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Vagus nerve stimulation for epilepsy in children and adults: assessment of longer term clinical and cost effectiveness in a randomised controlled trial

Submission date
12/03/2026

Recruitment status
Not yet recruiting

Registration date
29/04/2026

Overall study status
Ongoing

Last Edited
29/04/2026

Condition category
Nervous System Diseases

[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 600,000 people in the UK have epilepsy. For a third, medication is ineffective, referred to as refractory epilepsy, or 'drug-resistant epilepsy', which can severely impact quality of life and reduce life expectancy.
Brain surgery can help some with drug-resistant epilepsy by removing the problematic brain area, but identifying this area is not always possible, and surgery is only effective for 50-60% in the long term.
Another possible treatment is vagus nerve stimulation (VNS). This involves implanting a battery under the skin on the upper chest (like a pacemaker) and connecting it to the vagus nerve in the neck. Although VNS is approved for drug-resistant epilepsy, its long-term effectiveness and who it works for is not known. For example, we do not know how well it works for children or adults with epilepsy and intellectual disabilities, who make up half of NHS VNS recipients.
Our project aims to find out if VNS provides both short- and long-term benefits for people with drug-resistant epilepsy, including those with intellectual disabilities.

Who can participate?
We will recruit 300 participants from epilepsy surgery centres over four years, following them for a minimum of an additional two years. Participants will be over 5 years old with drug-resistant epilepsy unsuitable for, or which has failed, brain surgery. Around half will have intellectual disability.

What does the study involve?
Persons identified as suitable for VNS by a multi-disciplinary team will be invited. Those agreeing will be randomised: 150 to immediate VNS activation, 75 to activation after 6 months, and 75 to activation after 12 months.

What are the possible benefits and risks of participating?
Benefits: The research might help other people with epilepsy in the future.

Risks: Participants might have to wait a little while before their device is switched on. - Keeping track of seizures and answering questions takes time. - VNS can have some side effects such as a hoarse or croaky voice.

Where is the study run from?
The trial Sponsor is University of Liverpool and is being run by the Liverpool Clinical Trials Centre at the University of Liverpool (UK).

When is the study starting and how long is it expected to run for?
May 2026 to May 2032

Who is funding the study?
The trial is being funded by the NIHR Health Technology Assessment Programme (UK).

Who is the main contact?
The Chief Investigator is Professor Tony Marson
The Trial Manager at the LCTC is Stephanie Willshaw
vnstrial@liverpool.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Miss Stephanie Willshaw

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Additional identifiers

Central Portfolio Management System (CPMS)
63394

National Institute for Health and Care Research (NIHR)
167183

Study information

Scientific Title
Vagus Nerve Stimulation for epilepsy in children and adults: Assessment of Longer term clinical and cost Effectiveness in a Randomised controlled Trial

Acronym
VNS-ALERT

Study objectives
Primary objective:
To determine the clinical effectiveness of VNS versus no VNS at 6 months in people, with or without intellectual disability, aged 5 years and over with treatment refractory epilepsy

Secondary objectives:
1. To determine the clinical effectiveness of VNS versus no VNS at 12 months in people, with or without intellectual disability, aged 5 years and over with treatment refractory epilepsy
2. To determine the clinical effectiveness of VNS versus no VNS at 6 and 12 months in people with intellectual disability, aged 5 years and over with treatment refractory epilepsy
3. To determine the longer-term clinical effectiveness (beyond 2 years) of VNS
4. To determine whether the clinical effectiveness of VNS changes over time during longer term follow-up
5. To determine the effectiveness of VNS or no-VNS on patient and caregiver quality of life

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 30/03/2026, Yorkshire & The Humber - Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 207 972 25 04; leedswest.rec@hra.nhs.uk), ref: 26/YH/0012

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Open (masking not used)

Control
Active

Assignment
Single

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Epilepsy

Interventions

Patients will be recruited in hospital a minimum of one month prior to their VNS implantation surgery to allow for initial seizure diary completion.

To understand how effective VNS is, participants will be randomised to one of the following groups:
1. Immediate VNS activation
2. VNS activation after 6 months
3. VNS activation after 12 months

Each delayed activation arm will be compared to the standard care immediate activation arm, with the null hypothesis that there is no difference in outcome between the treatments. A total of 150 participants will be allocated to immediate activation, with 75 participants allocated to each delayed activation arm.

All participants in the trial will receive the best available standard care for any long-term symptoms they develop.

A randomised controlled trial design has been chosen as it is the most reliable way to assess the effects of treatment. The design is pragmatic in order to allow treatment to be administered based on clinical need. The trial is not blinded as it is not feasible to blind site staff or patients to VNS device activation.

Participants will mainly be recruited as part of standard epilepsy multi-disciplinary team MDT meetings where VNS implantation is discussed. Layered and proportionate participant information will be provided to allow an informed decision on participation. Once consent is obtained, demographic information and medical history will be collected, and participants will be provided with a seizure diary to collect seizure free days and seizure frequency for a minimum of one month prior to their VNS device implantation surgery.

A randomisation visit will be arranged between 2 weeks and 24 hours prior to the participant's VNS device implantation surgery. At this visit, details on anti-seizure medications will be collected and participants will complete questionnaires regarding their epilepsy, quality of life, and resource use. The site will randomise the participant to a trial arm, and participants will be informed of their allocation at the visit.

The initially completed seizure diary will be returned to the site team for upload at the VNS implantation surgery. Sites will provide a new blank seizure diary to participants at every visit for return at the subsequent visit.

Follow-up visits will align with standard care clinic visits every 6 months following VNS device implantation surgery. Participants will be followed for a minimum of 24 months, with follow-up continuing up to 24 months following the final randomised participant. Completed seizure diaries will be returned at each follow-up visit. Questionnaires will be completed at each follow-up up to 24 months, and then annually thereafter. Optional trial items include collection of a blood sample and a copy of a recent EEG to be transferred to a central repository for future research. In addition, informal carers will be asked whether they would like to consent to answering additional questions about their caring experience in line with the timepoints for the person with epilepsy.

There is a nested qualitative sub-study that will be explained at the initial MDT screening. Patients may consent to be contacted by the qualitative research team irrespective of participation in the main trial. The qualitative team will separately consent patients and or their

carers to complete interviews to explore experiences of VNS-ALERT and VNS devices more broadly. This will improve understanding of trial recruitment, as well as barriers and opportunities for improving information provision about VNS.

Public and Patient Involvement PPI groups have been extensively involved in the trial design. This input guided the development of the three arm design, allowing all participants to have a VNS device fitted and to continue in the trial if their device is activated outside their allocated trial arm. The dedicated PPI team has also contributed to the development of study materials, including the patient information leaflet, video, and seizure diary.

The Independent Data and Safety Monitoring Committee will meet regularly to review preliminary data and make recommendations about trial progress.

The results from this study have the potential to change standard care for people with treatment resistant epilepsy.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Vagus nerve stimulation

Primary outcome(s)
1. 'Seizure free days' at 6 months measured using Seizure diary (minimum of 1 month diary completion prior to timepoint) at VNS Implantation, 6 months

Key secondary outcome(s))
1. 'Seizure free days' at 12 months measured using Seizure diary (minimum of 1 month diary completion prior to timepoint) at VNS Implantation, 12months

2. 'Seizure free days' measured using Seizure diary (minimum of 1 month diary completion prior to timepoint) at VNS Implantation, 6, 12, 18, 24 months, then 6-monthly follow-ups to end of trial

3. Seizure frequency measured using Seizure diary (minimum of 1 month diary completion prior to timepoint) at VNS Implantation, 3m (post VNS activation), 6, 12, 18, 24 months, then 6-monthly follow-ups to end of trial

4. Seizure severity measured using Liverpool Seizure Severity Scale at Randomisation, 6, 12, 18, 24 months, then 12-monthly follow-ups to end of trial

5. Episodes of seizure requiring rescue medication, emergency department attendance or hospital admission measured using Site report, PLICS at Continuously throughout the study

6. Mortality measured using Site report at Continuously throughout the study

7. Symptoms of depression, anxiety, and anger measured using PROMIS short (anxiety, depression, and anger) at Randomisation, 6, 12, 18, 24 months, then 12-monthly follow-ups to end of trial

8. Quality of life of person with epilepsy measured using QoLCE / QoLIE / ELDQoL at Randomisation, 6, 12, 18, 24 months, then 12-monthly follow-ups to end of trial

9. Caregiver burden measured using CarerQoL-7D at Randomisation, 6, 12, 18, 24 months, then 12-monthly follow-ups to end of trial

Completion date
31/05/2032

Eligibility

Key inclusion criteria
1. Aged greater than or equal to 5 years
2. Has treatment refractory focal, generalised, or unclassified epilepsy
3. Epilepsy surgery MDT agrees that VNS should be offered as a treatment for epilepsy
4. Patient (and/or carer) has a good enough understanding of the English language to read and understand study documents

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
5 years

Upper age limit
120 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Previous VNS
2. Contraindication to VNS

Date of first enrolment
01/05/2026

Date of final enrolment
01/05/2030

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
England
L9 7LJ

Study participating centre
North Bristol NHS Trust
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
England
BS10 5NB

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
Lothian
Waverleygate
2-4 Waterloo PLACE
Edinburgh
City of Edinburgh
Scotland
EH1 3EG

Study participating centre
Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London
England
WC1N 3JH

Study participating centre
Greater Glasgow and Clyde
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
Scotland
G12 0XH

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
England
M6 8HD

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
England
LS9 7TF

Study participating centre

Cardiff & Vale University Lhb
Woodland House
Maes-y-coed Road
Cardiff
Wales
CF14 4HH

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

Sponsor information

Organisation
University of Liverpool

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date