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# Paired vagus nerve stimulation for improved upper limb function after stroke

**Submission date**
14/08/2017

**Recruitment status**
No longer recruiting

**Registration date**
16/08/2017

**Overall study status**
Completed

**Last Edited**
02/08/2021

**Condition category**
Circulatory System

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

## Plain English summary of protocol

Background and study aims
This is a study of a new device which aims to treat weakness of the hand and arm in people who have suffered a stroke. The device is made by a company called MicroTransponder, Inc which sponsors this study. The aim of this study is to assess a technique called vagus nerve stimulation (VNS) which is being tested to see if it may provide additional benefit when compared to intensive physical and rehabilitation therapy. The vagus nerve is a nerve located in the left side of the neck, which provides many important functions and has connections with many different parts of the brain. VNS is delivered by a device that is implanted under the skin just below the collar-bone. The device provides electric signals that activate the vagus nerve, which is then thought to cause release of important chemicals within the brain. VNS is already used to treat patients with health problems such as severe depression and epilepsy but it is not known if it is useful after stroke. Also, the settings and timing for VNS in stroke are different than used in epilepsy and depression. Animal experiments suggest release of these chemicals may help re-wiring of the brain and its ability to function after stroke. It is not known if this is the case in humans. VNS has been tested with rehabilitation therapy in two small studies and it looks like it might improve arm and hand weakness caused by stroke. This study is a larger study to try to prove that it works by assessing whether arm function improves more in patients who have VNS performed in addition to their intensive rehabilitation therapy compared to patients who undergo only additional intensive rehabilitation treatment.

Who can participate?
Patients aged 22 to 80 who had a stroke 9 months to 10 years ago and have arm and hand weakness

What does the study involve?
In order to receive VNS, a procedure is needed to implant the device and connect it via a small wire to the vagus nerve. The procedure takes about 90 minutes and is the same procedure performed for epilepsy and depression. All participants are implanted with the device and after a one-week surgery recovery period and another test assessment, all participants start 6 weeks of intensive rehabilitation, which includes sessions with physiotherapists and occupational therapists. Participants are randomly allocated to receive either the study treatment or the active-control treatment. The study treatment is VNS delivered during rehabilitation. The active

control treatment is rehabilitation (standard-of-care treatment) with only a small amount of VNS at the start of each session. There is a 3-month follow-up where assessments are done at 1, 30, and 90 days. This helps the study doctors determine if VNS works better than rehabilitation alone. After this period, the people who received the active control treatment can come back and receive more rehabilitation with VNS. Also, at this point all participants can use a magnet to trigger 30 minutes of VNS at home along with home exercises. After the VNS and 90 days follow-up, all participants are seen every 3 months over one year after VNS, and yearly after this. Participants who want to keep the device can continue using it at home, but they must be seen at least once a year.

What are the possible benefits and risks of participating?
If VNS looks like it helps, then it could be introduced into routine clinical practice. Since this study involves an implant, it involves quite a number of visits over the first 6 months and ongoing visits for as long as the device is implanted (but only once a year after the first year). The risks from the surgical implant include pain and bruising due to surgery or nerve damage. People who consider entering the study are given full details on potential risks and benefits.

Where is the study run from?
1. Queen Elizabeth University Hospital (UK)
2. Royal Victoria Infirmary (UK)
3. Barking, Havering and Redbridge University Hospitals NHS Trust (UK)
4. Mayo Florida (USA)
5. Rancho Los Amigos (USA)
6. TIRR Memorial Hermann (USA)
7. Thomas Jefferson University Hospitals (USA)
8. Ohio State University (USA)
9. Vanderbilt University (USA)
10. Weill Cornell Medicine (USA)
11. UT Chattanooga (USA)
12. UT Southwestern (USA)
13. Medical University of South Carolina (USA)
14. Burke Rehabilitation (USA)
15. Emory University (USA)

When is the study starting and how long is it expected to run for?
April 2017 to August 2019

Who is funding the study?
MicroTransponder Inc. (USA)

Who is the main contact?
Mr W Brent Tarver (public contact), brent@microtransponder.com (email added 18/04/2019)

### Study website
http://www.vnsstroketrial.com

# Contact information

### Type(s)
Public

**Contact name**
Mr W Brent Tarver

**Contact details**
2147 Swift Blvd
Houston
United States of America
77030

# Additional identifiers

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**
NCT03131960

**Secondary identifying numbers**
MT-St-03

# Study information

**Scientific Title**
A pivotal randomized study assessing vagus nerve stimulation (VNS) during rehabilitation for Improved upper limb motor function after stroke (VNS-REHAB)

**Acronym**
VNS-REHAB

**Study objectives**
Vagus nerve stimulation (VNS) performed during rehabilitation for subjects with upper limb motor deficits following stroke will provide more benefit than active-control (rehabilitation only) after 6 weeks of therapy.

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
West of Scotland REC 4, 03/08/2017, ref: 17/WS/0137, IRAS Project ID: 228128

**Study design**
Multicenter randomized blinded parallel partial crossover study (active control crosses over to active therapy after the randomized follow-up portion of the study)

**Primary study design**
Interventional

**Secondary study design**
Randomised cross over trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

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

## Health condition(s) or problem(s) studied
Subjects 9 months to 10 years post ischemic stroke who have upper limb deficits

## Interventions
All subjects are implanted with the Vivistim System® and then randomized to either study treatment or active-control treatment. The randomization will be stratified by age (<30, >30) and baseline FMA UE (20 to <35; >35 to 50).
1. Study treatment is vagus nerve stimulation (VNS) delivered during rehabilitation
2. Active control treatment is rehabilitation (standard-of-care treatment) with only a minimal amount of VNS at the start of each session intended to support blinding

This study has three distinct stages: Stage I, an acute blinded stage, Stage II, an unblinded stage through one year of standard VNS, and Stage III, an unblinded stage for yearly follow-up after one year of VNS. The control group crosses over to VNS treatment at Stage II.

Stage 1 lasts approximately 5 months. Stage II goes through one year of standard VNS. Stage III provides ongoing yearly follow-up for as long as the investigational device is implanted.

Stage I (Acute Blinded Stage – All Subjects):
Screening Visit 1: -6 weeks to -14 days prior to implant
Pre-Implant Assessment Visit 2: -14 to -2 days prior to implant
Implantation (Visit 3): Day of surgery (Day 0)
Stage I Pre-Therapy Baseline (Visit 4): Day 7 (+/- 7 days)
Stage I Treatment Sessions 1-18, Occurs over 6 Weeks: Day 7-49 (+/- 3 days) – 3 sessions per week
Stage I Post Assessment 1 (Visit 5): Day 50 (+/- 3 days) – 1 day after end of therapy
Stage I Post Assessment 2 (Visit 6): Day 80 (+/- 7 days) – 30 days after 6-weeks therapy
Stage I Post Assessment 3 (Visit 7): Day 140 (+/- 14 days) – 90 days after 6-weeks therapy

Stage II (Long-Term Unblinded Stage – VNS Treatment Arm):
6 Month Visit – VNS Arm – LT4: 150 days after end of Stage I (+/- 14 days)
9 Month Visit – VNS Arm – LT5: 240 days after end of Stage 1 (+/- 14 days)
12 Month Visit– VNS Arm – LT6: 330 days after end of Stage I (+/- 28 days)

Stage IIb (Cross Over to Acute Unblinded Treatment Stage – Control Arm):
Home Treatment: 60 days of home treatment
Stage IIb Baseline – Control Arm: 90 days after end of therapy. This occurred at V7 (end of Stage 1)
Stage IIb Treatment Sessions (1 to 18), Occurs over 6 Weeks: 3 sessions per week – start after V7
Stage IIb Post Assessment 1 – LT1: 1 day after last session of VNS: Stage IIb Post Assessment 2 – LT2

Stage II (Long-Term Unblinded Stage – Control Arm):
3 Month Visit-Control Arm – LT3: 60 days after end of Stage Ib (+/- 7 days)
6 Month Visit – Control Arm – LT4: 150 days after end of Stage Ib (+/- 14 days)
9 Month Visit – Control Arm – LT5: 240 days after end of Stage Ib (+/- 14 days)
12 Month Visit – Control Arm – LT6: 330 days after end of Stage Ib (+/- 28 days)

The primary objectives are to assess the efficacy and safety of the therapy. The study is intended to provide evidence that VNS paired with rehabilitation, in subjects suffering from upper extremity paresis after stroke, is a safe and effective treatment for recovery of upper limb motor function after stroke. It is the intent that this data support a PMA application to FDA.

The primary endpoint is the difference in the Fugl-Meyer Assessment, Upper Extremity portion (FMA-UE) score after 6 weeks of treatment in the paired VNS group compared to the control group (difference at Visit 5 compared to Visit 4).

### Intervention Type
Device

### Primary outcome measure
Impairment, measured using the Fugl-Meyer Assessment, Upper Extremity portion (FMA-UE) at Stage I: Visits 1, 2, 4, 5, 6 and 7; Stage II (VNS Treatment Arm): 6, 9 and 12 months; Stage IIb: 1 day and 30 days; Stage II (Control Arm): 3, 6, 9 and 12 months

### Secondary outcome measures
1. Upper extremity function, measured using the Wolf Motor Function Test (WMFT) at Stage I: Visits 2, 4, 5, 6, 7; Stage II (VNS Treatment Arm) 6, 9 and 12 months; Stage IIb: 1 day and 30 days; Stage II (Control Arm): 3, 6, 9 and 12 months
2. Health-related quality of life, measured using the Stroke Impact Scale (SIS) at Stage 1: Visit 4, 5, 7; Stage II (VNS Treatment Arm): 6 and 12 months; Stage IIb: 1 day; Stage II (Control Arm): 3 and 12 months
3. Stroke-specific quality of life, measured using Stroke Specific Quality of LIfe (SS-QOL) at Stage 1: Visit 4, 5, 7; Stage II (VNS Treatment Arm): 6 and 12 months; Stage IIb: 1 day; Stage II (Control Arm): 3 and 12 months
4. Activities of daily living, assessed using Motor Activity Log (MAL) at Stage 1: Visit 4, 5, 7; Stage II (VNS Treatment Arm): 6 and 12 months

### Overall study start date
01/04/2017

### Completion date
28/02/2020

# Eligibility

### Key inclusion criteria
1. History of unilateral supratentorial ischemic stroke that occurred at least 9 months but not more than ten 10 years prior to enrollment
2. Age >22 years and <80 years
3. FMA-UE score of 20 to 50 (inclusive of 20 and 50)
4. Ability to communicate, understand, and give appropriate consent. Subjects should be able to follow two-step commands

5. Right- or left-sided weakness of upper extremity
6. Active wrist flexion/extension; active abduction/extension of thumb and at least two additional digits

## Participant type(s)
Patient

## Age group
Adult

## Sex
Both

## Target number of participants
120 Implanted subjects

## Total final enrolment
108

## Key exclusion criteria
1. History of hemorrhagic stroke
2. Presence of ongoing dysphagia or aspiration difficulties
3. Subject receiving medication that may significantly interfere with the actions of VNS on neurotransmitter systems at study entry. A list of excluded medications will be provided to Investigators
4. Prior injury to vagus nerve, either bilateral or unilateral (e.g., injury during carotid endarterectomy).
5. Severe or worse depression (Beck Depression Scale > 29) (Beck et al., 1961)
6. Unfavorable candidacy for device implant surgery (e.g., history of adverse reactions to anesthetics, poor surgical candidate in surgeon's opinion, etc)
7. Current use of any other stimulation device, such as a pacemaker or other neurostimulator; current use of any other investigational device or drug
8. Medical or mental instability (diagnosis of personality disorder, psychosis, or substance abuse) that would prevent subject from meeting protocol timeline
9. Pregnancy or plans to become pregnant or to breastfeed during the study period
10. Current requirement, or likely future requirement, of diathermy during the study duration
11. Active rehabilitation within 4 weeks prior to consent
12. Botox injections or any other non-study active rehabilitation of the upper extremity within 4 weeks prior to therapy through the post-30 day visit (Visit 6)
13. Severe spasticity of the upper limb (Modified Ashworth ≥3) (Bohannon and Smith, 1987)
14. Significant sensory loss. Sensory loss will be measured using the Upper Extremity sensory section of the Fugl Meyer Assessment of Physical Performance. The assessment addresses light touch (2 items) and proprioception (4 items).The highest points attained is 12; subjects with scores less than 6 will be excluded from the study

## Date of first enrolment
19/08/2017

## Date of final enrolment
31/07/2019

# Locations

## Countries of recruitment
England

Scotland

United Kingdom

United States of America

## Study participating centre
**Queen Elizabeth University Hospital**
Glasgow
United Kingdom
G51 4TF

## Study participating centre
**Royal Victoria Infirmary**
Newcastle Upon Tyne
United Kingdom
NE1 4LP

## Study participating centre
**Barking, Havering and Redbridge University Hospitals NHS Trust**
Romford, London
United Kingdom
E15 4LZ

## Study participating centre
**Mayo Florida**
Jacksonville, FL
United States of America
32224

## Study participating centre
**Rancho Los Amigos**
Los Angeles
United States of America
90242

**Study participating centre**
**TIRR Memorial Hermann**
Houston, TX
United States of America
77030

**Study participating centre**
**Thomas Jefferson University Hospitals**
Philadelphia, PA
United States of America
19107

**Study participating centre**
**Ohio State University**
Columbus, OH
United States of America
43210

**Study participating centre**
**Vanderbilt University**
Nashville, TN
United States of America
37240

**Study participating centre**
**Weill Cornell Medicine**
New York, NY
United States of America
10065

**Study participating centre**
**UT Chattanooga**
Chattanooga, TN
United States of America
37403

**Study participating centre**

**UT Southwestern**
Dallas, TX
United States of America
75390

**Study participating centre**
**Medical University of South Carolina**
Charleston, SC
United States of America
29425

**Study participating centre**
**Burke Rehabilitation**
White Plains, NY
United States of America
10605

**Study participating centre**
**Emory University**
Atlanta, GA
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30322

**Study participating centre**
**Barts Health NHS Trust**
Royal London Hospital
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E1 1BB

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

**Study participating centre**

**NHS Grampian - Aberdeen Royal Infirmary**
University of Aberdeen
Foresterhill
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AB25 2ZN

# Sponsor information

**Organisation**
MicroTransponder Inc.

**Sponsor details**
2802 Flintrock Trace, #226
Austin
United States of America
78738

**Sponsor type**
Industry

**Website**
www.microtransponder.com

**ROR**
https://ror.org/03k61re15

# Funder(s)

**Funder type**
Industry

**Funder Name**
MicroTransponder Inc.

# Results and Publications

**Publication and dissemination plan**
The protocol has been approved by both the US FDA and the UK MHRA. A summary of the protocol is also available at clinicaltrials.gov. The full protocol and patient information sheet are

available on request but are not available online. The protocol will be included as part of any study publication; it may be published as a separate manuscript or may be included as part of the first results publication.

The intent is that the randomized portion of the study will be reported after the last study subject has data through this timepoint (Visit 7, 90 days after the completion of the 6-weeks of study therapy).

## Intention to publish date
28/02/2021

## Individual participant data (IPD) sharing plan
MicroTransponder is a small medical device company funded by private investors; MicroTransponder is the study sponsor, and is providing all funding for the study. Because of this, the study dataset will not be made available publicly to all. The study dataset is held by the clinical research organizations providing the study collection services and then by MicroTransponder. However, the full dataset is available to all clinical investigators, and the clinical investigators responsible for the study publication(s) will be utilizing the full dataset and statistical analysis plan analyses for the publication (and the chief investigator and others are establishing, reviewing and approving the SAP). Therefore participant level data is only expected to be provided to study investigators and, as necessary, for publication purposes; it is not expected to be made available to the general public.

## IPD sharing plan summary
Not expected to be made available

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | | 07/06/2019 | 02/08/2021 | Yes | No |
| Results article | | 24/04/2021 | 02/08/2021 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |