the protocol.

Section 11 – point of clarification, stating that reporting of safety events relating to MRI and PET-MRI will be done separately for patients taking part in the mechanistic substudy.

Section 12.3 participants in the mechanistic substudy will be offered structural and functional MRI without FDG PET tracer, if this is not available within an adequate timeframe.

Protocol amendments since version 5.0

An update to terminology throughout, with 'improved motor function' replaced by 'reduced motor impairment'.

Section 1.2 CTRU staff updates

Section 5.1.2 eligibility criteria updated to include information about patients receiving injections of botulinum toxin; and to include pregnancy testing for persons of child bearing potential and the exclusions for this.

Section 5.2 updated to include referrals from non-participating research sites

Section 5.4 updated to include provision for participants with reading difficulties.

Section 6.4 participants may opt out of receiving a reminder text.

Section 6.5 further simplification of device set-up. The requirement to log the lowest intensity perceived and maximum tolerated threshold is removed. Participants will be able to adjust stimulation intensity up to 5mA and they are asked to use the maximum tolerable setting, which may change on a daily basis.

Section 7.1 Trial Manager and Research Assistant will also be unblind to aid operational aspects of the trial.

Section 8.2.1 updated to clarify finger extension at the MCP joints in the MRC muscle strength scale

Section 10.2 updated to include questions about blackouts and episodes of fainting or any falls during and upto 2 hours after using the device.

Section 12.4.2 updated with detail of the serum biomarkers, storage analysis plan. Plasma sample collection will no longer be carried out; serum samples are sufficient and can be processed with more time flexibility.

Trial Summary

Trial title	**TRICEPS: TR**anscutaneous l**I**mb re**C**ov**E**ry Post-**S**troke
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	The National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme.

	Components of the mechanistic sub-study including the PET-MRI scans are funded by the NIHR Sheffield Biomedical Research Centre.
ISRCTN	ISRCTN20221867
Project start date	01/02/2022
Project end date	31/01/2026
Hypothesis, aims and objectives	Aim: To determine whether Transcutaneous Vagus Nerve Stimulation (TVNS) paired with rehabilitation therapy of the affected arm post stroke reduces arm motor impairment in participants with arm weakness following a stroke between 6 months to 10 years previously. Specific primary objectives: 1.) Determine whether non-invasive TVNS paired with self-delivered home rehabilitation therapy of the affected arm post-stroke reduces arm motor impairment at 3 months from the start of treatment compared to self-delivered home rehabilitation therapy alone. *Hypothesis 1: Participants receiving TVNS plus* rehabilitation therapy *for 12 weeks will attain greater motor improvement compared to home rehabilitation therapy alone.* 2.) [Redacted for blinding purposes] *Hypothesis 2: [Redacted for blinding purposes]* Specific Secondary Objectives: 3.) Determine whether the benefits of TVNS and self-delivered home rehabilitation therapy in reducing arm motor impairment observed at 3 months from the start of treatment are sustained. *Hypothesis 3: The beneficial effects of TVNS plus* rehabilitation therapy *will be sustained at 6 months* from the start of treatment. 4.) Determine whether TVNS and self-delivered home rehabilitation therapy improves other outcome measures related to sensory modalities, neurological deficit, quality of life, depression, general anxiety, fatigue, pain, spasticity, strength and activities of daily living.

	Hypothesis 4: TVNS will have a positive effect on other key outcome measures. 5.) Determine the safety of TVNS and self-delivered home rehabilitation therapy for participants. *Hypothesis 5: TVNS and self-delivered home rehabilitation therapy is a safe intervention for participants.* <u>Specific exploratory objective:</u> 6.) In an imaging sub-study, we will determine whether TVNS changes cerebral representation of the affected arm and how they translate to reduced arm motor impairment. *Hypothesis 6: TVNS plus* rehabilitation therapy *improves cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles which may trigger a greater reduction in arm motor impairment compared to* rehabilitation therapy *alone.*
Trial design	Double blinded, randomised, controlled, 3-arm 2-stage adaptive trial design. Participants will be randomised 1:1:1 to one of the three treatment groups. Randomisation ratio will be updated to 1:1 if a treatment is dropped at stage 1.
Internal pilot and interim analysis	There is an internal pilot with a STOP-GO decision following 6 months of recruitment to assess feasibility. The criteria will be based on recruitment and will recommend continuation where recruitment is 80% or higher (n≥36), continuation with changes where recruitment is 60 to <80% (n = 28-35) and cessation if < 60% expected recruitment (n<28). An interim analysis will be performed when 114 participants in total (38 per arm) have accrued Upper Limb Fugl-Meyer (ULFM) outcome data at 3 months from the start of treatment. The trial will stop early if it appears unlikely that the TVNS approach will work. If, on the other hand, there is an indication that TVNS combined with rehabilitation therapy could be beneficial, we will proceed to the next stage and add further participants to reach a definitive answer.
Setting	Approximately 15 UK stroke centres with experience in conducting rehabilitation studies.

Participants	A total of 243 participants (81 per group). <u>Inclusion Criteria:</u> ● Age 18 years or greater, ● Anterior circulation ischaemic stroke between 6 months - 10 years previously, ● Baseline ULFM total motor score 20-50 inclusive indicating moderate to severe arm dysfunction, ● At least 10 degrees of active wrist extension, 10 degrees of active thumb abduction/extension and 10 degrees active extension in at least 2 additional digits based on clinical assessment, ● Able to participate in therapy, provide feedback on adverse events and give appropriate consent based on clinical judgement. <u>Exclusion Criteria:</u> ● Significant other impairment of upper limb e.g., frozen shoulder, ● Severe spasticity (e.g. as identified by the ULFM) ● Health conditions that prevent engagement with physiotherapy e.g., advanced dementia, ● Severe aphasia and either a) informed consent unlikely based on consent support tool b) engagement with repetitive task training (RTT) difficult or c) inability to communicate adverse events from TVNS, ● Currently participating in another interventional stroke rehabilitation trial, ● Pregnant or trying to get pregnant, ● Pacemaker or another implantable electrical device, ● Has a cochlear implant or other similar device, ● Currently receiving therapy or treatment to reduce arm motor impairment and would not be willing to stop for the duration of the trial, ● Has previously experienced a haemorrhagic stroke. For all participants entering the mechanistic sub-study only: ● Contraindications to Magnetic Resonance Imaging (MRI) (e.g., metal implant), ● Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination. Additional criteria for PET-MRI:

	● Contraindications to Positron Emission Tomography (PET) (e.g., has a known allergy to FDG PET tracer), ● Has unstable diabetes.
Intervention & control groups	[Redacted for blinding purposes]
Primary outcome(s)	Primary Outcome Measure: Change in ULFM total motor score at 3 months from baseline (the start of treatment).
Secondary outcome(s)	Secondary Outcomes (each measured at 3- and 6-months from the start of treatment unless stated otherwise): **Continuous outcomes** Compared to baseline, changes in: 1. The ULFM total motor score at 6 months from the start of treatment to assess whether any observed effects at 3 months are sustained in the medium term. 2. Other components of the ULFM outcome (sensation, passive joint motion and joint pain). These assessments provide additional information on the motor impairment of the affected arm. 3. The Wolf Motor Function Test (WMFT) which will provide additional quantification of the motor impairment of the affected arm. 4. The Modified National Institute of Health Stroke Scale (mNIHSS) which is a systematic assessment tool that provides a quantitative measure of total stroke-related neurological deficit. 5. The Nottingham Extended Activities of Daily Living (NEADL) scale which is a tool to assess activities performed. 6. Stroke-Specific Quality-of-Life (SS-QOL) scale, which is a comprehensive measure of multiple effects in poststroke patients (e.g., social and psychological measures) and stroke specific topics (e.g., language, mobility, vision, and upper extremity function). 7. The General Anxiety Disorder Assessment (GAD-7) which is a severity measure for generalised anxiety disorder which causes considerable disability post-stroke. 8. Patient Health Questionnaire (PHQ-9) which is a measure of depression and causes considerable disability post-stroke. 9. The Neurological Fatigue Index for stroke (NFI-Stroke) which measures fatigue

	which is a common and disabling effect of stroke. 10. A Visual Analogue Scale (VAS) will be used to measure pain intensity. 11. The composite Modified Ashworth Scale (MAS) which measures muscle spasticity in the affected arm. 12. The composite Medical Research Council (MRC) Muscle Strength scale which measures muscle strength in the affected arm. **Ordinal outcomes** Outcomes are scores each measurement instrument: 13. The Modified Rankin Scale (mRS) which measures the degree of dependence in the daily activities of people who have had a stroke 14. The Modified Ashworth Scale (MAS) which measures muscle spasticity in the affected arm, scored at three locations. 15. The Medical Research Council (MRC) Muscle Strength scale which measures muscle strength in the affected arm, scored at four locations. **Binary outcome** 16. Whether a participant had experienced a clinically meaningful improvement of 6 points on ULFM total motor score outcome compared to baseline. <u>Safety outcomes</u> Safety will be assessed through recording adverse events (AEs) and serious adverse events (SAEs) experienced throughout the trial. <u>Mechanistic sub-study outcomes</u> MRI scans will be used to explore changes in cerebral blood flow and cortical representations of the affected arm at 3 months from the start of treatment, compared to baseline. PET will be used to explore changes in metabolism at 3 months from the start of treatment.
Duration of recruitment period and first enrolment date	26-month recruitment period, with a 2-month pause for interim analysis. Recruitment is expected to run from October 2023 - January 2025.
Duration of follow-up	There will be a 6-month follow-up period after recruitment ends. The total follow-up period is expected to run from April 2023 – July 2025.

Target sample size	The trial will require 228 participants in total (76 per group with ULFM outcome at 3 months. An interim analysis for treatment selection will be performed when 114 participants in total (38 per group have accrued ULFM outcome at 3 months. This assumes a 1:1:1 allocation ratio, 85% marginal power, and 2.5% one-sided familywise type I error. We expect a 6% dropout rate, so the initial sample size is inflated to 243 participants (81 per group). However, this dropout rate will be re-estimated at an interim analysis and the sample size adjusted accordingly.
Definition of end of trial	The end of the trial is defined as completion of the 6-month follow-up for the last participant (last participant, last visit (LPLV)).

2. Introduction

2.1 Background

Approximately 110,000 people have a stroke in the UK annually, costing the economy over £26 billion in direct and indirect annual costs [1]. Over 1 million people are living with post-stroke disability [1]. The high economic, personal, and social costs of this disability necessitate the need to develop novel treatments to enhance recovery.

Approximately 80% of stroke survivors experience upper limb weakness and, in 30-60%, this persists at 6 months [2]. Persistent arm weakness results in poorer quality of life (QoL), reduced employment, and diminished well-being [3], [4]. There are few effective treatment options available for these patients [5]. The development of new effective treatments to improve upper limb function after stroke is a high research priority for stroke survivors and their caregivers [4]. Arm recovery and function has also been identified by the James Lind Alliance (an alliance of patient's caregivers and clinicians) as a research priority in stroke [4].

Physiotherapy is the mainstay of treatment for post-stroke recovery. Several studies showed that physiotherapy can enhance upper limb recovery, even 6 months after stroke, when there is usually little or no further spontaneous improvement in motor function [5], [6]. Current National Institute for Health and Care Excellence (NICE) guidelines [7] recommend 45 minutes of physiotherapy five days a week to help stroke survivors recover limb function for "as long as they can participate, and where functional goals can be achieved". The basis of rehabilitation therapy and most other evidence-based upper limb interventions (e.g., constraint induced movement therapy, mirror therapy, mental practice, and gaming) is "repetitive task training" (RTT) in which the patient makes repeated movements of the arm directed towards a functional movement [6]. However, a recent Cochrane systematic review concluded that RTT is only partially effective (a standardised effect size of 0.25) [6]. As a result, many stroke survivors have persisting arm weakness following stroke, limiting their ability to self-care, and contributing to the costs to the National Health Service (NHS).

More recently, robot technology for post-stroke rehabilitation has gained considerable attention. Several randomised controlled trials (RCTs) have investigated the effects of

robot-assisted therapy for upper arm treatment [8], [9]. A meta-analysis of these studies indicates a modest benefit, with only small improvements in motor control (~2 points Upper Limb Fugl-Meyer ULFM arm) [8]. Little or no effects were found for upper limb capacity and basic activities of daily living (ADLs). There is therefore an urgent need for additional therapies that will positively impact arm recovery.

The Vagus Nerve (VN) is the tenth cranial nerve which runs from the brain stem to several organs of the body and is an important mediator of the parasympathetic nervous system. Recent studies have shown that it may have several other functions such as neuromodulation and enhancement of brain plasticity [10]. Vagus Nerve Stimulation (VNS) has been successfully used clinically to treat epilepsy and depression for decades [10]. Recently, VNS has also attracted considerable research interest in other diseases including in post-stroke recovery.

Several preclinical studies have shown that stimulation of the VN combined with ***simultaneous*** movement of the weak limb improves motor function of the limb. In rats with experimental stroke, delivery of VNS at the same time as successful "pulls" of a lever to obtain food led to more rapid and complete recovery of the stroke-affected limb. Importantly, VNS alone (without 'pulls' of the affected limb) did not result in improved limb function [11]–[13]. Mechanistic studies showed this was mediated by increased cortical representation for that limb [13]. This data suggests that VNS must be "paired" with the task being practised for the plasticity-inducing effects to occur. The precise mechanisms underlying improved recovery from stroke have not yet been fully elucidated but recent studies in rats and humans suggest that enhanced cerebral plasticity, synaptic connectivity and cortical representation when paired with a stimulus are important mechanisms [14]–[16].

Rodent studies have identified several molecular pathways that may help to explain VNS effects on plasticity. For example, VNS increases levels of brain-derived neurotrophic factor (BDNF), and IL-B, both key regulators of neuroplasticity. VNS also stimulates the release of acetylcholine (ACh) and noradrenaline, which act synergistically to induce plasticity [17]–[21]. In a rat study, the selective obliteration of the cholinergic cortical projections from the Nucleus Basilis completely offset the beneficial effects on limb function seen by pairing VNS with limb movements post-stroke [18]. Thus, the cholinergic system appears to be fundamental in mediating the effects of VNS-induced plasticity, although other pathways may also be involved. However, the precise mechanisms are still not well elucidated. A better understanding of the mechanisms could allow us to identify an imaging biomarker that would predict those that are likely to respond best to therapy. In addition, an understanding of the mechanisms could facilitate personalised, tailored treatment in terms of optimum duration and intensity of therapy.

2.2 Rationale for current trial

In previous literature, as summarised in Section 2.1, VNS requires invasive surgical insertion of the stimulator under general anaesthesia, as well as paired stimulation by a therapist, in hospital. These two requirements will potentially limit the implementation of this therapy in the real world even though the findings are remarkable. There is therefore a clear need for a simple, effective, non-invasive treatment that can be self-delivered by the patient at home.

It is now possible to stimulate the VN non-invasively through the skin using commercially available devices. We therefore propose a non-invasive solution that involves transcutaneous stimulation of the VN through its branch at the ear (TVNS)

[22], [23]. One commercial device, NEMOS (TVNS technologies, Germany), which is CE marked, has a specialised earpiece containing the stimulation electrodes which fit inside the horizontal depression of the outer ear (the "concha") where they stimulate the "auricular branch" of the VN. Studies with functional Magnetic Resonance Imaging (fMRI) have shown that transcutaneous auricular VNS (TVNS) with NEMOS device activates the same central vagal connections as surgically implanted VNS [15]. TVNS has not been evaluated as a means of enhancing limb recovery after stroke in large studies.

In a preliminary non-controlled proof of concept study of 12 participants, we showed that this non-invasive approach for stimulating the VN is feasible and tolerated [23]. Importantly, our study showed that when TVNS was combined with simultaneous rehabilitation of the affected arm (1hr rehabilitation therapy of the weak arm 3X per week for 6 weeks) it resulted in a remarkable 10.1 mean improvement in the ULFM motor score compared to baseline. Moreover, we also found there was an improvement in sensory function [24].

An additional strength of our proposed intervention is the inclusion of a smart wrist band (mbientlab Inc, Germany), which is also CE marked, that will activate the VN stimulator on arm movement. The smart wrist band can also record the frequency and extent of arm movements which will allow monitoring of adherence to the rehabilitation therapy regimen. These two innovations (non-invasive stimulation and activation of the stimulator on arm movement) allow independent delivery of a convenient and acceptable treatment at home without the need for invasive surgery**.** This will potentially benefit patients, caregivers, their families, and the NHS in terms of convenience, improved outcomes and cost savings.

2.3 Research question

Our main research question is:

Does TVNS combined with rehabilitation therapy reduce arm motor impairment in patients following a stroke that occurred between 6 months and 10 years previously?

3. Aims and objectives

3.1 Aim

The trial aims to determine the effects of post-stroke TVNS paired with self-delivered home rehabilitation therapy in reducing arm motor impairment and improving other key clinical outcomes, and to explore its mechanism of action in a multi-centre RCT with internal pilot to assess feasibility of recruitment.

3.2 Objectives and Hypotheses

<u>The primary objectives are to:</u>
1: Determine whether non-invasive TVNS paired with self-delivered home rehabilitation therapy of the affected arm post-stroke reduces arm motor impairment at 3 months from the start of treatment compared to self-delivered home rehabilitation therapy alone (control).

Hypothesis 1: Participants receiving TVNS plus rehabilitation therapy for 12 weeks will attain greater motor improvement compared to rehabilitation therapy alone.

2: [Redacted for blinding purposes]

Hypothesis 2: [Redacted for blinding purposes]

The secondary objectives are to:
3: Determine whether the benefits of TVNS and self-delivered home rehabilitation therapy in reducing arm motor impairment observed at 3 months from the start of treatment are sustained.

Hypothesis 3: The beneficial effects of TVNS plus rehabilitation therapy will be sustained at 6 months.

4: Determine whether TVNS and self-delivered home rehabilitation therapy improves other outcome measures related to sensory modalities, neurological deficit, QoL, depression, general anxiety, fatigue, pain, spasticity, strength and activities of daily living.

Hypothesis 4: TVNS will have a positive effect on other key outcome measures.

5. Determine the safety of TVNS and self-delivered home rehabilitation therapy for participants with arm weakness.

Hypothesis 5: TVNS and self-delivered home rehabilitation therapy is a safe intervention for participants with arm weakness.

Exploratory objective:
6: In an imaging sub-study, we will determine whether TVNS changes cerebral representation of the affected arm and how they translate to reduced arm motor impairment.

Hypothesis 6: TVNS plus rehabilitation therapy *improves cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles which may trigger a greater reduction in arm motor impairment compared to* rehabilitation therapy *alone.*

4. Trial Design

TRICEPS has a double blinded, randomised, controlled, 3-arm 2-stage, adaptive trial design (Figure 1). The trial includes an internal pilot with a STOP-GO decision following 6 months of recruitment to assess feasibility (see Section 8.4). Participants will be randomised 1:1:1 to one of the three treatment groups.

A mechanistic sub-study (see Section 12) will explore whether TVNS with concurrent rehabilitation therapy enhances cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles compared to rehabilitation therapy alone and whether this translates to reduced upper limb impairment.

A total of 243 participants will be randomised to the trial. We have assumed a 6% drop out rate to ensure a total 228 participants complete the primary outcome. Participants will be identified from referrals to stroke services, community stroke teams, and screening of local databases or The Sentinel Stroke National Audit Programme (SSNAP) databases across approximately 15 sites in the UK.

Trial adaptations

Adaptive features will allow a) selection of promising TVNS treatment(s) in stage 1 to progress to stage 2 and b) reassessment of dropout rate and adjust the sample size accordingly. See sample size for trial adaptation decision rules in Section 11.

Figure 1. Trial flowchart [Redacted for blinding purposes]

5. Selection of participants

This section covers the trial population, eligibility criteria, participant identification, consent process, screening procedures, and any other criteria that will affect participation in the trial including co-enrolment to other related trials.

The trial population will be participants who are not currently undergoing active rehabilitation therapy having experienced an anterior circulation ischaemic stroke between 6 months to 10 years previously and still have upper limb weakness.

Participant identification and screening procedures will be designed to identify potential participants who meet the eligibility criteria detailed in Section 5.1.

5.1 Eligibility criteria

5.1.1 Inclusion criteria

- Aged 18 years or greater;
- Anterior circulation ischaemic stroke at least 6 months to10 years previously;
- Baseline ULFM total motor score of 20-50 (inclusive) indicating moderate to severe arm motor impairment;

At least 10 degrees of active wrist extension, 10 degrees of active thumb abduction/extension, and 10 degrees active extension in at least 2 additional digits based on clinical assessment;
Able to participate in rehabilitation therapy, provide feedback on adverse events (AEs), and give appropriate informed consent based on clinical judgement.

5.1.2 Exclusion criteria
Has significant other impairment of upper limb, e.g., frozen shoulder;
Has severe spasticity (e.g. as identified by the ULFM);
Has health conditions that prevent engagement with rehabilitation therapy, e.g., advanced dementia;

- Has severe aphasia and either: a) informed consent unlikely based on the Consent Support Tool (CST) [25], b) engagement with RTT difficult, or c) inability to communicate adverse events from TVNS;
- Currently participating in another interventional stroke rehabilitation trial;
- Pregnant or trying to get pregnant*;
- On a pacemaker or another implantable electrical device;
- Has a cochlear implant or other similar device;
- Is currently receiving therapy or treatment to reduce arm motor impairment and would not be willing to stop for the duration of the trial;
- Has previously experienced a haemorrhagic stroke.
- Has received an injection of botulium toxin in the affected arm within the last 3 months. Note that patients who had an injection in the affected arm over 3 months ago are eligible to take part, but they must be willing to not have further injections for the duration of their participation in the trial (up to having 6-month data collection).

*person of child bearing potential (i.e. fertile following menarche and until becoming post-menopausal, unless permanently sterile) will be asked to perform a pregnancy test to ensure they are not pregnant. Participants will be advised that they must be

willing to use adequate contraception (if appropriate) during the 12-week period of using the TVNS device.

Note: permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.
Where pregnancy cannot be excluded on the basis of the above or is difficult to ascertain then a pregnancy test shall be carried out.

For all participants entering the mechanistic sub-study only:

- Contraindications to Magnetic Resonance Imaging (MRI) (e.g., metal implant);
- Has previously experienced or is likely to suffer severe anxiety or claustrophobia in relation to MR imaging examination.

Additional criteria for PET-MRI:

- Contraindications to Positron Emission Tomography (PET) (e.g., has a known allergy to FDG PET tracer);
- Has unstable diabetes.

A full screening assessment will be conducted when the participant attends for the MRI to ensure the safety of the participant. For persons of child bearing potential this screening will include the result of the pregnancy test* performed in the initial trial eligibility screen. Potential participants will be advised that they must be willing to use adequate contraception (if appropriate) during the overlapping 12-week period of using the TVNS device and the 3 month period between scans.

5.2 Participant identification

Participants will be identified through several possible routes as described below and summarised in Figure 2. The adoption of several routes aims to be inclusive and to identify a diverse population.

1.) Community Stroke Rehabilitation teams (or equivalent)

Sites will approach their community stroke rehabilitation (or equivalent) team leads directly about the trial and disseminate the participant information sheet (PIS) to therapists working with patients at home and who are a). coming to the end of, or no longer undergoing active rehabilitation therapy and b). still have upper limb weakness. Stroke rehabilitation teams will also be asked to identify patients who have previously finished rehabilitation therapy or have not previously had any rehabilitation therapy and still have upper limb weakness.

Potential participants will be provided with an invitation letter and PIS either in person, by email, or post.

2.) The Stroke Association, and relevant local organisations and media

As well as approaching community teams, we will link with the Stroke Association and advertise the trial on their website. We will put up posters about the trial in community care settings, e.g., in Sheffield there is an Assessment and Rehabilitation Centre (ARC) where patients go if they need rehabilitation beyond 6 months after their stroke.

We will also harness the new regional stroke networks (Integrated Stroke Delivery Networks, ISDNs) of which one of our co-applicants, Jessica Redgrave, is currently the clinical lead. There is a national drive to increase numbers of stroke patients recruited into research trials and there is a fortnightly national community rehabilitation and life after stroke meeting which is attended by rehabilitation therapy leads from all 20 ISDNs in the UK.

To improve representation of underserved groups, information sessions will be run by the central research team to advertise and discuss the trial with community groups where possible. As well as widening the potential participant pool this will also build trust between researchers and the local communities (see section 22).

Potential participants will be provided with an invitation letter and PIS either in person, by email, or post.

Where appropriate, local media or social media may be used to support recruitment, this may include the trial poster or leaflet being shared or an advertisement being placed. This advertisement will be based on information from the approved participant information sheet or leaflet. Contact details will be provided so potential participants can contact the research team.

3.) Database searches

In addition, using our experience of successful recruitment in VNSRehab [26] and our pilot TVNS study [23], we will ask sites to consider using available databases to identify potentially suitable participants. The method used for VNSRehab started with a request for SSNAP (routinely collected national audit) records of all stroke patients admitted to the site in the preceding 5 years and who were discharged with remaining neurological deficit. In Sheffield, this initial search resulted in approximately 4000 patients. However, by eliminating the deceased and those who were over the age of 80, 3000 patients remained. A further review of patients' records enabled the research nurse to identify and exclude unlikely participants e.g., those discharged to nursing homes or discharged with very severe stroke (The National Institute of Health Stroke Scale (NIHSS) > 25)[27] and/or co-morbidities such as dementia or advanced malignancy. The patients remaining were then sent information about the trial.

For this trial, potential participants identified through similar database searches will be sent an invitation letter and PIS (either via email or post) along with contact details to enable them to contact the trial team.

4.) Referrals from non-participating stroke care centres

Health care professionals at non-participating research sites may become aware of the trial and wish to refer potentially eligible patients under their care, to the central trial team at the University of Sheffield. Participants will be signposted to their nearest participating research centre.

Accessible versions of the PIS will be available to be sent to potential participants with known aphasia and for whom the clinical research team feel would benefit from this to aid their understanding. Where a potential participant is approached face-to-face the CST [25] may be used to assess the need for an accessible version of the PIS (See section 5.4 for details). The PIS has been produced in line with the Stroke Association Accessible Information Guidelines and aims to help support inclusion of participants with aphasia in research studies.

All potential participants who are approached directly about the trial will be recorded on an anonymised screening form with non-identifiable data. Where potential participants are not interested in the trial, or are ineligible, this will be recorded on the screening form. Where available we will record how the potential participants heard about the trial.

Figure 2. A flowchart identifying the participant flow, from participant identification to outcome measures. [Redacted for blinding purposes]

5.3 Eligibility screening

Upon receiving the PIS, potential participants interested in participating in the trial will be invited to telephone the research team whereupon questions about the trial will be answered and a telephone screening interview will be undertaken to ensure that the participant meets initial eligibility screening. This will include confirming that they have arm weakness following a stroke, whether they have a pacemaker, cochlear implant or other similar devices, and whether they are currently receiving any rehabilitation treatment for their impaired arm or are in a rehabilitation trial. *They will also be given a clear explanation of what participation would involve, including the number of appointments they would be expected to attend and whether they felt they could commit to this.* This explanation will be included at the initial screening stage to ensure that participants are fully aware of the commitment required in an attempt to reduce missed visits and incomplete data at later stages of the trial (see section 5.4).

Sites will also contact potential participants to whom they have provided the PIS to discuss the trial, follow up on their interest and conduct an initial telephone screening interview if appropriate. Potential participants meeting initial telephone screening inclusion criteria and are interested in taking part will be invited to a face-to-face enrolment appointment where informed consent and confirmation of eligibility will take place.

All potential participants who complete the telephone screening interview will be recorded on an anonymised screening form with non-identifiable data. Where potential participants are not interested in the trial, or are ineligible, this will be recorded on the screening form.

5.4 Informed consent process

Written consent will take place face-to-face in a clinical setting by the principal investigator (PI) or other appropriately trained member of the site research team who has been delegated to conduct this activity. Where possible the participant will provide informed consent, have their eligibility confirmed, baseline data for the main trial collected (See Section 12 for details of baseline measures for the mechanistic sub-study) and randomised in the same visit. However, this may be split into separate visits if required, for example if the participant is fatigued (see Figure 2).

For participants with aphasia and for whom the research team are concerned of their ability to adequately understand the standard PIS, the CST [25] may be used to assess eligibility and whether an accessible PIS, and accessible consent form should be used to aid comprehension. The accessible versions of the documents have been produced in line with the Stroke Association Accessible Information Guidelines and aim to help support inclusion of participants with aphasia in research studies.

Support for participants with reading difficulties can be provided e.g. audio recordings of patient information sheets and independent witness signature on the consent form.

We will adopt the approach used in the BEADS feasibility RCT for patients with post-stroke depression [28] to assess the need for accessible documents. The member of the research team obtaining consent will request verbal consent from the potential participant to conduct part A of the CST [25]. If the potential participant understands fewer than two key written or spoken words in a sentence, they would be considered ineligible as it is unlikely that they will be able to understand all the information required

to provide informed consent. If the potential participant understands at least two key written and spoken words, the accessible PIS and consent form should be provided.

The potential participants should be allowed as much time as needed to consider their participation. The potential participants should be informed about the potential risks and benefits of the trial, have the opportunity to discuss the trial with family or friends and be able to ask questions with a suitably trained and qualified member of the clinical or research team.

Potential participants will be made aware, during screening and consent, of the importance of complete data and the impact that missing data has on a trial as recommended by Hussain et al. 2022 [29]. The research team will make it clear to the participant the number of visits they will be asked to attend and the assessments that will be completed during these visits prior to obtaining consent and entering them into the trial. Where a participant expresses concern the research team will talk through these concerns and explain why these assessments and/or visits will take place.

Participation is entirely voluntary and choosing not to participate will not negatively influence the potential participant's treatment in any way. The right of the potential participants to refuse consent without giving reasons will be respected. Furthermore, the participant will remain free to withdraw from the trial at any time without prejudicing any further treatment (See Section 9.4 for further details of withdrawal).

Consent should be considered as part of an ongoing dialogue with the participant and should be re-confirmed verbally at each visit and trial procedure.

A record of the consent process detailing the date of consent and all those present will be recorded in the participants' hospital notes. The original consent form will be filed in the investigator site file, a copy retained in the hospital notes, and a second copy will be given to the participants.

If a participant is unable to initial the consent form due to arm function impairment, then they will be asked to mark the consent form and an independent witness, e.g., a family member or the clinical team not involved in the TRICEPS trial, will verify consent by countersigning the form.

Following consent, the participant's details will be recorded and entered on to the trial database. If consent is refused or if the potential participant is not eligible then the reasons for refusal or ineligibility will be requested (but they do not have to provide this if they do not wish to do so), and basic information will be recorded to enable completion of Consolidated Standards of Reporting Trials (CONSORT) diagram to enhance the interpretation of trial results.

The participants' GP will be informed of their participation in the trial.

5.5 Confirmation of eligibility

Final eligibility assessments will be conducted to confirm eligibility once informed consent has been obtained. This will include the ULFM assessment [22] to determine whether their ULFM score meets the inclusion criteria (20-50 inclusive). The PI or other appropriately trained member of the site research team who has been delegated to conduct this activity will also check and confirm eligibility against the criteria list in Section 5.1. Participants will only be randomised (Section 7) once eligibility and informed consent are confirmed.

5.6 Co-enrolment guidelines

Potential participants should not be enrolled if they are taking part in another trial involving stroke rehabilitation. If local sites are uncertain about whether studies meet this criterion, they should contact the Trial Manager or Chief Investigator (CI).

6. Trial treatment

[Redacted for blinding purposes]

6.4 Rehabilitation therapy

Each participant will be trained by a physiotherapist or occupational therapist (depending on the site) to self-deliver the therapy at home for 1 hour. Training will take place face-to-face in a clinical setting. The therapy will be tailored to the participant's own set of functional impairments but will involve RTT as recommended in NICE guidelines [7] such as turning cards, moving objects, opening, and closing bottles. The aim is for approximately 7 to 10 tasks with 30 to 50 repetitions each to be performed (300-400 task repetitions per session). In our previous related pilot study [23], all participants achieved this number of repetitions. Previous studies have suggested that this number of repetitions is required, as a minimum, to enhance plasticity [30] and is a feasible and acceptable level of intensity for stroke patients in the rehabilitative phase. Sites will be provided with training and a guidance document detailing what the rehabilitation therapy may include, and suggestions for how the exercises could be made more challenging as the participant progresses through the therapy programme, but they will use their own experience and clinical judgement when prescribing the therapy on a case-by-case basis.

A delegated member of the research team will contact the participant throughout the 12-week treatment period. As a part of these contacts, the member of the research team will enquire about any problems the participant is having with their rehabilitation therapy. If applicable, the therapy may be progressed, under the clinical guidance of the therapist (See section 9.1.3). If any problems are identified, the participant may be invited back to the research facility to deal with any problems.

A text message reminder will be sent to participants every 2 weeks reminding them to complete their rehabilitation therapy. Participants may opt out of receiving a reminder text.

6.5 TVNS device

All treatment groups, [Redacted for blinding purposes] will be given a stimulator, earpiece, wrist band, mobile phone and charger. Participants will receive training on how to use the device from a member of the clinical research team (Section 7.1).
Written and video-based training materials will also be provided for them to take home and watch at leisure. A set of "frequently asked questions" will be provided with answers to common queries regarding device usage.

[Redacted for blinding purposes]

The device will measure how long it has been worn for and the number of motion triggered stimulations. These data are stored on the mobile phone provided with the device.

A delegated member of the research team will contact the participant throughout the 12-week treatment period. As a part of these contacts, the member of the research team will enquire about any problems the participant is having with the TVNS device, such as device failure (see Section 9.1.2). If any problems are identified, that cannot be resolved over the phone the participant may be called back to the research facility to deal with any problems and retrain if needed.

We aim to invite the first 10-15 participants recruited in Sheffield, to re-attend their recruiting centre or to visit them in their homes to assess if the device is being used correctly, e.g., that it is being worn correctly and being charged. If any issues with the device are identified during these visits, participants will be retrained. The training provided to future participants may also be updated.
Participants will be provided with contact details for their local research team as well as the central research team and advised to contact a member of either team if they experience any problems with the device.

After the 12-week treatment period, the participant will return the TVNS device to the local or central research team as required. If required, couriering may be organised to retrieve the device from the participant's home address. Once the device is returned, the stimulation history will be downloaded from the mobile phone as a .csv file, deleted from the mobile phone and the device will be cleaned as per infection control procedures. Guidance will be provided to the site in the Researcher Manual and Device SOP.

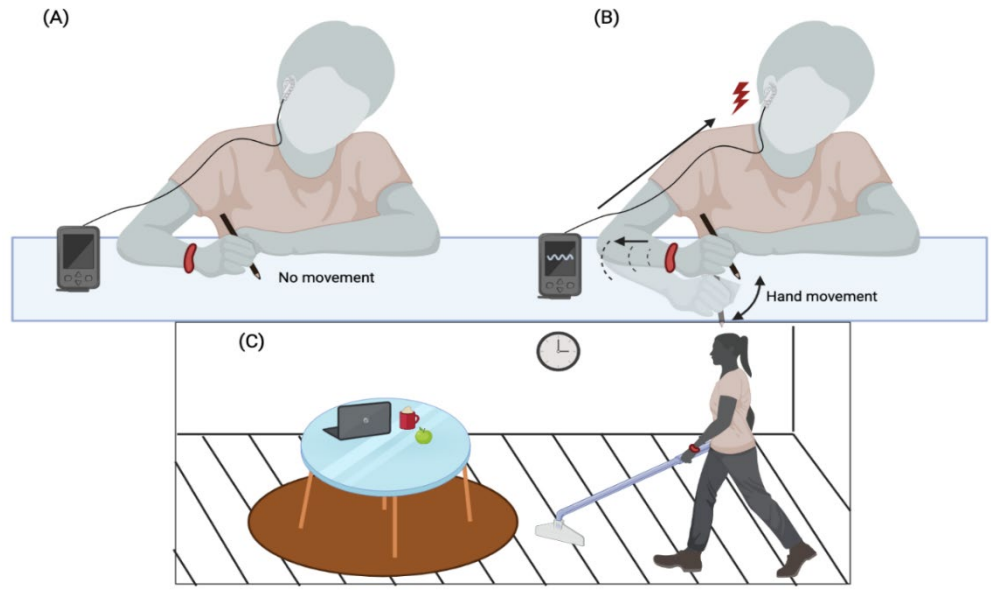

Figure 3. An illustration demonstrating how arm movement would activate TVNS on arm movement during self-delivered home therapy (A) and (B), and during ADLs (C).

6.6 Stopping treatment

Participants or clinicians may choose to stop trial-related treatment at any time, and this will be recorded in the trial database. Participants stopping trial treatment will revert to usual care at that site, but we will continue to obtain follow up data, unless the participant requests complete trial withdrawal.

6.7 Adherence to treatment

Data from the device (including stimulation intensity and the number/duration of motion triggered stimulations) will provide information on adherence to self-delivered home therapy. These data will be recorded on the mobile phone provided with the device and can be reviewed at face-to-face study visits.

7. Randomisation and enrolment

Eligible and consenting participants will be randomised using a centralised, validated, web-based randomisation system (SCRAM) hosted by Sheffield CTRU. This system has user-restricted functionalities that grant access rights to specific areas that are appropriate depending on the roles in the trial. Details of the randomisation are retained within the system.

Participants will be randomised 1:1:1 to one of the treatment groups using minimisation with a masked random probabilistic element to reduce the predictability of treatment allocation while achieving good balance across treatment groups with respect to several prognostic factors at stages 1 and 2 analyses. A prespecified number of initial participants will be randomised using simple randomisation, after this we will minimise with respect to age (≤60, >60 years), baseline ULFM score (20-35, 36-50), and biological sex at birth (male, female), stratified by recruiting site. Randomisation ratio will be updated to 1:1 and minimisation algorithm updated if a treatment is dropped at stage 1. A blinded Trial Statistician within the Sheffield CTRU will log on to the system and set up the randomisation by specifying the required details. These details will be inspected and approved by an unblinded Trial Statistician within Sheffield who is independent of the day-to-day conduct of this trial. Once the details have been approved, the Trial Manager will log on to the system to activate recruitment - at which point the randomisation system will be ready to be used by delegated site research staff to allocate participants.

Following informed consent, delegated research staff at sites will log on to the SCRAM system and enter details to confirm their eligibility and consent as well as minimisation factors.

Participants will be provided with the device as per their allocation and receive training on how to use it. They will also be advised whether they need to use the device whilst completing ADLs. For those participating in the mechanistic sub-study (see Section 12) they will not receive the device until after they have attended for their baseline MRI scan, and PET scan if applicable.

The treatment, depending on their assigned group, will then commence over a 12-week period from the point at which they receive the TVNS device.

7.1 Blinding

Knowledge of treatment assignment may consciously or subconsciously influence change in behaviour of trial participants and investigators which can bias trial results.

Participants who know that they have not received active treatment may be less likely to comply with the research protocol and are more likely to withdraw from the trial. Those aware that they are receiving active treatment may be more likely to provide exaggerated biased assessments of the effectiveness. We cannot also rule out that some participants may psychologically respond positively to active treatment even if the treatment is ineffective due to the placebo effect. Similarly, blinded research investigators may be less likely to focus their attention on participants in the active treatment group and therefore all groups will be given equal attention regardless of allocation.

In view of the above, depending on the site, only the research therapist (or research nurse) who will train participants on use of the TVNS device will be unblinded. The CTRU Data Managers/Trial manager/Research Assistant will also be unblind to aid in operational aspects of the trial. All outcome assessments will be completed by a blinded trial research nurse or therapist. We are using a sham control. The sham control device will be the same as the active device, but the stimulation will be set at the minimum stimulation intensity level.

[Redacted for blinding purposes]

Participant-facing documents will be designed in such a way that potential participants receive enough information to be able to make an informed decision about participation but will not disclose too much about the difference between the treatment groups, in order to preserve blinding.

If a member of the research team is unblinded or suspects that they have been unblinded it will be reported and recorded on the Unblinding CRF.

7.2 Unblinding

The Data Monitoring and Ethics Committee (DMEC) can request unblinded data and recommend trial termination to the Trial Steering Committee (TSC) on the grounds of safety or futility. If there is a medical concern, the PI at each site will be able check allocation if required to inform care.

Participants will be given the opportunity to be unblinded at the end of the trial. This will take place once all data entry and data cleaning has been completed and the final analysis plan has been signed off.

Participants in the [Redcated for blinding purposes] (control group) will not be offered the opportunity to use the active TVNS device after the trial has ended. This is because we do not know whether it provides any therapeutic benefit

8. Outcomes

8.1 Primary outcome

The primary outcome will be a change in ULFM [22] total motor score at 3 months from baseline (the start of treatment) (primary objective 1, Section 3.2). Each item on the ULFM is scored using a three-point ordinal scale (0, 1, or 2). Lower scores are associated with impaired functioning. The ULFM will be assessed by the research therapist or stroke nurse who have been trained in the assessment and delegated the activity.

8.2 Secondary outcomes (3 and 6 months)

8.2.1 Continuous outcomes

Compared to baseline, changes in the following will be measured at 3 and 6 months from the start of treatment, unless stated otherwise, to assess short and long-term effects:

1. The ULFM total motor score at 6 months from the start of treatment to assess whether any observed effects at 3 months are sustained in the medium term (secondary objective 3, Section 3.2).
2. Other components of the ULFM outcome measure (sensation [0-12], passive joint motion [0-24], and joint pain [0-24]) which will provide additional information on the impairment of the affected arm (secondary objective 4, Section 3.2).
3. The Wolf Motor Function Test (WMFT) [31], which will provide additional quantification of the motor function of the affected arm. Both functional ability and performance time will be measured. The WMFT is completed by an assessor and consists of 17 items: 2 items (7 and 14) are strength-based assessed by the weight lifted and grip, respectively, and remaining 15 items are function-based assessed using time to completion. Fifteen of the items are rated on a six-point scale from 0 (does not attempt with upper extremity being tested) through to five (does attempt, movement appears normal). Lower scores indicate a lower level of function. The specific WMFT outcomes relates to:
    a. the mean functional ability score based on the 15 functional ability tasks. This unweghted average score ranges from 0 to 5;
    b. the total time required to complete the 15 functional ability tasks (seconds);
    c. weight lifted as a measure of strength (task 7, lbs);
    d. grip strength (task 14, lbs).
4. The Modified National Institute of Health Stroke Scale (mNIHSS) [27], [32] which is a systematic assessment tool that provides a quantitative measure of total stroke-related neurological deficit. It involves 11 items which are scored on a 2-to-5-point scale, with 0 as normal, and there is an allowance for untestable items. The outcome relates to the mNIHSS total score, which ranges from 0 to 31. Higher scores indicate a more severe neurological deficit (secondary objective 4, Section 3.2).
5. The Nottingham Extended Activities of Daily Living (NEADL) [33] scale which is a tool to assess activities performed and is reported by the patient. It is a 22-item measure with the items covering 4 categories (mobility, kitchen activities, domestic activities and leisure activities). There are four possible responses to each activity (with an assigned score): Not at all (0), With help (0), On my own with difficulty (1) and On my own (1). The outcome relates to the total score ranging from 0 to 22 is calculated by summing the response scores across the 22 items. The higher the score represents greater independence (secondary objective 4, Section 3.2.
6. Stroke-Specific Quality-of-Life (SS-QOL) scale [34], [35]has 12 domains (energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity, vision, and work/productivity) and a total of 49 items across all domains. It is a self-reported measure which will address secondary objective 4 (Section 3.2). Each item is assessed on a 5-point scale (1 to 5) – thus, the total scores range from 49 to 245. The SS-QOL yields both

the overall summary score and domain specific scores. Higher scores are associated with better functioning. The outcomes relates to the:
    a. average overall score of all items across 12 domains (49 items)
    b. domain average scores of items specific to each domain
7. The General Anxiety Disorder (GAD-7) total score (secondary objective 4, Section 3.2). The GAD-7 is a validated severity measure for generalised anxiety disorder [36] which is a contributing cause of considerable disability post-stroke. This is a self-administered patient questionnaire assessing how often patients have been bothered by any of the seven considered problems over the past 2 weeks of assessment. There are four possible ordinal responses to each of the seven problem questions (with an assigned score): “not at all” (0), “several days” (1), “more than half the days” (2), and “nearly every day” (3). A total score ranging from 0 to 21 is calculated by summing the response scores across the seven items. A higher total score indicates a higher degree of severity of generalised anxiety disorder.
8. The Patient Health Questionnaire (PHQ-9) total score (secondary objective 4, Section 3.2). The PHQ-9 is a validated measure of depression [37] which causes considerable disability post-stroke [38]. This is a self-administered patient questionnaire assessing how often patients have been bothered by any of the nine considered problems over the past 2 weeks of assessment. There are four possible ordinal responses to each of the seven problem questions (with an assigned score): “not at all” (0), “several days” (1), “more than half the days” (2), and “nearly every day” (3). A total score ranging from 0 to 27 is calculated by summing the response scores across the nine items. A higher total score indicates more depressive symptoms.
9. The Neurological Fatigue Index for stroke (NFI-Stroke) (secondary objective 4, Section 3.2) which measures fatigue which is a common and disabling effect of stroke [39] The NFI-Stroke is a 12 item self-report measure comprised of a physical and cognitive scale and a 10-item summary scale (items 8 and 10 removed). Higher scores indicate a higher level of fatigue.
10. A Visual Analogue Scale (VAS) will be used to measure pain intensity (secondary objective 4, Section 3.2). It is a single item scale requiring patients to indicate the point on a line which they feel represents their current level of pain. Each end of the line is anchored by terms such as ‘no pain’ and ‘worst imaginable pain’. There is a score range of 0 to 100, the higher the score the greater the pain intensity.
11. The Modified Ashworth Scale (MAS) [41] which measures muscle spasticity in the affected arm (secondary objective 4, Section 3.2). The MAS will be assessed by a trial therapist at three locations (the shoulder, elbow and wrist). A composite score, calculated as a sum of the three MAS measurements taken at the shoulder, elbow and wrist. The total will range from 0 to 12 with lower scores indicating more normal muscle tone.
12. The Medical Research Council Muscle Strength Scale (MRC Muscle Strength Scale) [42], [43] which measures muscle strength in the affected arm (secondary objective 4, Section 3.2). The MRC Muscle Strength scale will be assessed by a trial therapist at four locations (shoulder, elbow, wrist and fingers). A composite score, calculated as the sum of the four MRC Muscle Strength Scale measurements taken at the shoulder, elbow, wrist and fingers. The total will range from 0 to 20 with higher scores indicated more normal muscle power.

8.2.2 Ordinal outcomes

Outcomes are scores each measurement instrument at 3 and 6 months from the start of treatment to assess short and long-term effects:

13. The Modified Rankin Scale (mRS) [40] which measures the degree of dependence in the daily activities of people who have had a stroke (secondary objective 4, Section 3.2). The mRS is a single item scale used to categorise the level of functional independence post-stoke. The score ranges from 0 to 6 with 0 indicating no symptoms, 5 indicating high levels of disability and 6 indicating death.
14. The MAS [41] which measures muscle spasticity in the affected arm (secondary objective 4, Section 3.2). The MAS will be assessed by a trial therapist at three locations (the shoulder, elbow and wrist), each single item ordinal scale ranges from 0 to 4, with 0 indicating normal muscle tone and 4 indicating the limb is rigid.
15. The MRC Muscle Strength Scale [42], [43] which measures muscle strength in the affected arm (secondary objective 4, Section 3.2). The MRC Muscle Strength scale will be assessed by a trial therapist at four locations (shoulder abduction, elbow extension, wrist extension and finger extension at the MCP joints), each single item ordinal scale ranges from 0 to 5, with 0 indicating no contraction in the muscle and 5 indicating normal muscle power.

8.2.3 Binary outcomes

To assess short and long-term effects, the outcome assessed at at 3 and 6 months from the start of treatment will be:

16. Whether a participant had experienced a clinically meaningful improvement of 6 points on ULFM total motor score outcome compared to baseline. This will aid the interpretation of the primary objectives and secondary objective 3 in Section 3.2.

8.3 Safety

To address secondary objective 5 (see Section 3.2) safety will be assessed through recording AEs and serious adverse events (SAEs) experienced throughout the trial. See Section 10 for full details of safety recording procedures.

8.4 Internal pilot feasibility outcomes and assessment criteria

There is an internal pilot with a STOP-GO decision following 6 months of recruitment to assess feasibility of recruitment. The decision criteria will be based on recruitment and will recommend continuation where recruitment is 80% or higher (n≥36), continuation with changes where recruitment is 60% to <80% (n = 28-35) and cessation if < 60% expected recruitment (n<28).

8.5 Mechanistic sub-study outcomes

The mechanism of action of TVNS in humans is not well understood. Our mechanistic study will show whether TVNS with concurrent rehabilitation therapy enhances cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles compared to therapy alone. We will also explore individual differences among good

and poor responders of TVNS, leading to neurobiologically validated stratification criteria (see Section 12 for details).

9. Assessments and procedures

9.1 Trial assessments schedule

Once participants are consented to the trial, screening assessments including general medical history and physical examination will be conducted. If any clinical concerns are identified which may impact on their participation in the trial this should be discussed with the CI and central research team. Baseline measures will then be taken.

The local research team will be provided with training and a Researcher Manual to support collection of these outcomes. See section 8 for further details of each measure. Where possible collection of all baseline and follow up outcome measures will be taken during the face-to-face appointments. Face to face appointments can take place either in the clinical setting or, where applicable, in the participant's home. The following measures **must** be taken in person by a member of the clinical research team: ULFM, WMFT, mNIHSS, MAS and MRC muscle Strength Scale. The remaining measures may be taken over the phone by a member of the clinical research team if required (e.g., the participant becomes fatigued and would struggle to complete all measures during one appointment). The remaining measures have been validated to be conducted over the phone [44]–[49].
Data will be collected at the time points listed below. Follow-up time points should be measured from when the participant receives the TVNS device (the start of treatment). A summary of the data collection time points is provided in Table 2.

9.1.1 Baseline

Baseline data collection will take place face-to face and will include the following:

- ULFM (recorded at eligibility screening),
- WMFT,
- mNIHSS,
- mRS,
- NEADL,
- SS-QOL,
- GAD-7,
- PHQ-9,
- NFI-Stroke,
- VAS
- MAS
- MRC muscle strength scale
- Participant demographics (e.g., age, ethnicity, sex, highest level of education)
- Medical history (including concomitant medication)

Additional data to be collected for those in the mechanistic sub-study only (see section 12):

- Structural and fMRI imaging
- Serum samples
- 18F-FDG PET-MRI (Participants consented and selected for PET scans only)

9.1.2 Treatment Review Contacts

The treating therapist or a delegated member of the research team at each site will aim to conduct video calls with participants throughout the 12-week treatment period. These contacts will focus on 1.) The participant's rehabilitation therapy 2.) Enquire about any problems with the TVNS device, such as equipment failure 3.) Enquire about any AEs. The contact will include checking that participants are undergoing their therapy correctly and, where applicable, progressing their therapy under the clinical guidance of the treating therapist. If any issues are identified with the device or their rehabilitation therapy that cannot be resolved during the call, the participant may be invited back to the research facility to deal with any problems or retrain if needed. The platform of the therapy video calls will be in line with current clinical practice at the recruiting site. If required, the contact can take place face-to-face at the research facility, or over the phone. Approximately 5 contacts should be made. A suggested schedule is summarised in Table 1. The member of the research team conducting the contact should not be the same member of the research team who will be collecting the outcome assessments from participants. This is due to potential unblinding. Participants will also be provided contact details for the research team.

Table 1. Suggested schedule for treatment review video/telephone calls or visit during the 12-week treatment period.

	Week											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** (3-month outcome assessments)
Treatment Review Contact	●		●		●		●		●			

9.1.3 Follow up at 3 months (~91 days)

Participants will be invited for a face-to-face follow up appointment with a research nurse / outcome assessor who is blind to their treatment allocation 3 months after their first day of treatment (the point at which they receive the TVNS device). The appointment can take place in the clinical setting or as a home visit, if applicable There will be a per protocol follow up window of - 5 days or + 14 days (86 - 105 days), however follow up will ideally take place within + 7 days (ideal follow up window 86 - 98 days). Participants will be asked to return the device when they attend this appointment. If there is a delay with their follow up appointment, they will be asked to stop using the device at ~91 days after they were given the device (start of treatment) and where required we will arrange for it to be returned to the research team.

The following data collection will take place at this appointment:

- ULFM,
- WMFT,
- mNIHSS,
- mRS,
- NEADL,
- SS-QOL,
- GAD-7,
- PHQ-9,

- NFI-Stroke
- VAS
- MAS
- MRC muscle strength scale
- Adverse events

Additional data to be collected for those in the mechanistic sub-study only:
- Structural and fMRI imaging
- Serum samples
- 18F-FDG PET-MRI

9.1.4 Follow up at 6 months (~182 days)

Participants will be invited for a face-to-face follow up appointment with a research nurse / outcome assessor who is blind to their treatment allocation 6 months after their first day of treatment (the point at which they receive the TVNS device). The appointment can take place in the clinical setting or as a home visit, if applicable. There will be a per protocol follow up window of - 5 days or + 14 days (177 - 196 days) however follow up will ideally take place within + 7 days (ideal follow up window 86 - 98 days).

The following data collection will take place at this appointment:
- ULFM,
- WMFT,
- mNIHSS,
- mRS,
- NEADL,
- SS-QOL,
- GAD-7,
- PHQ-9,
- NFI-Stroke
- VAS
- MAS
- MRC muscle strength scale
- Adverse events

At the end of the appointment, we will ask participants which group they think they were allocated to.

Table 2. Data collection time points

	Remote screening	Face-to-face enrolment appointment*	Baseline scan^	Treatment review	3 month follow up	6 month follow up
Telephone screening	x	-	-	-	-	-
Eligibility form	-	x	-	-	-	-
Informed consent form	-	x	-	-	-	-
Medical history and examination	-	x	-	-	-	-
ULFM	-	x	-	-	x	x
WMFT	-	x	-	-	x	x

mNIHSS	-	x	-	-	x	x
mRS	-	x	-	-	x	x
NEADL	-	x	-	-	x	x
SS-QOL	-	x	-	-	x	x
GAD-7	-	x	-	-	x	x
PHQ-9	-	x	-	-	x	x
NFI-Stroke	-	x	-	-	x	x
VAS	-	x	-	-	x	x
MAS	-	x	-	-	x	x
MRC muscle strength scale	-	x	-	-	x	x
Randomisation	-	x	-	-	-	-
Adverse events	-	-	-	x	x	X
Participants in the mechanistic sub-study only – all tasks completed in Sheffield						
MRI scan (and PET-MRI if applicable)			x		x	
Blood sample			x		x	
Adverse events			x		x	

*Where possible the face-to-face screening, baseline measurements and randomisation should all take place at the same appointment. However, this can be 2 visits if required.
^Visit only applicable for participants in the mechanistic sub study only.

9.2 Unscheduled visits

If it is identified during contact with the participant (either during treatment review calls or through the participant contacting the research team) that there is a problem with the rehabilitation plan or with using the device, then they will be invited in for an appointment. This appointment will explore the problem and may involve retraining on how to use the device. The research team will collect information on why the appointment took place and what action was taken during the appointment.

9.3 Follow-up after the interim analysis

At the time of an interim analysis it is expected that some participants will still be pending their 3 month follow-up. All participants will be followed up to 6 months regardless of whether an arm is dropped or the trial is stopped early for futility (see Section 11.1).

9.4 Participant withdrawals

Participants may wish to withdraw from trial treatment, or there may be a clinical need to withdraw the participant (e.g., the participant experiences another stroke, or a participant becomes pregnant). Participants who discontinue the treatment/intervention will continue to be followed-up and will remain in the trial, unless they request to be withdrawn as detailed in Section 6.6.

Participants may withdraw their consent for the trial at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and in the patient notes, and no further data will be collected for this participant for the trial. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the participant at the time of consent. Sheffield CTRU Standard Operating Procedure (SOP) ST003 Data Evaluation will be followed and includes

details of how cases should be handled if a participant specifically requests removal of their data from the trial.

Excessive participant withdrawal from follow-up has a negative impact on a study. Recruiting sites will explain the importance of remaining on trial follow-up to participants, and that changes to planned treatment need not imply withdrawal from the trial. Nevertheless, if participants do not wish to remain in the trial their decision must be respected. The related SOP within the Sheffield CTRU on participant discontinuation and withdrawal of consent (SSU003) will be followed.

A participant is defined as having completed the trial when they have completed the 6 month follow up assessments.

9.5 Loss to follow-up

Participants will be defined as lost to follow up if they do not complete the 6-month outcome assessments after all attempts to contact them are utilised. If a participant does not complete earlier follow up assessments (at 3 months) we will still approach at the 6 month follow up time point.

If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

International Council for Harmonisation (ICH) - Good Clinical Practice (GCP) requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Table 3. Adverse Event and Serious Adverse Event information

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. *(Refer to SOP PM017 Adverse Events and Serious Adverse Events for non-CTIMPs or the TRICEPS trial specific SOP for more details)*
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death, ● Is life-threatening*, ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation**, ● Results in persistent or significant disability or incapacity, ● Is a congenital anomaly/birth defect, ● Is otherwise considered medically significant by the investigator***.

Related AE/SAE	An AE or SAE which is related to a research procedure.
Adverse Device Effect (ADE)	An Adverse Event (AE) related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated SADE (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the device instructions for use (IFU) and the trial risk register. NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the device instructions for use (IFU) and the trial risk register. There are no ASADEs in the TRICEPS trial.
Device Deficiency (DD)	Definition of 'Device Deficiency (DD)': Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Identification

AEs and SAEs are defined as an event that occurs after the participant has been randomised and until completion of their 6 month follow up.

Participants will be asked for details of AEs during the treatment review contacts and during follow up appointments at 3 and 6 months. We will specifically ask participants whether they have experienced bradyarrhythmia (slow heart rate) or an irregular heartbeat and whether they have experienced any blackouts or episodes of fainting or any falls during and upto two hours after using the device. These will be recorded as an AE.
AEs and SAEs may also be identified by the research nurse, therapist or any other individual, at any point during the trial (e.g., during a follow-up, during contact with the participant, or during site monitoring).

10.3 Recording and reporting

When an event is identified the process for recording and reporting outlined in Figure 4 will be followed. All AEs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see Section 10.1). Sites are asked to enter all available information onto the trial database as soon as possible after the site becomes aware of the event. Please refer to Section 12.5 for reporting incidental findings from MRI.

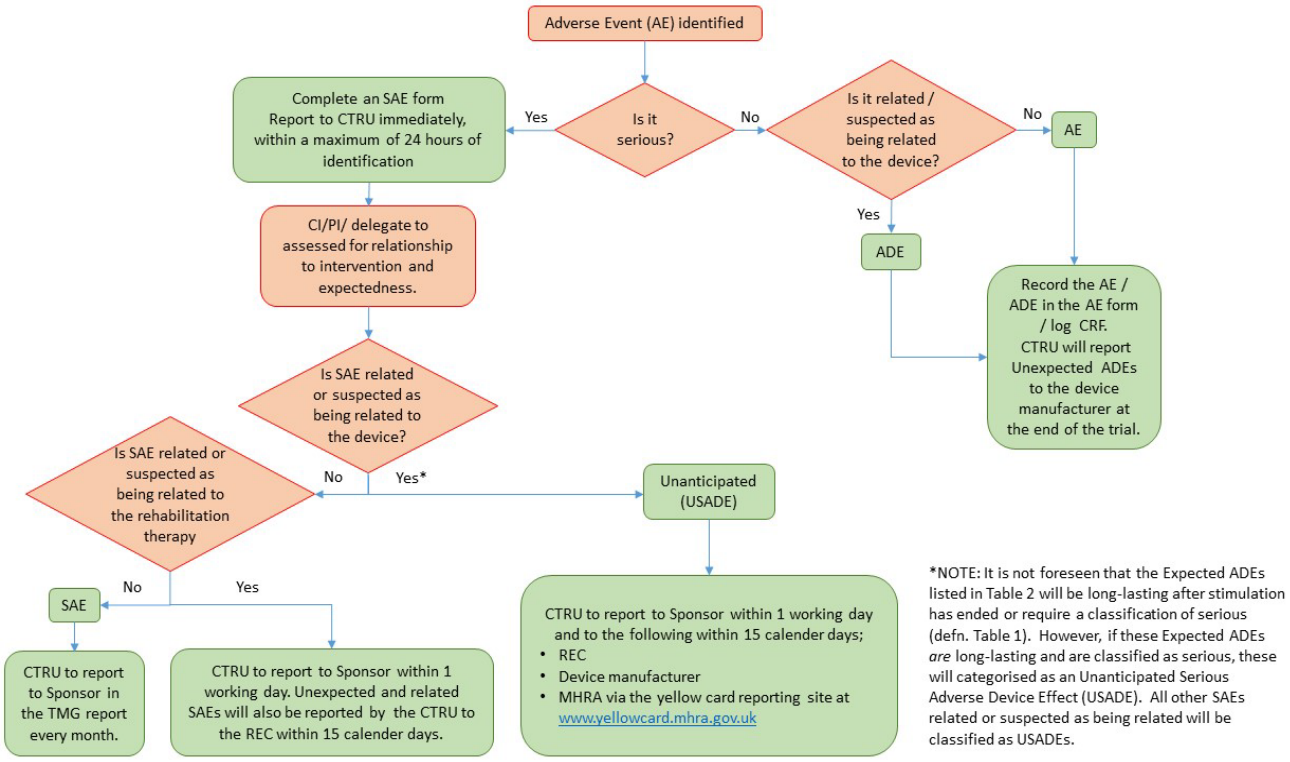

Figure 4. AE and SAE reporting and recording.

10.3.1 Expected AEs

The following AEs / ADEs in Table 4 are defined as expected for the TRICEPS trial.

Table 4. Expected AEs / ADEs.

Main clinical trial (TVNS + rehabilitation therapy)	**Mechanistic Sub-Study (MRI and PET-MRI)** - See section 12 for details
Skin irritation (ADE)	Injury during MR examination related to pacemaker, medical implant or other metallic object (failure of MR safety screening procedures) (AE)
Headache (ADE)	Allergic reaction to the radioactive tracer (AE)
Dizziness (ADE)	

Sore throat (ADE)	
Nausea (ADE)	
Upper limb pain / increased upper limb pain (AE)	

10.3.2 SAEs

All AEs / ADEs classed by the PI or delegate as serious will require more detailed information to be recorded in the participant CRF. In such cases, the event must also be reported to the Sheffield CTRU within one working day of the site becoming aware of the event (see Section 10.4).

SADEs

SADEs are not expected in the TRICEPS trial (see USADEs below).

USADEs

It is not foreseen that the Expected ADEs listed in Table 4 will be long-lasting after TVN stimulation has ended or require a classification of serious, as per the definition in Table 3. Hence ASADEs are not expected to occur in the TRICEPS trial. However, if these Expected ADEs *are* long-lasting and are classified as serious, these will categorised as Unanticipated Serious Adverse Device Effects (USADEs).

All other SAEs will be assessed for causality or 'relationship to the intervention' (TVNS device and rehabilitation therapy or the MRI/PET-MRI). SAEs that are related or suspected as being related to the device will be classified as USADEs.

This assessment should be made by a trained clinician, usually the PI using the following classifications:

- Reasonable possibility of being related
- No reasonable possibility of being related
- Not assessable

If a causality assessment is not provided by the site or causality is recorded as 'not assessable', the CI should review and attempt to make an assessment. If the CI deems the event to be related and unexpected it will be reported to the Research ethics committee (REC) as per the 'Additional reporting requirements for related, unexpected SAEs in line with the HRA SOPs for Research Ethics Committees. USADES will also be reported to the MHRA via the yellow card system and to the Device manufacturer. If the event is not assessable, it will be discussed with oversight committees and monitored for further similar events.

Unexpected Serious Adverse Events

CTRU will report all unexpected SAEs to the sponsor and DMEC. SAEs which are unexpected and related/ suspected to be related to the intervention will be reported further by the CTRU to the REC within 15 working days.

10.4 SAE notification procedure

All SAEs / USADEs should be reported to the CTRU immediately and within one working day from the point of identification. Sites should enter a diagnosis into the reporting form. If a diagnosis is unknown at the time of submission to CTRU, the form may be updated at a later date.

SAE notification procedure

- Details will be recorded on an SAE form (filed in the Investigator site file or downloaded from the AE eCRF page) and sent to the Sheffield CTRU dedicated email address: ctru-saes-group@sheffield.ac.uk
  The email account will be checked during office hours (between 9am and 5pm Monday to Friday).
- Receipt of the initial report will be confirmed within one working day. Sites should contact the trial team at CTRU if confirmation of receipt is not received within one working day.
- In the event that no clinical assessment can be made immediately, it is recommended that the SAE form is sent to the CTRU regardless, and an assessment is obtained as soon as feasible on a new SAE form and forwarded to the CTRU in Sheffield.
- Follow-up or corrections to information should also be reported on a new SAE form and forwarded to the Sheffield CTRU as soon as possible.
- Sheffield CTRU will be responsible for reporting SAEs to the sponsor, the DMEC, and the REC.

If alternative arrangements are required during holiday periods these will be documented in the trial specific AE SOP and CTRU will inform site staff.

10.5 Pregnancy Reporting

All pregnancies in trial participants should be reported to the CI and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. If a participant becomes pregnant during the course of the trial, they will be withdrawn from the trial treatment but will continue to be followed up as per protocol.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the criteria for seriousness, this would be considered an SAE.

Participants who are identified as pregnant during the course of the trial will be followed up by the research team to collect information on the outcome of their pregnancy.

A member of the clinical or research team will attempt to contact the participant around their expected delivery date to enquire about the outcome of the pregnancy (e.g., livebirth, miscarriage) and any congenital abnormailty in the newborn identified before or at delivery.

The DMEC and TSC will be advised at each meeting, of any pregnancies reported since their previous meeting.

10.6 CTRU responsibilities

CTRU will be delegated responsibility, by the Sponsor, for the reporting of SAEs to the REC as appropriate. CTRU will also keep investigators informed of any safety issues that arise during the course of the trial.

10.7 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

This section describes how the sample size was determined with rationale, timing and frequency of interim analyses, decision-rules at interim analysis, operating characteristics of the design, and statistical analysis principles.

11.1 Sample size, operating characteristics and interim decision-making criteria

On average, rehabilitation therapy alone has demonstrated an improvement of around 3 points on the ULFM compared to baseline [6]. An improvement **within a patient** of around 6 points in the ULFM total motor score from baseline is believed to be clinically meaningful as it is associated with beneficial improvement in arm function of greater than 50% [50][51].Therefore, our proposed TNVS treatments would need to demonstrate **an average** improvement of around 3 points ULFM compared to rehabilitation therapy alone to be clinically worthwhile for patients (See Figure 5). Furthermore, this 3-point minimum clinically important difference (MCID) relative to an assumed standard deviation (SD) of 5.5 (0.55 standardised effect size) is realistic and necessary to justify a change in clinical practice [26][50][51].

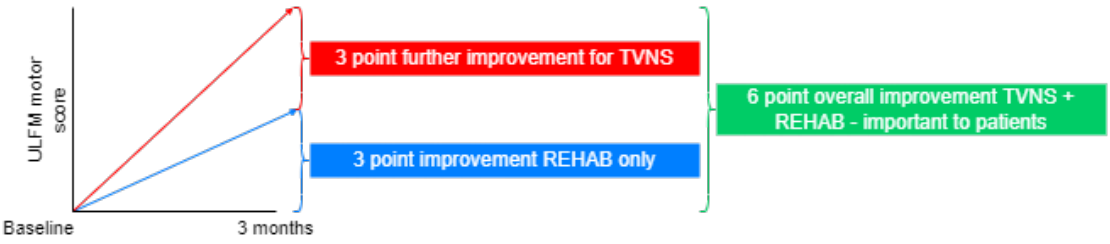

Figure 5. Justification for the 3-point minimum clinically important difference

The trial will require 228 participants in total (76 per group with ULFM outcome at 3 months. An interim analysis for treatment selection will be performed when 114 participants in total (38 per group) have accrued ULFM outcome at 3 months. This assumes a 1:1:1 allocation ratio, 85% marginal power, and 2.5% one-sided familywise type I error [52], [53]. We expect a 6% dropout rate [54] so the initial sample size is inflated to 243 participants (81 per group). However, this dropout rate will be re-estimated at an interim analysis and the sample size adjusted accordingly.

We chose a treatment selection rule to minimise the risks of dropping potentially effective TVNS treatments or selecting ineffective treatments at an interim analysis. A TVNS treatment will be selected to progress to stage 2 if the critical value is greater than 0.792. This corresponds to a 1-point ULFM mean difference in change compared to physiotherapy alone (shared control arm); 0.18 of the expected 5.5 (SD) [23], [24] and one-third of our targeted MCID. Such a small effect observed halfway through the trial will be very unlikely to improve close to or beyond our targeted MCID even if the

treatment is carried forward until the end. Thus, we will drop a treatment at an interim analysis if it fails to demonstrate an effect of more than one-third of the MCID.

Figure 6. An overview of the treatment selection and stopping criteria at interim analysis. * > 0.18 standardised effect size or > 1 point mean difference for an assumed standard deviation of 5.5.[Redacted for blinding purposes]

If no active TVNS treatment is promising at interim analysis (stage1), the trial will terminate for futility with 114 (38 per arm) participants (Figure 6). There is no scope for efficacy early trial stopping at an interim analysis so there is no efficacy stopping boundary.

At the end of the trial (if the maximum sample size is recruited), a treatment will be declared efficacious if the critical value is above 2.176. This has been chosen to guarantee that the chance of incorrectly rejecting at least one null hypothesis is controlled at 2.5% (for one-sided tests) [52]. With this design, a randomly selected participant in any one of the TVNS treatment arms (if effective) should have a 65% probability of showing clinical improvement compared to one selected from the rehabilitation therapy alone (shared control). If both TVNS treatments are efficacious, there is a 95% probability of declaring that one or both are effective. Table 5 presents the statistical characteristics of this design focusing on the chances of making correct and incorrect decisions about the efficacy of treatments at the end of the trial assuming four scenarios based on 10^6 simulations. For example, if both treatments showed an effect of 1-point mean improvement (or critical value of 0.792), there is a 22% chance of declaring that at least one of them is efficacious when in fact the effect is not clinically relevant.
The sample size, operating characteristics and stopping rules were calculated in R [55] using the MAMS package [53], and Stata [56].

Table 5. Operating characteristics of the 3-arm 2-stage design based on 1 000 000 simulations.

[Redacted for blinding purposes]

11.2 Analysis

Statistical Analysis Plans (SAPs) for the interim and final analyses will be written and circulated to the Trial Management Group and independent committees before being signed-off.

11.2.1 Analysis Populations

Modified intention-to-treat population (mITT): all eligible participants that are randomised with informed consent, and who have outcome data, regardless of non-compliance, protocol deviations or withdrawals that occur post-randomisation. Participants will be analysed based on the treatment they were randomised to. This will help us understand the effects of the interventions in participants with outcome data regardless of circumstances after randomisation.

Per-protocol population (PP): comprised of all eligible participants that are randomized with informed consent, received treatment as randomised, adhered to treatment (based on treatment compliance data), and had no major protocol deviations. This will help us to understand the effects of the interventions among those who have complied with the interventions as per trial protocol.

Safety population: comprised of all eligible participants with informed consent. The participants will be analysed based on the treatment they received.

For the purpose of the PP population, compliance will be defined based on the number of sessions completed and minimum duration participants spent with the TVNS duration as follows depending on the arm they were allocated to:

[Redacted for blinding purposes]

Further details of analysis populations will be provided in the SAP.

11.2.2 Statistical Analysis (interim and stage 2 analyses)

Interim and stage 2 efficacy analyses will be based on the mITT population. Sensitivity analyses will be performed for the PP population. Further sensitivity analyses will be performed that will include multiple imputation under different scenarios about missing data, where appropriate. Details about dealing with intercurrent events, such as death, will be given in the SAP. Reporting will adhere to the CONSORT extension for randomised adaptive trials [52].

A 90-day change in ULFM total score (primary and adaptation outcome) will be analysed using a mixed effects linear regression model adjusted for fixed effects covariates (baseline ULFM scores, age, and sex) and site (random effect). Treatment effects will be presented as the adjusted mean differences in change with multiplicity adjusted confidence intervals (CIs) and associated p-values.

At the interim analysis, treatment selection will be based on critical values from pairwise comparisons of each active TVNS treatment versus shared sham control. At the final (stage 2) analysis, a selected active TVNS arm will be declared if the critical value is above 2.17 (rather than the traditional 1.96) to account for treatment selection and multiple testing (see Section 11.2.1). Potential biases that can occur when estimating treatment effects after treatment selection is an ongoing debate in research so this will be explored in the SAP and appropriate methods used to reduce bias if it is viewed as concerning.

Changes in ULFM at 6 months and continuous secondary outcomes at 3 and 6 months (detailed in Section 8) will be analysed using mixed effects linear regression models adjusted for fixed effects covariates (corresponding baseline scores, age, and sex) and site (random effect). Adjusted mean difference in change in these outcomes will be presented with 95% CIs with no adjustment for multiple testing.

For ordinal outcomes, clinical interest is on whether there is a shift in the distribution of scores at follow-up that is attributed to treatment. As such, ordinal outcomes will be analysed using a propotional-odds cumulative logit model (ordinal logistic regression model). The proportion of participants achieving at least 6 points improvement in ULFM total motor score (at 3 and 6 months) compared to baseline will be analysed using a mixed effects logistic regression model adjusted for fixed covariates (baseline ULFM scores, age, and sex) and site (random effect). Adjusted difference in proportions between each TVNS compared to control with associated 95% CIs will be post-estimated via margins.

Analysis of safety events will be done descriptively and also modelled appropriately (where necessary) to account for repeated events per participant and follow-up period (e.g., using a negative binomial regression model).

Reporting of safety events relating to MRI and PET-MRI will be done separately for patients taking part in the mechanistic substudy.

11.2.3 Dealing with pipeline/overrunning participants

At an interim analysis, it is expected that some participants would have been randomised and received treatment but with pending 3 months follow-up. These participants with pending interim data will not be included in the interim analysis. In the event when an arm or trial is stopped early, supplementary analyses will be performed that include all outcome data collected after interim analysis.

11.2.4 Subgroup analyses

Subgroup analyses will be undertaken to explore the effect of important variables related to the participant and their treatment on the primary outcome. These subgroups are:

- Age (≤60 or >60 years)
- Baseline ULFM score (20-35 or 36-50)
- Biological sex at birth (male, female)
- Side of hemiparesis (left or right)
- Time since stroke (<12 months, >12 months)

Baseline mNIHSS score (0-4 = minor, 5-20 = moderate, 21-31 = severe)
In addition, we will explore the impact of the number of sessions of treatment achieved on the effects of the intervention in selected treatment arm(s) compared to the control.

12. Mechanistic sub-study

12.1 Aim

The overall aim of the mechanistic sub-study is to explore whether TVNS with concurrent rehabilitation therapy enhances cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles compared to rehabilitation therapy alone and whether this translates to reduced upper limb motor impairment.

A better understanding of the mechanisms could allow us to identify functional imaging biomarkers that would predict those that are most likely to respond to therapy. In addition, an understanding of the mechanisms could refine future TVNS therapy and facilitate personalised, tailored optimisation of treatment in terms of duration and intensity of therapy.

12.2 Mechanistic outcomes

The mechanism of action of TVNS in humans is not well understood. Our mechanistic study will explore whether TVNS with concurrent rehabilitation therapy enhances cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles compared to therapy alone. We will also explore individual differences among good and poor responders of TVNS, leading to neurobiologically validated stratification criteria.

We will measure changes in cerebral blood flow and cortical representations of the affected arm at 3 months, compared to baseline.

12.3 Recruitment

Participant Identification
Subjects recruited in Sheffield or surrounding sites, and able to travel to Sheffield,[Redacted for blinding purposes] will be approached to undergo a mechanistic study. Participants from Sheffield and nearby centres will be invited for a 60-minute brain scan using the GE MR scanner in Sheffield at baseline and at 3 months (post-treatment). Up to 20 of those participants [Redacted for blinding purposes] will also be asked to have a PET scan at the same visit. This will be done via a PET-MRI scanner. Initial funding has been granted for 17 PET-MRI scans and we will be requesting funds for this to be increased (see section 17 for funding details). The PET scan is optional and is not a requirement to take part in the sub-study. Participants will be approached and consented until the recruitment target for the sub-study is reached.

Eligibility and Consent
Participants who are randomised to [Redacted for blinding purposes] will be provided with a PIS and have the sub-study discussed with them. If they are interested in taking part, they will have their eligibility confirmed by the PI or appropriate member of the research team who has been delegated to do so. This will involve confirming that the participant does not have any contraindications to MRI or PET.

For participants with aphasia (identified by the CST [25]), an accessible consent form may be provided which has been produced in line with the Stroke Association Accessible Information Guidelines.

Following confirmation of eligibility, written informed consent will be obtained from all participants. They will then have an appointment made to attend for the PET/MRI scan. The MRI appointment should take place as soon as possible after the enrolment appointment where baseline measures were obtained. If the appointment is more than 4 weeks from when the enrolment appointment took place, then the baseline measures will need to be repeated and eligibility re-assessed (see Figure 2).

If it is anticipated that either the PET scanning facilities or FDG PET tracer will not be available during an adequate timeframe for the participant's participation in the study, we may offer the participant the option of structural and functional MRI without concurrent FDG PET.

Safety
All participants will undergo further screening when they attend for the MRI to establish safety for MR scanning.

For female participants of a child-bearing age, pregnancy status will be confirmed with a pregnancy test prior to them undergoing the scan / injection of the radioactive tracer. Potential participants will be advised that they must be willing to use adequate contraception (if appropriate) during the 3 month period between scans.

The PET-MRI will be conducted under fasting conditions, participants will be advised to not eat or drink for 6 hours prior to their appointment. When the participant attends for the PET-MRI we will test their blood glucose level, if it is outside of the range 4 to 10mmol/l then they will not be able to have the PET-MRI. They will proceed with the MRI only.

The PET scan will require a single 250MBq administration of 18F FDG, the radiation dose will be 4.8mSv.

PET scans will be subject to prior approval from the Administration of Radioactive Substances Advisory Committee (ARSAC).

Sample size
The sample size for the sub-study is based on feasibility rather than a formal power calculation. A target of 40 participants (20 per group) will be recruited before the interim analysis, the mechanistic sub-study will have a power of ≥ 82% to explore effect sizes of ≥ 0.7 of an SD (any continuous MRI outcomes) for a 10% two-sided test assuming a 0.5 conservative correlation between baseline and 3 months outcome measures. There is no available data to indicate ranges of plausible and expected effect sizes.

12.4 Methods

12.4.1 Neuroimaging

Image acquisition
We will use 18F-FDG-PET to determine glucose metabolism in the brain and multimodal MRI (T1, T2, DTI, FLAIR, ASL, task and resting state fMRI) to assess whether TVNS with concurrent rehabilitation therapy enhances cortical plasticity, cerebral blood flow and brain energy and oxygen metabolic profiles compared to therapy alone. While the subjects are in the PET/MR scanner, they will perform an arm movement task. The task includes six conditions: moving their fingers, wrist, or elbow with either left or right arm following the instructions displayed on the projector screen. The task has 3 blocks; and each block contains approximately 40 movements and 40 resting periods each lasting for a few seconds. Between each movement and resting conditions, there will be a random delay period between 0 and 1000ms to discorrelate adjacent events. Before having the scans, we will ensure participants can undertake the task. This task will be used to map out the representations for fingers, wrists, and elbows for the impaired and unimpaired arms on primary motor cortices.

Image analysis

We will co-reregister PET images with high resolution T1 MRI and compute the standard uptake value ratio (SUVR) values across the cortex. The change of glucose metabolism will be computed by subtracting SUVR between pre- and post-TNVS in each brain regions. Then, we will compare the difference between control and TNVS treatment groups to assess whether TNVS modulates energy metabolism using ANCOVA model controlling for age, sex and other covariates. MRI images will be processed to measure regional brain structure to assess the extent of regeneration neighbouring lesion sites (T1), regional cerebral blood flow (ASL) and connectivity (DTI and resting state fMRI). Task based fMRI will be used to map out the representation of different parts of the arms using standard general linear model (GLM) methods [57]. Like the PET analysis, we will also compare the control and TNVS groups for their changes in different MRI metrics between pre- and post-treatment using the ANCOVA model. We will also graphically explore relationship between changes in imaging metrics with changes in motor scores (ULFM) and use appropriate statistical measures to quantify relationship (e.g., Spearman's rank correlation for linear relationship). We will use standard imaging analysis software including SPM, FSL and FreeSurfer. The image analysis will be exploratory and therefore may be adapted.

12.4.2 Serum samples

We will collect serum samples for all 40 participants at baseline (pre-treatment) and post-intervention (3 months). Written consent will be obtained from the participant for this collection and use. For individuals undergoing a PET scan, the samples will be collected prior to PET-tracer injection. Blood samples will be centrifuged at room temperature within four hours of collection. The serum supernatant will be aspirated, frozen in aliquots (approximately 2mL total) and stored at -70 to -80 degrees Celsius at the Sheffield Institute for Translational Neuroscience, University of Sheffield.

We propose to assess the serum concentration of up to 10 cytokines including Vascular Endothelial Growth Factor (VEGF), Tumour Necrosis Factor (TNF alpha) and Interleukin 6 (IL-6). The full proposed list of cytokines being measured are detailed in Table 6. These biomarkers have been selected based on pre-clinical evidence from rodent models of stroke indicating that they are implicated in invasive VNS or tVNS-mediated improvements in angiogenesis and neurogenesis. Samples from the first 4 participants will be run in triplicate with quality control to check the reliability of the assay for each cytokine. The remainder of the samples will be analysed together at the end of the study. Some of the proposed cytokines may be excluded from the final analysis if the assay is unreliable or if research suggests the additional information gained from an individual cytokine is redundant.

The samples will be analysed using the soluble cytokine quantification service at the Flow Cytometry Core Facility at the University of Sheffield. Changes in serum cytokines over time will be assessed using an appropriate parametric or non-parametric statistical test e.g. a two-way ANOVA to determine the mean difference and 95% confidence interval. Cytokines will be correlated with clinical outcomes at 3 months (including the FMA-UE) using Pearson's correlation coefficient. Significance will be set at $p < 0.05$. There is no available data to indicate ranges of plausible and expected effect sizes for the serum cytokines studies in humans with chronic stroke; as such, a power calculation for this sub-study cannot be performed.

The serum biomarker substudy is funded through the NIHR Sheffield Biomedical

Research Centre.

Inflammation	Interleukin 1 Alpha
	Interleukin 1 Beta
	Interleukin 2
	Interleukin 4
	Interleukin 6
	Interleukin 8
	Interleukin 10
	Tumour Necrosis Factor Alpha
	Interferon Gamma
Angiogenesis	Vascular Endothelial Growth Factor

Table 6 – Proposed list of inflammatory cytokines to be analysed in mechanistic substudy

12.5 Incidental findings

If MRI or PET-MRI identify a clinical concern or medical problem, then this will be reported to the participant's GP along with a copy of the MRI report. It will be the GP's responsibility to take appropriate action.

13. Trial supervision

13.1 Trial Steering Committee

The role of the TSC is to provide supervision of the protocol, and statistical analysis plan (SAP), to provide advice on and monitor the trial, to review information from other sources, consider recommendations from the DMEC and make recommendations on closing the trial prematurely. The TSC will meet at regular intervals, as defined in the TSC terms of reference. The CI, Statistician, CTRU Oversight, Trial Manager, Sponsor Representative will be invited to the TSC, in addition to an independent Chair, and members with clinical expertise, statistical expertise and PPI representation.

13.2 Data Monitoring and Ethics Committee

The DMEC will review reports provided by the CTRU to assess the progress of the trial, the safety data and the critical endpoint data as required. The DMEC will meet at regular intervals, as defined by the DMEC charter. The CI, statistician and Trial Manager will be invited to open DMEC meetings. When necessary, other members (e.g., data manager) may also be invited.

13.3 Trial Management Group

The trial will be supervised on a day-to-day basis by the TMG run in accordance with SOP GOV001 Trial Management Group. This group reports to the TSC. At each participating centre a local PI will report to the TMG via the staff at the Sheffield CTRU.

The core TMG will meet regularly approximately once every two months but rising to at least once per month as required, for example before key milestones (ethical approval, recruitment initiation etc.).

The CI, CTRU Oversight, Trial Manager, Statistician, Data Management, treating therapists, Sponsor Representative and co-applicants (including a PPI representative) will be invited to the meetings.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) 2018 will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield CTRU who adhere to their own SOPs relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the trial in accordance with SOP (SOP DM009 Data Management Plan).

Trial participants will be assigned a unique study ID number at screening to identify them throughout the trial, and to link all of their clinical information recorded on the trial database and on any paper CRFs, as well as any correspondence between CTRU and participating centres about them.

Data will be entered onto the trial database. The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant trial information regarding each participant. The trial manual provided to all sites to support trial procedures and documentation will provide further information on the requirements of source data.

Trial records will be stored for 15 years after the completion of the trial before being destroyed.

14.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving SOP Procedure (SOP PM012 Archiving). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

15. Data access and quality assurance

The trial database will reside on Prospect, Sheffield CTRU's in-house data management system. Prospect uses industry standard techniques to provide security, including password hashing and encryption of data transmission using SSL/TLS. Access to the system is controlled by usernames and passwords, and comprehensive privilege management ensures that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

A member of staff at each site will enter data from source documents into the trial specific Prospect database when available. Validation rules will be defined within

Prospect, and automated validation reports will regularly check the data against these rules: discrepancies will be generated for site and central staff to look into. Discrepancies will be tracked and resolved within the system. All data entries and corrections are logged within the electronic audit trail.

Participant names and contact details will be collected and entered on the database in order to facilitate follow-up data collection. Access to these personal details will be restricted to users with appropriate privileges and will not be included in the data exported from the database for analysis.
Participating investigators shall agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the Centre in which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation with each site, which may be carried out face-to-face or remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU SOPs.

Central monitoring and site monitoring will be undertaken at a level appropriate to the detailed risk assessment and will be documented in the Site Monitoring Plan (SMP).

15.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial or the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC in writing within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware in-line with SOP PM011 Protocol and GCP Non-Compliances & Serious Breaches.

15.4 Site monitoring

On-site and/or remote monitoring will be performed according to the SMP and in line with the Sheffield CTRU Site Monitoring SOP.

Regular monitoring of sites will occur throughout the trial as specified in the SMP and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the participant are being protected and
3. Trial is conducted in accordance with the approved protocol and trial agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Trial Monitor. The Trial Monitor will inspect CRFs (either on site or remotely) throughout the trial, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs. A remote review of a sample of consent forms will also be completed, and sites will be requested to send consent forms securely to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

A close-out visit (on-site or remote) will be performed after the LPLV at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

CTRU staff will also complete central monitoring which will include a review of entered data for possible errors and missing data points.

16. Publication

Results of the trial will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the trial will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

TRICEPS is funded by the NIHR Efficacy and Mechanism Evaluation (EME) programme (project number: NIHR133169), with details drawn up in a separate agreement. The views expressed are those of the author(s) and not necessarily those of NIHR or the Department of Health and Social Care. Components of the mechanistic sub-study including the PET-MRI scans are funded by the NIHR Sheffield Biomedical Research Centre.

18. Ethics approval & regulatory compliance

Before initiation of the trial at participating sites, the protocol, informed consent forms and information materials to be given to the participants will be submitted to an NHS REC and to the Health Research Authority (HRA). Any further amendments will be submitted and approved by the HRA and REC as relevant.

The trial will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place. CTRU SOP RA003 Ethical and Regulatory Approvals will be followed.

Important protocol modifications (e.g., changes to eligibility criteria, outcomes and analyses) will be communicated to relevant parties including funders, investigators, REC, HRA, and trial registries.

The trial will be conducted in accordance with this protocol and ICH GCP.

19. Sponsor and site approval

Before initiation of the trial at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of trial participants will not commence at a site until a letter of
of Confirmation of Capacity and Capability (CCC) has been issued, a Site Initiation Visit (SIV) has taken place and access given to site staff for the database. Green light provision has been delegated to CTRU by the sponsor.

20. Trial Organisation and Responsibilities

20.1 Principal Investigators

Each site will have a local PI who will be delegated responsibility for the conduct of research at their centre and must sign the delegation log to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in trial procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

20.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.
The CTRU Trial Manager will be responsible for supplying investigator site files to each collaborating centre after relevant REC approval and local R&D CCC has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the SMP and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient & Public Involvement (PPI)

The trial's PPI members will be involved in aspects of the trial design, management, analysis, and dissemination.

During the outline and full stages of the grant application for this trial, patients who have suffered a stroke were asked for their input/comments. Stroke survivors identified arm rehabilitation as a research priority.

This trial includes input from the Sheffield Stroke and Aphasia Group (SIG), comprised of members who have either suffered a stroke or have had their lives affected by a stroke. The SIG have previously assisted with the initial protocol of pairing upper limb activities and TVNS and provided qualitative feedback during the pilot study. SIG members also tested the TVNS device prior to recruitment commencing. This feedback has been used to refine the methodologies used within TRICEPS.

PPI members will be invited to TMG meetings and TSC meetings where they will be given the opportunity to discuss the trial and ask any questions. PPI meetings will also be held bi-monthly. Our published results in peer-reviewed journals will inform stroke rehabilitation guidelines.

22. Equality, Diversity and Inclusion (EDI)

A number of steps will be taken to ensure Equality, Diversity and Inclusion (EDI) throughout the trial.

We will collect screening data to monitor recruitment and report the baseline characteristics to the oversight groups at meetings. We will work with sites to improve representation as necessary. We will include training on EDI in our site set-up visits and encourage completion of the NIHR training on cultural competency, EDI and the INCLUDE project. We will also request consent to record the ethnicity of the recruiter as part of an assessment into the potential influence of recruiter characteristics

The PIS and recruitment video will be translated into other languages which will be determined during site assessment depending on need. Interpreter services will also be utilised where necessary. We also have accessible versions of the participant facing documents, including the consent form and PIS available for participants with aphasia. These documents have been produced in line with the Stroke Association Accessible Guidelines. A member of the clinical research team may use the CST [25] to assess if an accessible document is required. Posters and leaflets have been made to introduce the study in a clear and accessible way

To improve representation of underserved groups, information sessions will be run to advertise and discuss the trial with community groups where possible. As well as widening the potential participant pool this will also build trust between researchers and the local communities.

23. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical trial.

Standard NHS indemnity operates in respect of the clinical treatment that is provided.

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