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

Submission date
03/11/2022

Recruitment status
Recruiting

Registration date
07/12/2022

Overall study status
Ongoing

Last Edited
07/03/2025

Condition category
Circulatory System

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] 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 2026

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, triceps@sheffield.ac.uk

Study website
http://www.triceps-trial.com/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
308254

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 53862, IRAS 308254

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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

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

Secondary outcome measures
Measured at baseline, 3 and 6 months from the start of treatment, unless stated otherwise:
1. Upper limb motor function assessed using the ULFM 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 ULFM 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 ULFM total motor score outcome compared to baseline

Overall study start date
01/02/2022

Completion date
31/01/2026

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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 243; UK Sample Size: 243

Key exclusion criteria
1. Has significant other impairment of upper limb, e.g., frozen shoulder
2. Has severe spasticity (Modified Ashworth score of ≥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
31/07/2025

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Pulross Community Centre
47a Pulross Road
Stockwell
London
United Kingdom
SW9 8AE

Study participating centre
Brownley Green Health Centre
171 Brownley Road
Wythenshawe
Manchester
United Kingdom
M22 9UH

Study participating centre
Northenden Health Centre
489 Palatine Road
Northenden
Manchester
United Kingdom
M22 4DH

Study participating centre
Melbourne Centre Surgery
Swithland House
352 London Road
Leicester
United Kingdom
LE2 2PL

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre

Montagu Hospital
Adwick Road
Mexborough
United Kingdom
S64 0AZ

Study participating centre
Bodmin Hospital
Boundary Road
Bodmin
United Kingdom
PL31 2QT

Study participating centre
Heart of Hounslow Centre for Health
92 Bath Road
Hounslow
United Kingdom
TW3 3EL

Study participating centre
St Mary's Hospital
Green Hill Road
Leeds
United Kingdom
LS12 3QE

Study participating centre
Aintree Hospital
Therapies Department
Lower Lane
Fazakerley
United Kingdom
L9 7AL

Study participating centre
Moseley Hall Hospital
Alcester Road
Moseley

Birmingham
United Kingdom
B13 8JL

Study participating centre
St Lukes Hospital
Little Horton Lane
Bradford
United Kingdom
BD5 0NA

Study participating centre
West Pottergate Medical Practice
Earlham Road
Norwich
United Kingdom
NR2 4BX

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
University Hospital Llandough
Penlan Road
Llandough
Penarth
United Kingdom
CF64 2XX

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

London
United Kingdom
E1 1FR

Study participating centre
Royal Bournemouth General Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Yeatman Hospital
Hospital Lane
Sherborne
United Kingdom
DT9 3JU

Study participating centre
King's College Hospital
Stroke Research Office
Academic Neuroscience Centre
Ruskin Wing
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
South Petherton Community Hospital
Bernard Way
South Petherton
United Kingdom
TA13 5EF

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor details
Northern General Hospital
Herries Road
Sheffield
England
United Kingdom
S5 7AU
+44 (0)114 226 5941
dipak.patel12@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.sth.nhs.uk/

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

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/07/2026

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, Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No