

# A trial investigating the effectiveness of vagus nerve stimulation during rehabilitation therapy in patients with a weak arm following a stroke

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|--------------------------|-----------------------------|---|
| <b>Submission date</b>   | <b>Recruitment status</b>   | <input checked="" type="checkbox"/> Prospectively registered    |
| 03/11/2022               | Recruiting                  | <input checked="" type="checkbox"/> Protocol                    |
| <b>Registration date</b> | <b>Overall study status</b> | <input type="checkbox"/> Statistical analysis plan              |
| 07/12/2022               | Ongoing                     | <input type="checkbox"/> Results                                |
| <b>Last Edited</b>       | <b>Condition category</b>   | <input type="checkbox"/> Individual participant data            |
| 20/01/2026               | Circulatory System          | <input checked="" type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Over 15 million people suffer a stroke worldwide annually. One third are left with arm weakness causing difficulties with daily activities. Whilst rehabilitation therapy does help after stroke, the benefits are modest. In a recent trial, stimulating the vagus nerve (VN) while the participant moved their weak arm resulted in better arm recovery compared with therapy alone. However, the stimulator was surgically implanted, and the VNS was triggered by a therapist in hospital. In this study the VN will be stimulated in a non-invasive way at home. The VN will be stimulated through the skin via an earpiece using a TVNS device. This study aims to determine whether transcutaneous vagus nerve stimulation (TVNS) paired with rehabilitation therapy of the affected arm after stroke improves motor function in participants with arm weakness following a stroke. In a sub-study, the researchers will also assess if TVNS produces changes in the brain via fMRI and, in some cases, PET scans.

### Who can participate?

Patients aged 18 years and over who have arm weakness following a stroke between 6 months to 10 years ago and are no longer undergoing active rehabilitation therapy

### What does the study involve?

Participants will be randomly allocated to receive either sham TVNS (very low stimulation) or active TVNS. Some participants will also be asked to wear the TVNS device whilst undertaking activities of daily living. Participants will wear the TVNS device when completing the self-delivered rehabilitation therapy for 1 hour per day, 5 days per week for 12 weeks. The rehabilitation therapy plan will be tailored to each participant, completed at home, and includes repetitive tasks such as turning cards, moving objects, opening, and closing bottles. Participants will be followed up at a face-to-face appointment at 3 and 6 months after starting treatment. The follow-up appointments enable outcome assessments of the intervention.

### What are the possible benefits and risks of participating?

By taking part in this study, participants will be directly helping to inform the future evidence base of interventions for people with arm weakness after stroke. Participants will be given a

tailored 12-week rehabilitation therapy programme to do at home and a TVNS device to use for the duration. This may be of benefit to some participants who may not be receiving any other therapy for their arm weakness. The TVNS device is usually well tolerated but previous studies have found some side effects. These are mild skin irritation (in 15% of cases), headaches (less than 5% of cases), dizziness, sore throat and nausea (all in less than 2% of cases). The nerve that is stimulated in this study can affect the heart rhythm but there has been lots of research using this device in humans with no concerns about the safety of the participants. Some participants may find participation in the trial time-consuming as it will require attendance at a minimum of three face-to-face appointments, in addition to the 12-week treatment period completed at home.

Where is the study run from?

About 15 stroke centres across the UK will be taking part in the study and it will be managed by the Clinical Trials Research Unit at the University of Sheffield (UK)

When is the study starting and how long is it expected to run for?

February 2022 to January 2027

Who is funding the study?

National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?

Kirsty McKendrick, [kirsty.mckendrick@sheffield.ac.uk](mailto:kirsty.mckendrick@sheffield.ac.uk), [triceps@sheffield.ac.uk](mailto:triceps@sheffield.ac.uk)

## Contact information

**Type(s)**

Scientific

**Contact name**

Miss Kirsty McKendrick

**Contact details**

Clinical Trials Research Unit

ScHARR

The University of Sheffield

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## Additional identifiers

**Clinical Trials Information System (CTIS)**

Nil known

**Integrated Research Application System (IRAS)**

308254

**ClinicalTrials.gov (NCT)**

Nil known

**Central Portfolio Management System (CPMS)**

53862

## Study information

### Scientific Title

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

### Acronym

TRICEPS

### Study objectives

Primary hypotheses:

Hypothesis 1: Participants receiving transcutaneous vagal nerve stimulation (TVNS) plus rehabilitation therapy for 12 weeks will attain greater motor improvement compared to home rehabilitation therapy alone.

Hypothesis 2: Participants who receive TVNS while undertaking activities of daily living in addition to TVNS during rehabilitation therapy for 12 weeks will attain even greater benefit.

Secondary objectives:

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

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

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

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

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Approved 12/10/2022, East of England - Cambridge Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8286; cambridgecentral.rec@hra.nhs.uk), ref: 22/EE/0209

### Study design

Randomized; Interventional; Design type: Treatment, Device, Imaging, Rehabilitation

### Primary study design

Interventional

### Study type(s)

Treatment

## **Health condition(s) or problem(s) studied**

Stroke

## **Interventions**

Participants will be allocated to receive TVNS plus self-delivered rehabilitation therapy for 1 hour, 5 times a week for 12 weeks, or sham TVNS (the earpiece will produce negligible stimulation) plus self-delivered rehabilitation therapy for 1 hour, 5 times a week for 12 weeks. Some participants may also be asked to wear the device whilst doing activities of daily living for 1 to 8 hours on the therapy days.

## **Intervention Type**

Device

## **Phase**

Not Applicable

## **Drug/device/biological/vaccine name(s)**

Not provided at time of registration

## **Primary outcome(s)**

Upper limb motor function assessed using the Upper Limb Fugl-Meyer (ULFM) total motor score at 3 months from the start of treatment

## **Key secondary outcome(s)**

Measured at baseline, 3 and 6 months from the start of treatment, unless stated otherwise:

1. Upper limb motor function assessed using the ULMF total motor score at 6 months from the start of treatment
2. Sensation, joint range of motion and joint pain assessed using other components of the ULMF outcome measure
3. Motor function of the affected arm assessed using the Wolf Motor Function Test (WMFT)
4. Total stroke-related neurological deficit measured using the Modified National Institute of Health Stroke Scale (mNIHSS)
5. The degree of dependence in the daily activities of people who have had a stroke, measured using the Modified Rankin Scale (mRS)
6. Activities of daily living assessed using the Nottingham Extended Activities of Daily Living (NEADL) scale
7. Stroke-specific quality of life measured using the Stroke-Specific Quality-of-Life (SS-QOL) scale
8. Generalised anxiety disorder assessed using the General Anxiety Disorder (GAD-7) total score
9. Depression assessed using the Patient Health Questionnaire (PHQ-9) total score
10. Fatigue assessed using the Neurological Fatigue Index for stroke (NFI-Stroke)
11. Pain intensity measured using a Visual Analogue Scale (VAS)
12. Whether a participant had experienced a clinically meaningful improvement of 6 points on ULMF total motor score outcome compared to baseline

## **Completion date**

31/12/2027

## **Eligibility**

### **Key inclusion criteria**

1. Aged 18 years or greater
2. Anterior circulation ischaemic stroke between 6 months and 10 years previously
3. Baseline ULFM of 20-50 (inclusive) indicating moderate to severe arm dysfunction
4. At least 10 degrees of active wrist extension, 10 degrees of active thumb abduction /extension, and 10 degrees of active extension in at least 2 additional digits
5. Able to participate in rehabilitation therapy, provide feedback on adverse events (AEs), and give appropriate informed consent based on clinical judgment

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Mixed

**Lower age limit**

18 years

**Upper age limit**

100 years

**Sex**

All

**Total final enrolment**

0

**Key exclusion criteria**

1. Has significant other impairment of upper limb, e.g., frozen shoulder
2. Has severe spasticity (Modified Ashworth score of  $\geq 3$ )
3. Has health conditions that prevent engagement with rehabilitation therapy, e.g., advanced dementia
4. Has severe aphasia and either: a) informed consent unlikely based on consent support tool, b) engagement with RTT difficult, or c) inability to communicate adverse events from TVNS
5. Currently participating in another stroke rehabilitation trial
6. Pregnant or trying to get pregnant
7. On a pacemaker or another implantable electrical device
8. Has a cochlear implant or other similar device
9. Currently receiving therapy or treatment to improve arm function and would not be willing to stop for the duration of the trial
10. Has previously experienced a haemorrhagic stroke

For all participants entering the mechanistic sub-study only:

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

Additional criteria for PET-MRI:

1. Contraindications to Positron Emission Tomography (PET) (e.g., has a known allergy to FDG

PET tracer)

2. Has unstable diabetes

A full screening assessment will be conducted when the participant attends for the MRI to ensure the safety of the participant.

**Date of first enrolment**

01/10/2023

**Date of final enrolment**

31/07/2026

## Locations

**Countries of recruitment**

United Kingdom

England

Wales

**Study participating centre**

**Royal Hallamshire Hospital**

Glossop Road

Sheffield

England

S10 2JF

**Study participating centre**

**John Radcliffe Hospital**

Headley Way

Headington

Oxford

England

OX3 9DU

**Study participating centre**

**Pulross Community Centre**

47a Pulross Road

Stockwell

London

England

SW9 8AE

**Study participating centre**  
**Melbourne Centre Surgery**  
Swithland House  
352 London Road  
Leicester  
England  
LE2 2PL

**Study participating centre**  
**Doncaster Royal Infirmary**  
Armthorpe Road  
Doncaster  
England  
DN2 5LT

**Study participating centre**  
**Montagu Hospital**  
Adwick Road  
Mexborough  
England  
S64 0AZ

**Study participating centre**  
**Bodmin Hospital**  
Boundary Road  
Bodmin  
England  
PL31 2QT

**Study participating centre**  
**Heart of Hounslow Centre for Health**  
92 Bath Road  
Hounslow  
England  
TW3 3EL

**Study participating centre**  
**St Mary's Hospital**  
Green Hill Road  
Leeds

England  
LS12 3QE

**Study participating centre**

**Aintree Hospital**  
Therapies Department  
Lower Lane  
Fazakerley  
England  
L9 7AL

**Study participating centre**

**Moseley Hall Hospital**  
Alcester Road  
Moseley  
Birmingham  
England  
B13 8JL

**Study participating centre**

**St Lukes Hospital**  
Little Horton Lane  
Bradford  
England  
BD5 0NA

**Study participating centre**

**West Pottergate Medical Practice**  
Earlham Road  
Norwich  
England  
NR2 4BX

**Study participating centre**

**Sunderland Royal Hospital**  
Kayll Road  
Sunderland  
England  
SR4 7TP

**Study participating centre**  
**University Hospital Llandough**  
Penlan Road  
Llandough  
Penarth  
Wales  
CF64 2XX

**Study participating centre**  
**Royal London Hospital**  
HASU (Hyper Acute Stroke Unit)  
Ward 11C Research Office  
Whitechapel Road  
Whitechapel  
London  
England  
E1 1FR

**Study participating centre**  
**Royal Bournemouth General Hospital**  
Castle Lane East  
Bournemouth  
England  
BH7 7DW

**Study participating centre**  
**Yeatman Hospital**  
Hospital Lane  
Sherborne  
England  
DT9 3JU

**Study participating centre**  
**South Petherton Community Hospital**  
Bernard Way  
South Petherton  
England  
TA13 5EF

**Study participating centre**

**Royal Hallamshire Hospital**  
Glossop Road  
Sheffield  
England  
S10 2JF

**Study participating centre**

**Royal Bolton Hospital**  
Minerva Road  
Farnworth  
Bolton  
England  
BL4 0JR

## Sponsor information

**Organisation**

Sheffield Teaching Hospitals NHS Foundation Trust

**ROR**

<https://ror.org/018hjpz25>

## Funder(s)

**Funder type**

Government

**Funder Name**

National Institute for Health and Care Research

**Alternative Name(s)**

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

**Funder Name**

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR133169

## Results and Publications

### Individual participant data (IPD) sharing plan

Requests for patient level data and statistical code should be made to the corresponding author and will be considered by members of the original trial management group, including the chief investigator and members of CTRU, who will release data on a case by case basis. Data will be shared following the principles for sharing patient level data as described by Smith et al (2015) [1]. The data will not contain any direct identifiers, we will minimise indirect identifiers and remove free text data, to minimise the risk of identification.

### IPD sharing plan summary

Available on request

### Study outputs

| Output type                                   | Details                       | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|-------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Protocol article</a>              |                               | 26/03/2025   | 22/09/2025 | Yes            | No              |
| <a href="#">HRA research summary</a>          |                               |              | 28/06/2023 | No             | No              |
| <a href="#">Participant information sheet</a> | Participant information sheet | 11/11/2025   | 11/11/2025 | No             | Yes             |
| <a href="#">Study website</a>                 | Study website                 | 11/11/2025   | 11/11/2025 | No             | Yes             |