Investigating the tolerability and feasibility of transcutaneous vagus nerve stimulation following aneurysmal subarachnoid haemorrhage

tVNS in aSAH

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Confidentiality Statement:
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so by the Chief Investigator.

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1. Study Synopsis/Profile

Study title	Investigating the tolerability and feasibility of transcutaneous vagus nerve stimulation following aneurysmal subarachnoid haemorrhage
Study short title	tVNS in aSAH
Study design	Two-arm randomised controlled trial
Study participants	**Inclusion criteria:** • Age >18 • Admitted to STH neurosurgery • Confirmed aneurysmal SAH on vascular imaging • Within 5 days of 'Securing' aneurysm (i.e., successfully coiled or surgically following rupture) **Exclusion criteria:** • Current or prior use of a vagus nerve stimulation • Symptomatic bradycardia or PPM insertion • Complete heart block • Implantation of any other electrical stimulator (e.g. DBS)
Planned sample size	30 participants (15 in each arm)
Planned study period	36 months
Planned recruitment period	24 months
Study assessments	• Deliver TVNS using the parasym device for 45 minutes twice daily for 5 days following aSAH intervention (coiling or clipping) ○ Pulse width 25ms, frequency device standard (25 Hz), at maximum tolerated intensity, or

	20MA for patients who cannot report the maximum tolerated intensity • Clinical follow-up on discharge and at 1 month
Objectives	***Primary*** To establish the tolerability, and feasibility of tVNS in patients following aSAH, including; • Monitor tolerability for tVNS ○ Symptom severity scores of mild or moderate in less than 1/3 of participants able to report symptoms • Assess study feasibility ○ recruit >1 patient per month of recruitment ○ >80% of recruited patients completing primary outcome measures ***Secondary*** • Monitor safety criteria for tVNS ○ No SAEs reported to tVNS ○ Unexpected AEs in less than 1/3 of participants • Explore clinical outcomes including: ○ rates of clinical or radiological DCI ○ inpatient mortality ○ inpatient length of stay ○ Rate of complications: seizures, hyponatraemia, rebleed, hydrocephalus • Outcome measures using questionnaires on discharge and at 1-month ○ Disability assessment: modified Rankin Score, Barthel Index ○ Assess frequency and severity of headache: Likert scale • Explore mechanisms of action: ○ Inflammatory markers at baseline and 5 days • Explore response to tVNS: ○ Near-infrared cerebral spectroscopy ○ Heart rate variability ○ Pupillary reactivity

2. Research Questions

Is transcutaneous nerve stimulation a tolerable and feasible intervention to potentially improve clinical outcomes in aneurysmal subarachnoid haemorrhage (aSAH)?

3. Abstract/Summary

Background

Subarachnoid haemorrhage (SAH) is a type of brain bleed, which can be complicated by issues including delayed cerebral ischaemia (DCI) which causes stroke like symptoms, such as weakness, in up to 30% of patients.[1] Current treatments for DCI focus on improving blood supply but fail to address other important factors including reducing inflammation.[2]

Stimulation of a nerve in the neck called the vagus nerve, which can be done through the skin (transcutaneous vagus nerve stimulation, tVNS) is known to relax blood vessels and reduce inflammation and is approved in other conditions such as epilepsy.[3,4] In animals, vagus nerve stimulation improves survival after aSAH, and is being studied in humans to reduce headaches after aSAH.[5,6]

There is a theoretical role of tVNS in improving outcome after aSAH. We aim to study whether tVNS is tolerated, and feasible in aSAH.

Methods

This is a single centre, pilot randomised controlled trial (RCT); the participants will receive either tVNS or 'sham' tVNS, twice daily for 45 minutes for 5 days. We will monitor tolerability (symptoms) and feasibility (recruitment rates) for recruited patients. Secondary outcomes will include rates of side effects, complications from SAH, outcomes on discharge and 4 week follow up, and exploration of mechanisms of action and response to tVNS including levels of serum inflammatory markers (IL-1B, IL-4, IL-6, IL-10 and TNFa), functional near infra-red spectroscopy (f-NIRS), heart rate variability (HRV) and pupillary light reactivity (PLR).

Results

Rates of complications, side effects and recruitment will be reported descriptively and we will undertake simple between-group statistical analyses on secondary outcome measures. If proven to be tolerated and feasible, this study will provide the basis for a future larger trial design.

4. Aims of the Study

The aims of the study will be to conduct a pilot RCT to investigate whether tVNS is a tolerable and feasible treatment for acute aSAH. To understand this we will recruit participants who have recently undergone acute securing procedures follow acute aSAH (coiling or clipping of aneurysm) to a 5 day programme of intervention (active tVNS vs sham) and collect outcome data (primary and secondary as per outcomes section). We will evaluate whether pre-defined success criteria are achieved for tolerability and feasibility and explore signals of effect on clinical outcome measures and mechanistic measures. Non-invasive vagal nerve stimulation has not been

studied in the acute period following aSAH outside of the remit of reducing headache. This should offer critical insights as to whether this intervention has potential to take forward to a larger phase 2/3 clinical study.

5. Background

Delayed cerebral ischaemia (DCI) is a multifactorial sequela of aneurysmal subarachnoid haemorrhage (aSAH) which occurs in up to 30% of patients, usually within 14 days of ictus.[1] Diagnosis is by means of clinical and radiological assessment of a new neurological deficit in the absence of other causes.[2] Alongside rebleeding, DCI is the strongest predictor of in-hospital mortality after aSAH and has a significant impact on morbidity.[1]

The pathophysiology of DCI is complex and poorly understood, but emerging evidence supports a multifactorial model which includes arterial vasospasm, inflammatory processes, localised coagulopathy, and failure of cerebral autoregulation – this represents a vasculopathic progress, rather than purely vasospasm.[7] Current management strategies for DCI focus on overcoming vasospasm, primarily by inducing hypertension, although this fails to address other important factors in the disease pathophysiology such as the inflammatory process.[2] Interventions that target a multiple pathophysiological pathways may offer greater clinical benefits.

Several studies are ongoing to address the utility of novel therapeutic targets in DCI. Vagus nerve stimulation (VNS) is known to have vasodilatory and anti-inflammatory effects and is licensed in other conditions including migraine and epilepsy.[3,4] In animal models, transcutaneous VNS (tVNS) has been found to reduce aneurysm rupture rates and improve survival after aSAH.[8] Studies are ongoing to establish its efficacy in reducing post-SAH headache.[5] However, there have been no studies investigating the use of tVNS in delayed cerebral ischaemia.

6. Plan of the Investigation

6.1 Methodology

This is a single centre, pilot, randomised controlled trial. 30 participants who have suffered an aneurysmal subarachnoid haemorrhage and had their aneurysm secured (coiled or clipped successfully).

The intervention will take place for 45 minutes twice a day for 5 days after securing the aneurysm. The placebo group will receive the same intervention, but the device will be in 'sham' mode (i.e. attached to the earlobe).

It is not known whether tVNS is tolerable, and feasible in aSAH, but standard device settings will be used in accordance with a majority of other studies. Similarly, the optimal therapeutic duration is not known – 45 minutes twice a day is a similar usage to other studies. A 5-day course has been chosen because it covers the highest risk period for DCI and is feasible for the research team to deliver.

6.2 Design

This is a single centre pilot, single blind, randomised, placebo – controlled study.

This has been chosen as it will demonstrate feasibility and tolerability, whilst providing early data to indicate whether tVNS may provide benefit in this setting, supporting the development of a larger RCT to establish whether it is a statistically significant benefit.

Patients may be able to tell the different between an activated device and sham (where the device is applied to the earlobe instead of the tragus). However, they will not experience both settings, and we will make no clear distinction of exactly what they should feel.

6.3 Setting

The patients will be inpatients under Neurosurgery at the Royal Hallamshire Hospital. All outcome measures will be collected at recruitment, discharge and 1 month following discharge. They will undergo the TVNS intervention as an inpatient for 5 days.

6.4 Participants

Inclusion criteria:

- Age >18 yrs
- Admitted to STH neurosurgery
- Confirmed aneurysmal SAH on intracranial vascular imaging
- Within 3 days of 'Securing' aneurysm (i.e., successfully endovascularly coiled or surgically clipped following rupture)

Exclusion criteria:

- Current or prior use of a vagus nerve stimulation device
- Symptomatic bradycardia
- Complete heart block
- Presence of other implanted electrical stimulator (e.g. DBS)
- Pregnancy

6.5 Sample Size

A sample size of at least 30 has been chosen based on the number or participants required for the purposes of a feasibility assessment.[9] It is also a practically feasible number of participants to recruit based on annual admission numbers of patients to the RHH and the timeframe of the recruitment period.

6.6 Recruitment

Potential participants with aSAH will be identified on admission to neurosurgery at RHH and approached about the study by the clinical treating team on the basis of convenience sampling. If they are interested in the study, they will be provided with an information sheet again and the opportunity to discuss the study with a member of the research team. If they are willing to take part in the study written informed consent will be obtained, after a screening consent support tool is used to ensure the patient had adequate comprehension.

Capacity to consent to the study would be determined by the treating clinical team and confirmed by the research team according to the principles of the mental capacity act (MCA, 2005). Where the patient lacks capacity to consent (including sedated/intubate patients), a personal or nominated consultee can provide advice on what they feel the patients' wishes would be if they had capacity. The treating clinical team would

introduce the study to the consultee and an information leaflet given to them. The consultee would then have the option to sign a consent form if they believed the patient would agree to participate. In accordance with the MCA 2005, ongoing consent or assent would be sought from the individual or consultee at each study visit, before any research activity at the that visit is undertaken. Consultees may advise at any point that they believe the person's wishes about participation have changed and they should therefore be withdrawn from the study. Agitated patients will not receive the intervention if they are unable to tolerate it.

6.7 Outcome Measures

Primary Outcome Measures – success criteria:

- Monitor tolerability for tVNS
  - Symptom severity scores of mild or moderate in less than 1/3 of participants able to report symptoms (based on Likert Scale 1-5; 1 representing no issues; 5 representing severe symptoms)
- Assess study feasibility
  - recruit >1 patient per month of recruitment
  - >80% of recruited patients completing primary outcome measures at 4 weeks follow up

These outcome measures will be collected during the participants inpatient stay over the intervention period using a data collection proforma (appendix) and taken from recruitment records kept contemporaneously. Safety assessment of SAEs / AEs will be collected each intervention day by our research team.

Secondary Outcome Measures:

- Monitor safety criteria for tVNS
  - No SAEs reported to tVNS
  - Unexpected AEs in less than 1/3 of participants
- Explore clinical outcomes including:
  - rates of clinical or radiological DCI (%)
  - inpatient mortality (%)
  - inpatient length of stay (days)
  - rate of complications: seizures, hyponatraemia, rebleed, hydrocephalus (%)
- Outcome measures using questionnaires on discharge and at 1-month
  - Disability assessment: modified Rankin Score, Barthel Index
  - Assess frequency and severity of headache: Likert scale
- Explore mechanisms of action:
  - Inflammatory markers at baseline and 5 days
- Explore response to tVNS:
  - Near-infrared cerebral spectroscopy
  - Heart rate variability
  - Pupillary reactivity

These will be measured during the inpatient hospital stay up until discharge (Figure 1).

- Outcome measures using questionnaires at on discharge and at 4 week follow-up
  - Disability assessment: modified Rankin Score, Barthel Index
  - Assess frequency and severity of headache: Likert scale (1-10 where 1 is non-existent and 10 is extremely severe)
- Explore mechanisms of action measured at baseline and at the end of intervention (5 days):
  - Inflammatory marker analysis at baseline and 5 days (IL-1B, IL-6, IL-10, TNFa)
  - Concurrent WCC, CRP and infection will be recorded at these time points as these may confound results
- Explore response to tVNS:
  - Near-infrared cerebral spectroscopy
  - Heart rate variability (HRV) parameters using a commercially available heart rate monitor - (SDRR – standard deviation of the inter-beat-interval ms; RMSSD – the root mean square of successive differences between heartbeats ms; LF power – power of HRV distributed in the low frequency (0.04 – 0.15) band indicative of sympathetic nervous activity; HF power – power of HRV distributed in the high frequency (0.15 – 0.4) band indicative of parasympathetic nervous activity; LF/HF ratio) [10-12]
  - Pupillary reactivity (constriction and dilatation amplitudes mm; constriction speeds ms, latency ms)[13]. Confounders including eyedrops that may influence pupil size will be recorded

6.8 Subject Withdrawal, Breaking the Blind and Trial Discontinuation Rules

Participants will be advised that they can withdraw from the study at any time without giving a reason and without this affecting their clinical care. Any data already collected will be analysed with permission from the patient. A member of the research team will confirm the patient is happy to continue with the longitudinal study at their clinical follow up appointments.

We will record data including number of patients admitted with aneurysmal SAH, number eligible, number recruited, dropout rates, and reasons for these. Participants will be given the opportunity to get involved in a public patient involvement group (PPI) at completion of the study.

6.9 Intervention

We are using tVNS settings that are widely used in other neurological conditions (epilepsy, migraine)[14]. These include:

- Pulse width - 25ms
- Frequency – device default (20 or 25Hz)
- Intensity – below pain threshold.
- Frequency – 45 minutes twice daily. On the basis of similarity to other studies, practicalities on the ward and clinical scenario

We have chosen a duration of 5 days based on the usual clinical pathway of inpatient management at the Royal Hallamshire Hospital, and have chosen to deliver the treatment twice daily to optimise the dose. This is a pilot study with feasibility outcomes and as such we will be exploring the feasibility of this treatment regimen.

The Parasym Device will be applied to the left tragus (figure 1) as this is the most common site for tVNS delivery in neurological studies and is associated with few afferents to the heart.

The intervention is aimed at supplementing routine clinical care, and as such, the doses of tVNS can be interrupted for care activities (therapy sessions, examinations, assessments etc) and resume afterwards. The overall minute duration will aim to remain 45 minutes twice daily.

Figure 1. Anatomy of the ear and the tragus (a). Parasym attached to the tragus (b)

The active intervention will be compared to sham tVNS where the vagal nerve stimulator will be attached to the earlobe instead of the tragus, in keeping with evidence that this does not cause vagus nerve stimulation and is in line with sham methods used in other studies. We do not anticipate that patients will have the intervention long enough to become familiar with the common sensations associated with true tVNS intervention. At the end of the intervention period, participants will be asked if they thought they had received true of sham tVNS to understand the blinding ability of the sham.

We will use the FNIRS Lumo ecosystem (Gower labs) to assess cerebral blood flow in the frontal lobes. We will complete a protocol where 6 optodes are placed bilaterally over the frontal and prefrontal cortices. We will complete and record resting state signals of oxyhaemoglobin and deoxyhaemoglobin for 5 minutes while patients are layed in bed with their eyes closed (or wearing an eye patch). Following the 5-minute rest phase, vagal nerve stimulation or sham stimulation will start

depending on the participants randomisation and signal acquisition will continue for 5 minutes. After this time, the stimulation will cease and a further 5 minutes of resting signal acquisition will be completed. The data acquired during this protocol will undergo processing (adjustment for background and physiological noise) and data analysis using recommended software (Homer 2/3). Data analysis will look to compare signal acquisition between resting and stimulation states and will evaluate any lasting effects of stimulation following termination. We will perform this on the first and last day of the intervention, before and after stimulation respectively.

We will be using Reflex Pupillometry to measure pupillograms in response to a light stimulus during an intervention session for all participants. This will be done at a different time to the Lumo FNIRS assessment. Recording of the pupillary response will follow the following protocol; 3 baseline measures taken 1 minute apart prior to stimulation will represent baseline pupillograms (which will be averaged). Following this, stimulation (active or sham) will start and 3 times pupillograms will be measured at 1 minute intervals following initiation. After completion of the treatment session, 3 further pupillograms separated by 1-minute intervals will be measured - that will constitute the recovery phase. We acknowledge that environmental influences (ambient light intensity, equipment noise and administered medications may confound pupillography, however this analysis is exploratory.

6.10 Study Protocol

Patients (or their representatives if they lack capacity) who are eligible for entry into the will be approached by the treating clinical teams with information about the study. Those who are interested will be given an information sheet and time to consider the study. Those keen to participate will sign a consent form (or assent form for those that lack capacity) and baseline outcome measures will be performed.

Enrolled participants will be issued with a study number and randomised 2:1 (SealedEnvelope Ltd) stratified according to age (<65 and ≥ 65 years). They will then receive either active tVNS stimulation (tragus) or sham (earlobe), twice daily for 45 minutes per session for 5 days. We do not anticipate discharges from hospital earlier than 5 days as this is not routine practice in the neurosurgical unit.

Primary outcome measures of tolerability and feasibility will be collected daily by researchers delivering the intervention, and secondary outcome measures will be collected at the end of intervention or on hospital discharge as detailed in figure 2.

Following discharge from hospital participants will return for follow up clinic assessment at 4 weeks where questionnaire measures of functional recovery and adverse event reporting will be undertaken. After this the participants involvement in the study will be complete.

Figure 2: Study Schedule for Outcome Measures

	Baseline visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 (EOT)	discharge	At 4 weeks
Eligibility screening	X							
Informed consent	X							
Randomisation	X							
Socio-demographic data	X							
Clinical data collection	X						X	
Questionnaires: Disability - mRS, BI, headache likert scale	X						X	X
Reporting of side effects, adverse events and tolerability		X	X	X	X		X	X
Intervention reporting – settings delivered, duration of intervention		X	X	X	X			
Pupillometry + recording of prescribed eye drops	X					X		
Heart rate variability	X					X		
fNIRS	X					X		
Monitor blood test results (secondary outcome measures), collection of data on WCC/CRP and infection status	X	X	X	X	X		X	
Inflammatory marker analysis	X					X		

EOT = End of treatment; BI = Barthel Index;

fNIRS = Functional near infra-red spectroscopy

7. Data Management

7.1 Statistical Analysis

The analyses will be undertaken on statistical software (PRISM) and will compare the two groups. Rates of complications and outcomes will be reported descriptively. Data integrity will be checked by two researchers and inputted contemporaneously. Each researcher will be trained in outcome measures prior to study initiation.

We anticipate approximately 50% of participants will be unable to complete questionnaires due to confusion / low GCS etc. This is exploratory and if this is the case then these outcome measures will not be taken forward in the next stages of future trials. Otherwise we anticipate very few missing data in terms of the primary outcome measures and the objectively measured secondary outcomes due to the fact that we will have a researchers based on the neurosurgical units throughout the recruitment and intervention periods collecting and recording data.

7.2 Statistical Opinion

This is a pilot study which hopes to form the basis of further grant funding for a larger study. This is a provisional study to demonstrate tolerability and feasibility. Further statistical advice would be sought should further funding be granted for future study. Primary outcome data will be reported descriptively (proportions, %).

Continuous data will be compared using parametric or non-parametric analyses depending on whether data distribution is normal or not. Categorical data will be compared using Chi-square or one-way ANOVA. However, due to the small sample size, appropriate power to detect significant differences for these measures will not be reached. This is primarily an exploratory study and most data will be reported descriptively.

Between group differences in baseline characteristics will be compared using parametric (T-Tests) and non-parametric (Mann – Whitney U, Chi squared) tests, depending on normality of distribution.

A secondary outcome of this study is safety of TVNS in patients who have suffered a subarachnoid haemorrhage. Utilising the definition of SAE, if no SAE's are reported which are deemed related to tVNS by the research team, then we can be 95% confident that the true SAE rate lies between 0 and 12%.[15]

7.3 Confidentiality

Participant information (socio-demographic, clinical, outcome measure assessment) will be recorded on paper clinical research forms that will be furnished with a study number rather than the patient identifiers. This will then be transferred to an encrypted electronic database stored on a password protected Sheffield Teaching Hospitals research laptop, access to which will be restricted to researchers entering data and performing statistical analyses. Each study participant will be assigned a unique ID number, which will be the only "identifier" linked to data collected. A separate enrolment log will be kept updated by the researcher and held within a study file separate to the study site file. This will link these numbers to the participant's personally identifiable information. In this way, the participants' data will be "pseudo-anonymised" and no identifiable information will be kept with the actual study data.

The research laptop, study site file and enrolment log will be stored in a locked office at Sheffield Teaching Hospitals, RHH. Participants will undergo baseline and follow up data collection at the stroke unit at the RHH. Rooms there are private and data collection will be conducted in a confidential manner.

7.4 Data Collection, Handling and Storage Record Keeping

Data from the study will be inputted directly onto paper documents that will act as the source documents and be stored in a locked cabinet in a locked room.

Data analysis will take place on a STH laptop that is password protected.

The PI will check all source documents before submitting to minimise the chance of any data errors.

7.5 Data Storage

Data will be collected and retained in accordance with the Data Protection Act 1998. Paper copies of source data and consent forms will be stored in locked cupboard in the Royal Hallamshire Hospital. Electronic data collected will be stored on a password protected computer in the STH computer network. The data will be accessible only to the study team and the trust approved research and governance auditors. The data will be stored within the STH archiving facility for 5 years after completion of the study.

8. Study Management

8.1 Project Plan

Activity	Time Frame
Ethical Approvals	August 2023 – January 2024
Recruitment	January 2024 – June 2025
Closed to Recruitment, in Follow up	July 2025
Closed to Recruitment, Follow up complete	August 2025
Data Analyses	August 2025 – October 2025
Write up	November – December 2025
Dissemination	January 2026 onwards

8.2 Project Management

The principal investigator will have overall responsibility for the study and will supervise, monitor and review any work undertaken by the research team. They will also be responsible for the data collection and analysis of the outcome measures. All SAH patients in the eligible time frame will be approached.

9. Expertise

Mr Matthew Myers is an academic neurosurgery ST2 trainee in Sheffield Teaching Hospital NHS Foundation Trust since 2022.

Dr Ali and **Professor Majid** are academic consultants in neurology stroke and Geriatrics and have experience in running clinical trials and supervising academic fellows, MSc and PhD students.

The project team (Dr Ali, Prof Majid) will meet twice monthly to discuss problems that arise with recruitment and data analysis. The Principal Investigators will have overall responsibility for the study and will supervise, monitor and review work undertaken, the data collected and analysis performed.

10. Ethical Issues

10.1 Ethical Considerations:

The Investigator asking for consent and the Participant Information Sheet (PIS) will inform the potential participant that participation is entirely voluntary and their medical care will not be affected by their decision. The PIS and Informed Consent Form (ICF) will be given to the potential participant, and they will be given adequate time to read and understand the information and ask any questions prior to consenting. They will be informed that they have the right to withdraw at any time without giving reason and this will not affect their medical care or legal rights. The participants' rights to information and consent, confidentiality and privacy are and will be respected and upheld throughout the duration of this study. For any eligible patients who lack capacity and cannot consent form themselves, consent will be sought from the next of kin or personal representatives. The decision to include patients who lack capacity has been taken as it is likely this will form a significant proportion of the aSAH population, and thus to ensure our research is generalisable to as many that benefit as possible including this group is critical. We have a wealth of evidence demonstrating the safety of this intervention in acute stroke and other acute neurological conditions [Redgrave et al]. All members of the research team have undergone GCP training. If assent to participate has been obtained from personal representatives and the participant regains capacity during the intervention period then informed consent from the participant themselves will be obtained prior to continuation with study activities. Participants are free to withdraw from the study at any time without giving a reason and without it affecting their clinical care or legal rights. The study data already collected will be withdrawn up until the time it is anonymised.

10.2 Declaration of Helsinki

The CI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

10.3 Guidelines for Good Clinical Practice

The CI will ensure that this study is conducted in accordance with relevant regulations and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-Good Clinical Practice.

All research active staff will have completed the GCP training or re-fresher training within the last 3 years (in line with STH Trust Requirements).

10.4 Expenses and Benefits

There is no anticipated direct benefit of this study to participants, but it is hoped the study will help support the use of a novel technology to improve outcomes after SAH.

10.5 Other Ethical Considerations

PIS, PIL and consent forms attached, which state participation is entirely voluntary, will always be provided to the patient, or NOK if the patient is unconscious and then given to the patient when they have capacity. The participant or legal representative will be given adequate time to ask questions and read the additional documentation. They have the right to withdraw at any time without giving a reason and this will not affect their future medical care.

There is no anticipated direct benefit of this study to participants, but it is hoped that the information obtained will help to identify a biomarker for therapeutic application in future trials.

11. Service Users and Patient and Public Involvement

The research team have met with the PPI stroke panel on 17th November 2023 and received positive feedback with discussion points actioned.

12. Dissemination

The overall findings of this study will be presented locally to the academic directorates of Neuroscience. The research team will also aim to present the findings at international scientific meetings and will write up the findings for publication in peer – reviewed journals. The study will be registered with Sheffield Teaching Hospitals and will be advertised on the University of Sheffield website under the Biomedical Research Centre page and be registered on ClinicalTrials.org.

13. Taking the Work Forward

The pilot data generated from this project will contribute towards future grant submissions. This pilot work would look to generate an application to fund a multi-centre trial involving a larger number of participants to evaluate the effect of tVNS on reducing complications following SAH. We would look to apply to an NIHR funding stream for the funding of a further study to establish whether tVNS has a statistically significant impact on improving outcomes after SAH.

14. Intellectual Property (IP)

No IP is anticipated from the completion of this study.

15. Costing Schedule

The funding for this project will be provided by the stroke research account within the Academic Directorate of Neurosciences at Sheffield Teaching Hospitals.

Matthew Myers is an academic trainee funded by the NIHR with dedicated academic time. He will be involved at all stages of the project. Masters students may be recruited to assist in participant recruitment and data collection. No additional members of staff will need to be funded.

The necessary devices, including TVNS and lumos, are already available to the department and research team at no additional cost.

16. Funding Arrangements

The funding for this project will be provided by the stroke research account within the Academic Directorate of Neurosciences at Sheffield Teaching Hospitals.

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