Safety and efficacy of non-invasive Vagus Nerve Stimulation (nVNS) in the treatment of headache in Subarachnoid Hemorrhage (SAH) (the VANQUISH study)

Principal Investigator: Tania Rebeiz

Version Number: 6

12 January 2023

1 TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Safety and efficacy of non-invasive Vagus Nerve Stimulation (nVNS) in the treatment of headache in Subarachnoid Hemorrhage (SAH)
Study Description:	This is a single site, randomized, sham-controlled, double-blind study assessing the feasibility, safety, tolerability, and efficacy of non-invasive VNS (nVNS) in the treatment of headache in subarachnoid hemorrhage (SAH). We hypothesize that two-two minute noninvasive stimulations of the cervical branch of the Vagus nerve, every 5 hours, is efficacious in safely reducing headache intensity and frequency in patients with headache due to SAH, during the patient's intensive care unit (ICU) stay. After screening and obtaining informed consent, eligible patients diagnosed with SAH on head scans, admitted to the Neurosurgical Intensive Care Unit (NSCU) at Northshore University Hospital will be randomized to either the treatment (stimulation of the cervical branch of the Vagus nerve) or sham (inactive stimulation) group. Pain intensity will be evaluated every 4 hours. Non-invasive stimulation will be performed

	every 5 hours. Device related adverse events, mean headache intensity, and mean and peak morphine equivalence dosage during the study period will be compared between the VNS group and the sham group. Patients will be on continuous telemetry with frequent vital sign measurement. Opiate related adverse events will also be monitored.
Locations	North Shore University Hospital Lenox Hill Hospital Yale University Hospital- for specimen processing
Objectives:	
	The primary objective of this study is to examine the safety and efficacy of nVNS as a treatment for headache in subarachnoid hemorrhage (SAH).
Endpoints:	The primary safety endpoint for this study is the incidence of device related serious adverse events. The primary outcome measurements for effectiveness is: -The difference between the active and sham treatment groups in morphine equivalence dosage Secondary endpoints include descriptive comparisons between the active and sham treatment groups in: - The difference between the active and sham treatment groups in the mean daily headache intensity - The difference between total overall morphine equivalence dosage between the active and sham group per subject during study -Opiate related adverse events (such as urinary retention, constipation, sedation, respiratory depression, nausea, vomiting and pruritis)
Study Population:	This is a pilot study of 40 subjects. We will enroll men and woman 18 – 75 years of age. Patients with alcohol and drug addiction will be

	excluded. Our patient population mostly represents the New York state area, mostly Long island and Queens as we are the main referral hospital to that area.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	The Northwell system has a policy that most subarachnoid hemorrhages admitted to our affiliated hospitals get transferred to the Northshore University Hospital Neurosurgical Care Unit as it is the tertiary Neuro-interventional and Neurosurgical Unit of the system. As a result, those patients are automatically transferred to our unit, where screening and enrollment can be initiated.
Description of Study Intervention:	The intervention consists of a transcutaneous non-invasive stimulation of the cervical branch of the vagus nerve (nVNS) using gammaCore, an FDA approved device for the treatment of migraine and cluster headache. This will be compared to the sham device, which is the same device which does not stimulate the nerve. Stimulation frequency will be identical to the frequency used in previous nVNS studies for the treatment of migraine headache. Dosing will be as described in this protocol. The IRB approved healthcare provider will show the subject how to stimulate the cervical branch of the Vagus nerve transcutaneously, and will increase the amplitude/intensity gradually. If pain or discomfort is felt, the amplitude will be decreased to a comfortable level. Rescue pain killers (acetaminophen, opiates) will be given as needed. In the sham group, the sham device will be applied in the same location and at the same frequency as in the treatment group.
Study Duration:	Study period is up to 10 days starting 24 hours post successful treatment of the aneurysm.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening and randomization Days -1-5	Enrollment/Baseline Days 2-5 till discharge from NSCU	Step down unit Neurosurgical floor	Final Study discharge
Informed consent	X			
Demographics	X			
Medical history	X			
Administer study intervention		X	X	
Concomitant medication review	X	X	X	X
Physical exam (including height and weight)	X	X	X	X
Vital signs (temperature, BP, HR, Oxygen saturation)	X	Hourly and as needed	X	X
Height	X			
Weight	X	X		X
Performance status	X	X	x	X
Hematology	X	X	X	
serum chemistry	X	X	X	
Pregnancy test	X			
EKG (as indicated)	X	x	As needed	
Daily narcotic use	x	x	x	
Adverse event review and evaluation	x	x	x	x
Radiologic/Imaging assessment (CT, MRI, CTA/CTP, angiogram)	X	x	x	x
Patient satisfaction assessment				x
Complete Case Report Forms (CRFs)	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Subarachnoid hemorrhage (SAH) is a devastating condition, most commonly due to trauma and aneurysm rupture, and carries significant mortality and morbidity. About half of the survivors are left with disability. Some of the known complications are aneurysm re-rupture, seizures, central fever, delayed cerebral ischemia (DCI) and hydrocephalus (ref). SAH induces a systemic inflammatory immune response (SIRS) and over activated sympathetic nervous system. As a result, patients are monitored carefully in the intensive care unit, with frequent neurologic examination. The most common presenting sign is headache, which worsens in the first week.(1) The hallmark of this headache in SAH is that it is often described as “the worst headache of my life”. Evaluating a cohort of patients with aneurysmal SAH, Magalhães et al., showed that headache lasts on average 12.5 days, and that anxiety was a risk factor for persistent headache.(2) In addition, headache is one of the most common cause of readmission in SAH, leading to an increase in healthcare cost.(3) Non-enhanced cat scan (CT) of the head

showing blood in the subarachnoid space confirms the diagnosis of SAH. Unfortunately, there are no guidelines on the management of headache due to SAH, this is possibly due to the limited therapeutic interventions. Most pain killers fail to control headache intensity and carry risks. Physicians resort to opiates which can cause central nervous system (CNS) depression, alter the neurologic examination and lead to unnecessary tests, increasing hospital length of stay and healthcare cost. Opiates can cause ileus and urinary retention which are commonly seen in the Intensive Care Unit (ICU) setting. In addition, the over usage of opiates due to its potent analgesic effect has led to what we are currently experiencing in the United States, an opiate epidemic. A recent study showed that on day 4-5 post SAH ictus, patients use a daily mean morphine equivalent dose of 18 mg intravenously. In addition, some patients were prescribed a maximum total daily dose of 16 mg of Decadron.(4) There is lack of strong evidence advocating the use of Decadron in the management of headache due to SAH. However, it is frequently used given the assumption that it decreases the inflammation caused by the blood products, thought to be involved in the pathogenesis of headache, as a result, decrease headache intensity. However, steroids can cause immunosuppression, hyperglycemia, decrease wound healing, peptic ulcers, and has been shown to increase mortality in traumatic brain injury. Acetaminophen is frequently used, but not effective in controlling pain, and care should be taken to avoid toxic levels.(1) In a prospective study, Morad et al., showed that continuous usage of opiates and acetaminophen failed to attenuate severe headache in SAH patients, even though the daily mean intravenous morphine equivalence of 15.7 mg was used, with no significant decline in usage during the hospital stay. The authors suggest the need for a more effective and safe therapeutic intervention.(5) Headache is the major complaint in patients with SAH and is very disabling, leading to days of pain and suffering. Unfortunately until today, there are no effective treatments. Vagus nerve stimulation has been shown to have nociceptive effect and could potentially help safely manage headache in this patient population. In addition, vagus nerve stimulation activates the parasympathetic nervous system (SAH is a hyperactive sympathetic response) and has anti-inflammatory properties that could potentially prevent secondary brain injury (DCI and stroke) seen in aneurysmal SAH (a-SAH). The FDA recently approved the noninvasive form, which has been proven to be safe and efficacious in controlling different types of headaches, which share similar pathophysiology to SAH related headache, making it an attractive therapeutic option for this patient population.

2.2 Background

Headache related to SAH is thought to be due to meningeal irritation from the blood products which activates an inflammatory cascade, leading to pain. SAH causes upregulation of the NMDA receptors as a result magnesium, an antagonist of the NMDA receptor is being investigated as a treatment for SAH related headache.(6) Cortical spreading depression commonly seen in SAH patients could also be involved in headache pathogenesis. It is frequently seen in migraine with aura. Vagus Nerve Stimulation (VNS) has been FDA approved for many years for the treatment of refractory seizures and depression. Recently, the FDA approved the transcutaneous form, which stimulates the cervical branch of the vagus nerve for the treatment of migraine and cluster headaches, pathologies that share similar

pathophysiology (inflammation, cortical spreading depression) to headache and secondary brain injury caused by subarachnoid hemorrhage. This is a very attractive way of stimulating the nerve avoiding the surgical complications of the invasive form, with strong evidence showing safety and efficacy in multiple patient populations.

Some of the potential beneficial effects of nVNS in subarachnoid hemorrhage patients are (Figure 1):

1-Analgesic Effect: Oshinsky et al showed that nVNS could reverse allodynia in animal model, by reversing the rise in extracellular glutamate levels in the trigeminal nucleus seen when the meninges are infused with inflammatory mediators.(7) VNS has also been shown to inhibit trigeminal nerve firing when animal dura was stimulated.(8) Functional imaging in individuals receiving nVNS shows the deactivation of the spinal trigeminal nucleus.(9) The trigeminal nucleus is the major sensory nucleus for pain.

2- Cortical spreading depression (CSD) is a wave of electrical depolarization often seen in patients with traumatic brain injury, strokes, subarachnoid hemorrhage and migraine. A recent study detected 120 CSD with subdural electroencephalogram (ECoG) in 8 out of 9 patients with aneurysmal SAH. The frequency of CSD peaked between days 5 and 7. Clustering of CSD correlated with the hypoxemia and development of delayed ischemic neurologic deficit.(10) It is postulated that inhibiting cortical spreading depression could provide neuroprotection. In SAH animal model, noninvasive VNS has been shown to significantly reduce CSD.(11) Patients with migraine with aura are at increased risk of having strokes, this is thought to be due to CSD. Inhibiting CSD with VNS could potentially help reduce headache in SAH and prevent delayed cerebral ischemia and strokes.

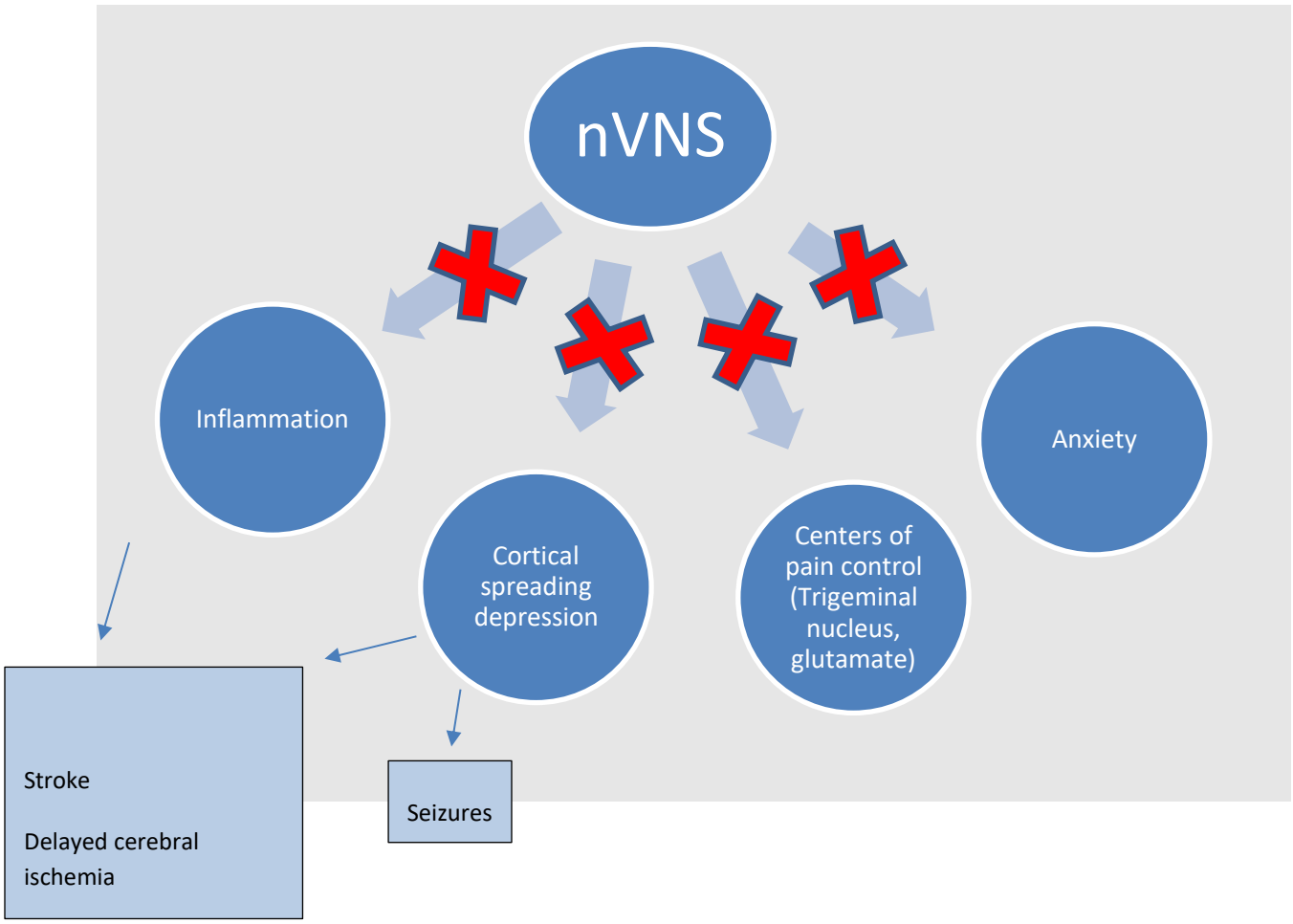
3- Inflammation: Vagus nerve has been shown to control the neuroendocrine immune axis. It regulates the immune system through the Hypothalamus Pituitary Adrenal (HPA) pathway and modulates the release of inflammatory mediators through the spleen and immune cells.(12) There are multiple ongoing human studies using VNS for the treatment of autoimmune diseases like rheumatoid arthritis and Crohn's disease. These inflammatory mediators are thought to be involved in the pathogenesis of headache and secondary brain injury in SAH patients. nVNS has been shown to decrease the rate of aneurysm rupture and improve outcome in a mouse model of intracranial aneurysm. (13)

4- Psychiatric disorders: A recent pilot study revealed that VNS could have a potential beneficial effect in the treatment of anxiety.(14) In addition, there is an ongoing study evaluating nVNS in generalized anxiety disorder, chronic pain, depression and PTSD.(15, 16) Magalhães et al. showed that anxiety is a risk factor for persistent headache in SAH .(2)

5- Seizures: VNS is FDA approved for the treatment of refractory seizures. Seizures are commonly seen in SAH, and often physicians use prophylactic antiepileptic's in SAH, although this is not recommended due to the side effects of the antiepileptic's. nVNS could potentially prevent seizures in patients with SAH.

In summary, through the deactivation of the pain centers, inhibition of CSD, reduction of inflammatory markers and glutamate levels, and being an antagonist of the NMDA receptors thought to be involved in SAH headache pathogenesis, nVNS could be an effective analgesic in patients with SAH. (Figure1)

Figure 1: Mechanism of action of Vagus nerve stimulation



A recent meta-analysis reviewing 3 randomized controlled trials for cluster headache, one randomized trial for migraine, and multiple observational studies, concluded that nVNS is effective and safe in the treatment of headache.(17)

Table taken from a systematic review on the clinical evidence of devices in the treatment of migraine and cluster headache (18)

Device	Study	Authors	CE marked	FDA cleared	AAN Classification of Evidence	GRADE
nVNS	Acute migraine treatment*	Tassorelli *et al* **21**	Yes	Yes	I	High
	Migraine prevention*†	Silberstein *et al* (EVENT)**31**	Yes	No	II	Low
	Acute CH treatment	Silberstein *et al* (ACT1)**22**	Yes	Yes¶	NA	High
		Goadsby *et al* **23**			NA	High
	CH prevention‡	Gaul *et al* **24**	Yes	Yes	NA	High
		Marin *et al* **25**			NA	Moderate
e-TNS	Acute migraine treatment	Chou *et al* **26**	Yes	Yes	NA	Moderate
	Migraine prevention*	Schoenen *et al* **27**	Yes	Yes	III	Moderate
	Acute CH treatment§	NA	No	No	NA	NA
	CH prevention§	NA	No	No	NA	NA
sTMS	Acute migraine treatment	Lipton *et al* [28]	Yes	Yes	NA	Moderate
	Migraine prevention	Starling *et al* **29**	Yes	Yes	NA	Low
	Acute CH treatment§	NA	No	No	NA	NA
	CH prevention§	NA	No	No	NA	NA

Given the potential benefits and its safety profile, nVNS could potentially help control headache and secondary brain injury due to SAH.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Major side effects of VNS historically have been due to the surgical procedure or the continuous on-off stimulation. With transcutaneous VNS, one can avoid these side effects. Per the gammaCore instructions for use (IFU), some of the potential reversable complications are dyspnea, dysgusia, and muscle twitching or pain during the stimulation.(19) Per the IFU, other mild to moderate complications are: “Paresthesia or dysesthesias lasting beyond the treatment period, skin irritation due to allergic reaction to gel, diarrhea, nausea/vomiting, or loss of appetite, sweating, fatigue, depressed mood, tinnitus, progression of headache symptom, abnormal heart rhythm. Potential risks associated with non-invasive vagus nerve stimulation that may be moderate to severe: progression of headache symptoms, syncope, light-headedness, and/or dizziness”.(19)

A recent systematic review of 51 studies evaluating the safety of noninvasive VNS, revealed that it is safe and well tolerated with minimal side effects. Skin irritation was the most common side effect, followed by headache accounting for 3.6% and nasopharyngitis in 1.7% .(20) Cardiac side effects are one of the most feared complications of invasive VNS. However, the review, which included patients with previous cardiac disease, found that cardiac side effects from nVNS on either side are minimal, accounting for only 1 out of the 1322 patients. The individual developed symptomatic bradycardia after nVNS.(20) In addition, there are ongoing studies evaluating the usefulness of nVNS in heart failure. Other rare complications are dizziness, facial palsy, nausea and vomiting. In addition, Redgrave et al could not show that side effects correlated with nVNS dose.(20) nVNS has not been studied in patients with subarachnoid hemorrhage or brain aneurysms, however the invasive form has been used in patients with cerebral vascular malformations, and we are unaware of any cases in the literature of intracranial hemorrhage due to VNS. There is an ongoing clinical trial on safety of noninvasive VNS, in moderate traumatic brain injury which include “operative intracranial lesions”.(21) A recent pilot study with invasive VNS in chronic stroke showed that it was feasable, tolerable and safe.(22) Given the lack of human studies in aneurysmal SAH, only patients with completely treated aneurysms will be part of the study. It is important to include this patient population given the potential benefits of VNS in controlling secondary brain injury (strokes and delayed cerebral ischmia) thought to be due to inflammation and cortical spreading depression. These secondary complications seen in a-SAH are not typically seen in other causes of SAH. In addition, a recent study on nVNS in a mouse model with cerebral aneurysm ahowed that daily stimulation of the vagus nerve could be actually protective and decreased the risk of aneurysmal rupture(13). Other vascular malformations will be excluded, given that their interventional treatment is more complicated. It is unknown if nVNS has long-term side effects, however, studies have shown that most common long-term complications seen in the invasive

form were due to recurrent surgeries for device malfunction (battery and lead replacement). This is bypassed with the nVNS.

2.3.2 KNOWN POTENTIAL BENEFITS

gammaCore has been successfully studied for the acute and preventive treatment of cluster and migraine headache.(19) It has been proven to decrease headache intensity, and prevent migraine attacks. To this point it has not been studied in patients with headache due to SAH. Given the shared pathophysiology (inflammation, cortical spread depression) and the potential of deactivating the nociceptive center, nVNS could potentially alleviate SAH related headache, decreasing the usage of opiates and steroids and thereby decreasing their side effects. This could potentially decrease the ICU and hospital length of stay, decrease the readmission rate from headache due to SAH, decrease the outpatient usage of opiates and prevent opiate dependency.
In addition, nVNS could also provide neuroprotection against stroke, one of the most feared complication in a-SAH. Stroke in a-SAH is thought to be due to vasospasm of blood vessels caused by inflammation and cortical spreading depression leading to ischemia. In animal model, noninvasive VNS has been shown to significantly reduce CSD.(11) In addition, nVNS has anti-inflammatory properties. Experimental animal studies have shown that VNS has the potential of improving outcome in critical illnesses through its anti-inflammatory effects which could potentially extend to sepsis, intracranial hemorrhage, ventilator related lung injury, postoperative cognitive dysfunction, myocardial ischemia and reperfusion injury. One of the postulated mechanisms, is that it regulates α7nAChR which regulates inflammation.(23) Animal studies have shown that stimulating the α7nACh decreases inflammatory markers.(24) Through inhibiting CSD and controlling inflammation, nVNS could potentially prevent secondary brain injury (strokes and DCI) seen in a-SAH patients.

Studies have also shown that VNS enhances neuroplasticity, which could fasten recovery. Animal studies on intracranial hemorrhage showed that VNS improves functional recovery.(25) Multiple ongoing studies are evaluating the beneficial effects of VNS in improving functional recovery during rehabilitation of patients with strokes.(22) nVNS could potentially help recovery from SAH.

In Summary, some of the immediate potential benefits of non-invasive VNS could include: control of headache intensity, decreasing the side effects of narcotic and steroid use, prevent DCI and strokes due to SAH, prevent seizures, decrease the SIRS response by regulating the sympathetic nervous system and regulating α7nAChR, and decrease ICU and hospital length of stay due to decrease usage of opiates leading to loss of neurologic examination and leading to unnecessary testing.

Some of the long-range potential benefits might include decreased readmission rates from headache due to SAH, decrease outpatient usage of opiates, and prevent opiate dependency and improving recovery through enhancing neuroplasticity.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although the risks of nVNS in SAH population are unknown, a recent study in a mouse model of SAH showed that it decreased aneurysmal rupture rate and improved outcomes in those with ruptured aneurysm. The authors noted the potential for nVNS in humans and the ability to translate their research to human studies.(13) To minimize risks, if an aneurysm has been identified to be the cause of the SAH, patients will only be enrolled when the aneurysm has been completely treated. In addition, while in the NSCU, patients will be continuously monitored via telemetry, with frequent BP measurement. Studies conducted on patients with migraine and cluster headache were conducted as outpatient. Our patients are continuously monitored, and the medical staff are well equipped to treat any medical emergency. Vagus nerve stimulation will only be administered if the vital signs are stable (SBP>100 mmHg, MAP>60 mmHg, HR>60, Oxygen saturation > 90%).

3 OBJECTIVES AND ENDPOINTS

The primary outcome measurement for effectiveness is:

-The difference between the active and sham treatment groups in mean daily morphine equivalence dosage during study

Secondary endpoints include descriptive comparisons between the active and sham treatment groups in:

- The difference in mean daily headache intensity during the study
- The difference between total overall morphine equivalence dosages per subject during study
-Opiate related adverse events (such as urinary retention, constipation, sedation, nausea, vomiting and pruritis)
- The difference in cytokines levels and brain permeability markers in the blood and/or CSF before and after stimulation and between the sham and active device group
- Effects of VNS on brain permeability measured through CT perfusion studies
-The difference in modified rankin scale at hospital discharge and during outpatient follow up. This will be collected retrospectively from the follow up outpatient visit.

Exploratory analyses will include descriptive comparisons of the rates of stroke, vasospasm, DCI, seizure, central fever and severity of vasospasm between the active and sham treatment groups.

OBJECTIVES	ENDPOINTS
Primary Objective:	

Incidence of device related serious adverse events.	Proportion of patients with device related adverse events
The difference between the active and sham treatment groups in mean daily morphine equivalence dosage during study	Morphine equivalence dosage will be calculated per day.
<u>Secondary Objectives</u>	
The difference between the active and sham treatment groups in the mean daily headache intensity during the study	Headache intensity will be measured throughout the day and a mean daily headache intensity will be calculated.
The difference between total overall morphine equivalence dosage between the active and sham group per subject during study	Total morphine equivalence dosage for the duration of the study will be calculated.
Incidence of opiate related adverse events (such as urinary retention, constipation, sedation, respiratory depression, nausea, vomiting and pruritis)	Number of patients with of urinary retention, constipation, sedation, nausea, respiratory depression, vomiting and pruritis.
The difference in cytokines levels and blood brain permeability markers in the blood and/or CSF before and after stimulation and between the sham and active group	When possible, cytokines levels and permeability markers will be measure in the blood and/or serum just before the first vagus nerve stimulation and approximately 24 hours later, after the 11:30 AM stimulation session. If possible, this will be repeated on day 5 and 7 post-ictus as it is the period of cerebral vasospasm

	Immunologic investigations include but not limited to, measurement of inflammatory protein levels, RNA sequencing of leukocyte and stimulation assays.
Evaluate the effects of VNS on blood brain barrier integrity	The integrity of the blood brain barrier will be evaluated through CT perfusion if performed as standard of care.
Exploratory objectives	
Comparisons of the rates of stroke, vasospasm, DCI, seizure, and central fever between the active and sham treatment groups	Neuroimaging upon admission and at discharge will be compared and evidence of new strokes will be noted. The presence of DCI (change in neurologic examination thought to be due to vasospasm) will be evaluated. Transcranial doppler velocities will be compared between the active and sham groups The number of days with central fever will be compared between the active and sham groups Incidence of seizures will be compared between the active and sham groups
Effect of nVNS on severity of cerebral vasospasm during DSA	Rate of change in the severity of cerebral vasospasm will be noted before and during or after nVNS

4 STUDY DESIGN

4.1 OVERALL DESIGN

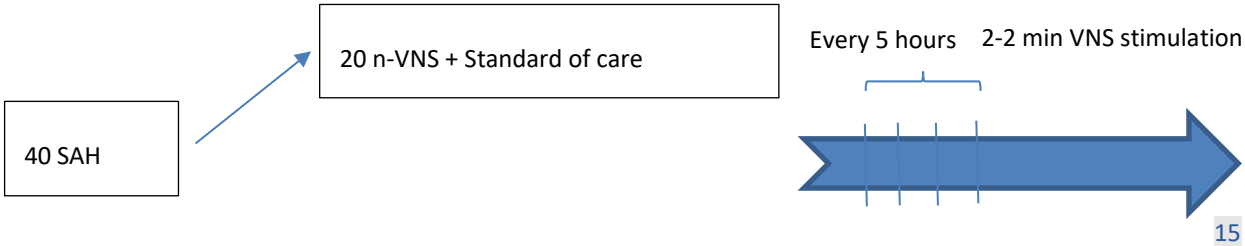
This is a single site, randomized sham controlled, double blinded, and parallel group study comparing the efficacy and safety of transcutaneous VNS in the management of headache

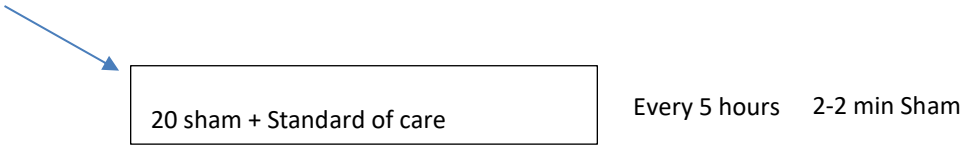
related to subarachnoid hemorrhage. We will screen patients diagnosed with subarachnoid hemorrhage who are admitted to Northshore University Hospital Neurosurgical Critical Care Unit. These are patients admitted under our care. Eligible patients will be enrolled after signing the informed consent. Enrollment will be performed between days 1 and 5 of aneurysm treatment. Subjects will be randomized into one of the two groups below:

1. Group 1: Control (patients will receive treatment using an inactive VNS device)
2. Group 2: Treatment (patients will receive treatment using an active VNS device)

The Biostatistics Unit at the Feinstein Institute for Medical Research [BU-FIMR] will develop a randomization plan for the study using the Biostatistics Randomization Management System [BRMS]. BRMS is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using a personal computer with internet access. A randomization allocation will be generated by the BU-FIMR using the method of permuted blocks. Details of the randomization procedure, including required record keeping will be further developed upon approval of the protocol. The treatment group will receive 2, 2 minute stimulations every 5 hours delivered by a blinded provider. The person assessing the pain intensity, vital signs, and giving pain killers and the participants will be blinded. Pain will be rated pre and post stimulation by the blinded caregiver. During NSCU stay at each stimulation, patients will be on continuous telemetry, and vital signs will be recorded before and at the end of the treatment and hourly for the rest of the day by the blinded caregiver. The control group will receive a sham device, the device is physically identical to the active device, and however no stimulation will be delivered. Patients in either group will be informed that they might feel a tingling sensation or muscle twitch with either device. Before the stimulation is initiated, vital signs will be checked. This includes HR, SBP, MAP, and oxygen saturation. If vital signs are stable, defined as HR>60 beats per minute, SBP> 100 mmHg, MAP> 60 mm HG, and saturation > 90% on room air, nasal cannula or face mask, the stimulation will be provided. In addition, both groups will receive standard of care abortive medications. Pain is usually assessed every 4 hours and as needed, and abortive medications are given depending on the intensity of the headache. 40 patients will be enrolled, and VNS will be performed for up to 10 days.

Figure: Protocol





4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a randomized sham-controlled pilot study. The patients and the person assessing the patient's response will be blinded. Standard medical care treatment will be provided to both arms of the study.

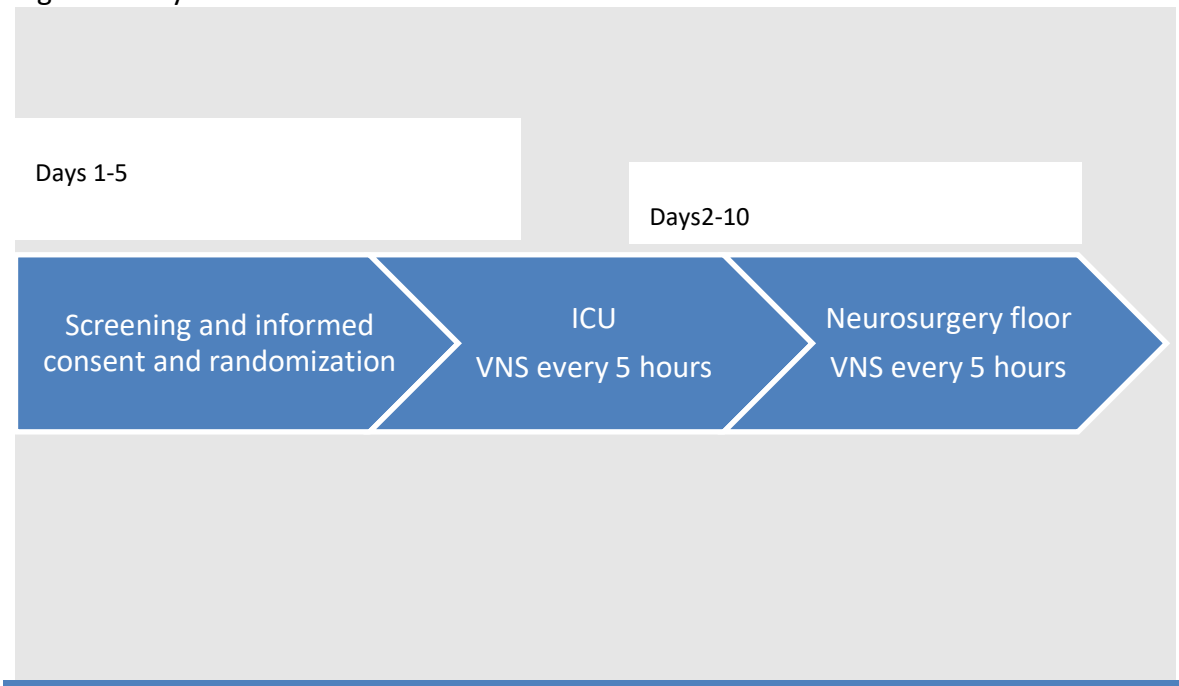
4.3 JUSTIFICATION FOR DOSE

This will be a transcutaneous stimulation of the cervical branch of the Vagus nerve to avoid the operative complications of invasive VNS. Stimulation frequency will be similar to what was has been used in studies on headache.(17) Patients will receive a dosage based on the instructions from the gammaCore IFU: the physician or patient will start stimulating the cervical branch of the Vagus nerve and will gradually increase the amplitude to the most comfortable stimulation level.

4.4 END OF STUDY DEFINITION

The study intervention will be up to 10 days in length. Vagus stimulation will be performed 4 times daily (approximately at 6:30AM, 11:30AM, 4:30PM and 9:30PM). Data collection will continue till hospital discharge. If the participant becomes hemodynamically unstable, defined as hypotension requiring vasopressors the VNS will be held for safety purposes. However, it will be resumed, once the patient is stabilized, off vasopressors for 48 hours. If the patient is being hemodynamically augmented for symptomatic vasospasm, n-VNS will not be withheld as the beneficial effects of n-VNS on symptomatic vasospasm will be investigated in this study.

Figure: Study Timeline



5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants must fulfill all of the inclusion criteria in order to be eligible for the study:

- Established signed and dated informed consent form
- Can be enrolled within 5 days of cerebral aneurysm treatment.
- CT of the head revealing blood in the subarachnoid space
- Subject has ruptured cerebral aneurysm or SAH patients who do not have vascular malformation on cerebral angiogram.
- Subject is male or female 18 -75 years of age
- Subject is alert able to verbalize pain at the time of enrollment
- Subject reports pain of 7 and greater on a 10 Point Pain numeric rating scale or presenting with severe headache.
- Female of reproductive age must have a negative pregnancy test (Urine or blood test)

nVNS will only be performed if vital signs are stable (HR>60, SBP> 100 mmHg, MAP> 60 mmhg, and saturation > 90% on room, nasal cannula or face mask). Then the vagus nerve will be stimulated.

5.2 EXCLUSION CRITERIA

Patient who meets any of the following criteria will be excluded:

- Use of any concomitant electrostimulation devices (Pacemaker, defibrillator, deep brain stimulation.)
- Unsecured ruptured aneurysm defined as aneurysm that has not been surgically or endovascularly treated. Previous carotid surgeries or known history of carotid artery disease
- Screws, metals or device in the neck
- History of secondary or tertiary heart blocks, ventricular tachycardia, SVT (including atrial fibrillation)
- Alcoholics (CAGE scale of 2 or greater). If patients are on CIWA protocol for alcohol withdrawal, the patient will be excluded from the study.
- Drug addicts or chronic opioid users confirmed by history or with urine toxicology showing opiates or cocaine
- Traumatic subarachnoid hemorrhage
- Thin cortical subarachnoid hemorrhage not due to a cerebral aneurysm

Fria

5.3 LIFESTYLE CONSIDERATIONS

There will be no lifestyle modification related to the study

5.4 PRE-SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (pre-screen failure) because of unsecured aneurysm intubated or has symptomatic hydrocephalus or symptomatic bradycardia may be rescreened once the aneurysm is secured, patient is extubated and stabilized, and EVD is placed. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The neurosurgical critical care unit (NSCU) at Northshore University Hospital is the main referral unit for the healthcare system for patients with subarachnoid hemorrhage. All transferred patients
are admitted to the NSCU, as a result, patients can be easily identified by the research team on a daily basis. Every day, the neurointensivist or the research coordinator will evaluate which patients admitted to the NSCU have been diagnosed with subarachnoid hemorrhage. If an aneurysm is found to be the cause of the SAH, surgical or endovascular treatment of the aneurysm is typically performed within 72 hours of diagnosis. Patients will be included in the study once the aneurysm has been treated. The primary investigator, or sub investigators will take consent from the patient. The primary investigator will ensure that the sub investigators and research assistants are trained and knowledgeable of the research protocol. Patients enrolled in the study will be followed up to 10 days starting 24 hours post successful treatment of the aneurysm unless discharged earlier from the hospital.

We admit on average 110 SAH cases a year. If we assume that 50% satisfy our inclusion criteria, and that 70% will sign the inform consent, we should be able to reach our target number in approximately 12 months. Patients identified in the NSCU will be approached by the research team, and the study will be explained tothem.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

GammaCore has received FDA approval/clearance for the treatment of acute migraine and acute or preventive treatment of cluster headache. It has not been studied for the treatment of headache in SAH. Given the shared pathogenesis of headache in SAH and migraine, we would like to test the device in SAH patient population. Per the GammaCore IFU: “gammaCore Sapphire™ (non-invasive vagus nerve stimulator) is a multi-use, hand-held, rechargeable, portable device consisting of a rechargeable battery, signal-generating and -amplifying electronics, and a control button for the subject to adjust the signal amplitude. GammaCore Sapphire provides visible (display) and audible (beep) feedback on the device and stimulation status. A pair of stainless steel surfaces, which are the skin contact surfaces (stimulation surfaces), allows the delivery of a proprietary electrical signal. Tubes of electroCore-approved gel are provided with each unit. The subject applies the gel to the stimulation surfaces to maintain an uninterrupted conductive path from the stimulation surfaces to the skin on the neck. The stimulation surfaces are capped when not in use. gammaCore Sapphire produces a low-voltage electric signal consisting of five 5000-Hz pulses that are repeated at a rate of 25 Hz. The waveform of the electric pulses is approximately a sine wave with a peak voltage limited to 24 V when placed on the skin and a maximum output current of 60 mA.(19). Each stimulation is designed to be applied for two minutes (120 seconds), after which the device automatically turns off. Each device allows for multiple stimulations”.(19)

6.1.2 DOSING AND ADMINISTRATION

Two-two minute transcutaneous stimulations will be administered every 5 hours (approximately 6:30AM, 11:30 AM, 4:30 PM and 9:30 PM) with no relation to meals. Some patients might miss few stimulations as they might be getting a procedure, have unstable vital signs, or refuse the stimulation, amongst other reasons that might make stimulation not feasible. If vital signs are stable (HR > 60 beats/minute, and SBP> 100 mmHg and MAP> 60 mmhg and saturation > 90% on room, nasal cannula or face mask,), nVNS or Sham will be initiated. We will start by placing gel on the skin of the neck, the device will be placed in direct contact with the gel and the skin. The stimulation will be performed by the patient, with assistance from an IRB approved personnel if the patient is uncomfortable performing it. The stimulation intensity will be increased as directed by the gammaCore pamphlet. Patients will be informed that they may or may not feel a tingling sensation with the investigational device and the sham device. Two 2 minutes stimulation will be provided. Tolerance will be assessed during and directly after stimulation and every 5 hours afterwards as directed by the intensivist on call.

If a digital subtraction angiography is being performed for vasospasm, nVNS will be delivered to assess its effect on cerebral vasospasm.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Electrocore is providing gammaCore devices, providing expertise related to study design and execution and will provide device training prior to study initiation. ElectroCore will not be involved in the acquisition of data. Devices will be tracked using a device accountability log.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

gammaCore (nVNS) Sapphire(19)

The device or its immediate package will bear a label with the following information:

1- The name and place of business of the manufacturer, packer, or distributer
2- The quantity of contents
3- The following statement “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use”
4- The labels will describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions

6.2.3 PRODUCT STORAGE AND STABILITY

“gammaCore should be stored at room temperature away from moisture • Range: 0°C to 38°C (32°F to 100°F), Humidity: 10% to 90%, Barometric Pressure: 80 to 101 kPa Replace cap after each use, Store the device in such a way (eg, drawer or shelf) that the cap remains in place and are not accidentally removed”. (19)

6.2.4 PREPARATION

Per the gammaCore pamphlet “Charge your device before first use. Allow 6 to 7 hours for a full charge. High temperatures may increase the charging time. If the device has no charge, it takes only a few minutes to charge an additional two to three treatments. Monitor battery life and charge as needed to maintain adequate number of treatments on device”(19)

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To minimize bias, this will be a randomized controlled trial. Patients will be randomized using variable block design, assigning patients 1:1 to the treatement group n-VNS and sham group, with concealment of allocation. Participants and the provider assessing the pain scale, providing the pain killers and assessing for adverse events will be blinded.

6.4 STUDY INTERVENTION COMPLIANCE

The trial will be evaluated on a daily basis if there are active patients enrolled. The principle investigator will meet monthly with the study coordinator, research assistant and co-investigators evaluating the adherence with the study protocol.

The vital signs, medication administered, and pain assessment will be recorded as standard of care in our electronic medical record SUNRISE.

6.5 CONCOMITANT THERAPY

Patients will be given standard of care medication for delayed cerebral ischemia prophylaxis and opiates and acetaminophen for pain control. Opiate addicts and patients on chronic opiates at home will be excluded.

6.5.1 RESCUE MEDICATION

Rescue pain killers will be given per standard of care in both groups.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The study intervention will be held during procedure days, or if the participant gets intubated, or is in shock (cardiogenic, distributive or septic). During non-procedure days, or once extubated and stabilized and participant becomes alert the study intervention can be resumed.

In addition, as stated earlier, if HR< 60 beats/min, SBP<100 mm HG, or MAP< 60 mm HG and oxygen saturation < 90 %, the intervention will be postponed.

If hemodynamic instability or unstable arrhythmia occur during the VNS, and is thought to be due to the VNS by the investigator, the participant will be discontinued from the study procedure, however, will be followed until discharge from the hospital.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive the study intervention for more than 3 consecutive days

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

There should be no loss of follow up as this is an inpatient study. The study will last for up to 10 days.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Per standard of care, patients presenting with signs of SAH like acute severe headache, will get a diagnostic head CT which confirms blood in the subarachnoid space. If patients have symptomatic hydrocephalus (altered mental status with CT head consistent with

hydrocephalus) an external ventricular drain will be placed. Most patients will get either a CT angiogram or a conventional angiogram to rule out a vascular malformation, especially if there is no history of trauma. If an aneurysm is detected, the standard of care is to treat it as soon as possible. Usually, an aneurysm iseither coiled or clipped (craniectomy or craniotomy). Every patient admitted with subarachnoid hemorrhage will get graded accordingly to their headache intensity, level of consciousness and neurologic deficits with the Hunt Hess grade (table 2). Their CT scans also get graded (modified fisher scale mFS) according to the thickness and location of blood (table 3). All subarachnoid hemorrhage (unless there is minimal amount of blood and no vascular malformation) are admitted to the Neurosurgical care unit (NSCU). Detailed physical examination, including the NIHSS, history, including medication history, past medical, surgical history, and social history are recorded in the medical records. North Shore University hospital NSCU is the referral center for most of the hospitals in Northwell health care system. Most aneurysmal SAH patients get transferred to our unit. Per standard of care, all women of child bearing age, admitted to the NSCU get a urine or blood pregnancy test, patients suspected of abusing drugs get urine toxicology. Once in the NSCU, patients get vital signs and neurologic assessment every hour, and pain assessment every 4 hours and as needed. The length of stay in the intensive care unit depends on the amount of blood on the head scan (mFS). Patients with higher mFS are more prone to get delayed cerebral ischemia. As a result, per standard of care, patients with SAH get almost daily transcranial dopplers to monitor for cerebral vasospasm, frequent head scans, occasionally brain perfusion studies and MRI of the brain. Patients are monitored for central fever (vital signs, blood cultures), cerebral salt wasting with frequent BMP and urine output measurements, seizures with PRN electroencephalograms (EEG). Once out of the critical care period, (vasospasm usually starts at day 3 post bleeding and peaks at day 10), patients get transferred to a regular neurosurgical floor before being discharged home or to rehabilitation. On average patients stay in the NSCU between 2-21 days. All patients admitted to the NSCU with SAH will be screened and evaluated for the inclusion and exclusion criteria after obtaining an informed consent.

Screening involves reviewing the medical records following HIPPA regulation for: Age, gender, ethnicity, presence of aneurysm, day of rupture, etiology of the SAH if not aneurysmal, radiologic (Angiogram, CT head) and medical history before and after the aneurysm is secured, Glasgow coma score before and after aneurysm repair, modified fisher scale (mFS), Hunt-Hess grade (HHS), time of ictus, history of alcohol and drug abuse, presence of hydrocephalus on head CT, presence of an external ventricular drain (EVD) , date of EVD placement, new HHS after EVD placement, clipping or coiling. Medical records will be reviewed for the past medical history (pacemaker, defibrillator, history of CHF, arrhythmias, cervical carotid disease, history of a headache disorder like migraine or cluster headache), physical examination, labs will be reviewed which includes but not limited to pregnancy test and urine toxicology. Headache intensity and opiate, steroids and acetaminophen usage are recorded in the electronic medical record. The presence of vasospasm and delayed cerebral ischemia will be noted.
Once found eligible satisfying the inclusion and exclusion criteria, and informed consent signed, patients will be randomized to either the treatment group or the control group. The same data will be recorded for both groups. The treatment period will start once admitted in the NSCU and will last for up to 10 days.

During the NSCU stay, patients areevaluated for pain every 4 hours. If vital signs are stable (SBP> 100 mmHg and HR> 60 beats per minutes with no arrhythmia on telemetry, MAP> 60 mmHg and oxygen saturation > 90%) patient will receive either the treatment (nVNS) or the Sham device every 5 hours. Headache intensity will be evaluated every four hours. In addition, vital signs will be noted just after stimulation, and hourly afterwards or as ordered by the physician. The daily mean morphine equivalence dosage will be recorded. Concomitant medications will be recorded.

During the ICU length of stay, the following will be assessed and recorded per standard of care :

- Transcranial dopplers (TCD)
- Neuroimaging (CT head, MRI brain, angiograms, CT perfusion with permeability study)
- EVD weaning and day of start of weaning
- Presence of vasospasm, delayed cerebral ischemia, Central fever, Cerebral salt wasting. These are usually recorded in the medical record.
- Urinary retention documented as frequent straight catheterization for more than 3 days
- Constipation evaluated by the need for enema, suppository, lactulose or magnesium oxide administered
- Blood tests, CSF studies
- EEG results
- Neurologic examination including Glasgow coma score, and NIHSS
- Delirium score

When Transcranial dopplers are being done as per standard of care, we will assess the changes in transcranial velocities around the time of the stimulation of the Vagus nerve.

When possible, we will draw blood or in case there is an EVD we will also collect CSF for biomarkers. Not more than 5 ml of blood will be drawn before the 11:30 am stimulation session of the Vagus nerve. This will be repeated approximately 24 hours later, at 11:30 am post VNS stimulation session. This might be repeated on days 5 and 7 post-ictus
In case there is an EVD, 2 cc of CSF from the drain and 20 cc of CSF that is otherwise discarded will be drawn before the 11:30 am stimulation session of the Vagus nerve. Another 2 cc of CSF from the drain and 20 cc of CSF that is otherwise discarded will be drawn approximately 24 hours later, at around 11:30 am post VNS stimulation session. This might be repeated on days 5 and 7 post-ictus.
The CSF will not be taken from the proximal port of the EDV unless it is being tested for CSF cell count or cultures as per standard of care. This is in order not to increase the risk of infection.
Deidentified blood and CSF will be sent to Dr. Lauren Sansing, academic chief in the department of stroke and vascular neurology, Yale, 300 George St suite 353, 06511.

IF CT perfusion is being performed per standard of care between days 3-10, blood brain permeability will be evaluated and results will be compared between the sham group and the active device group.

During the period of the study after the patients are discharged from the ICU to the Neurosurgical floor, we will evaluate their daily headache intensity and morphine equivalence dosage, in addition to their TCD results, Neuroimaging and EEG results, neurologic examination and vital signs.

Table 2: Hunt-Hess Score in aneurysmal SAH: (26, 27)

1. Asymptomatic, mild headache, slight nuchal rigidity
2. Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3. Drowsiness, confusion, mild focal neurologic deficit
4. Stupor, moderate-severe hemiparesis
5. Coma, decerebrate posturing

Table 3: Modified Fisher Scale:(28)

- **grade 0:** no subarachnoid hemorrhage (SAH), no intraventricular hemorrhage (IVH)
- **grade 1 f**ocal or diffuse, thin SAH, no IVH
- **grade 2** thin focal or diffuse SAH, IVH present
- **grade 3** thick focal or diffuse SAH, no IVH
  grade 4: thick focal or diffuse SAH, IVH present

8.2 SAFETY AND OTHER ASSESSMENTS

nVNS has been proven to be safe. However, the risks of VNS in SAH population are not known. In order to minimize the risks, if an aneurysm has been identified to be the cause of the SAH, patients will only be enrolled if the aneurysm has been completely treated. This information will be pulled from the medical record. Past medical and surgical history, respiratory and hemodynamic state will be pulled from the medical record. Vital signs and neurologic examinations are usually performed every 1 to 4 hours depending on the acuity of each case, and pain assessment evaluated every 4 hours and as needed. In the NSCU, patients are on continuous ECG analyzes via telemetry. Stimulation will only be given if HR >60 and the SBP>100 mmHg, MAP> 60 mmHg and oxygen saturation is >90% for safety concerns. The presence of intolerable pain at the stimulation site, skin irritation, hoarseness, and change in the taste, shortness of breath, chest pain, nausea, and vomiting will be evaluated.

Safety outcomes:

- Rate of Symptomatic bradycardia defined as a drop in HR to less than 60 beats per minutes with symptoms, not due to nimodipine. The timing of nimodipine relative to the VNS will be recorded. All patients are on telemetry during the stimulation.
- Rate of drop in blood pressure, defined as a drop in blood pressure requiring fluid resuscitation or vasopressor support thought to be due to the device.
- Rate of side effects: presence of intolerable pain at the stimulation site, skin irritation, nasopharyngitis, hoarseness, dysgeusia, shortness of breath, chest pain, nausea and vomiting.

Figure

Days 1-3 Screening

- Total n=40
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document
- Randomize

Days 2-4 till discharge from ICU Baseline assessments/ Study Intervention

- Administer initial dose of study intervention
- Obtain daily cumulative dosage of all pain medication
- Evaluate presence of evolving stroke on head CT or MRI brain
- Evaluate seizures documented on EEG
- Complete vital signs before and after each stimulation and daily trend
- Questionaire for side effects from VNS post every stimulation
- Trend in daily Transcranial dopplers (TCD)
- Incidence of symptomatic vasospaspm
- Presence of central fever
- Patient satisfaction

Discharge from the hospital or day 10 post-ictus

End of the study

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of the nVNS and/or Standard of Care Treatments, whether or not considered device-related or drug-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event is defined as in the view of the investigator, the occurrence of any of the following complications:

Death
A life-threatening adverse event such as any hemodynamically unstable arrhythmia
Prolongs existing hospitalization
Results in persistent or significant incapacity or disability

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

8.3.2.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities like skin irritation, transient dysgeusia, transient hoarseness, vomiting, mild pain at the stimulation site during stimulation.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning, like mild shortness of breath, chest pain and reversible facial palsy.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". Like hypotension requiring treatement, hemodynamic stable arrhythmia, severe dyspnea requiring medical treatment

8.3.2.2 RELATIONSHIP TO STUDY INTERVENTION

Using the investigator clinical judgment, the relation of the adverse events to the use of the device will be reported as,

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or

chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.2.3 EXPECTEDNESS

Some of the expected adverse events are: application site discomfort, application site irritation/redness, local pain, face/head/neck area (including toothache), muscle twitching and/or contractions, face/head/neck area (including facial droop and/or lip pull), headache/migraine, dizziness, tingling, pricking, or a feeling of "pins and needles" on the skin where the device is applied (paresthesia/dysesthesia)

Additional expected adverse events, which have been associated with other VNS devices, are cough, gastrointestinal discomfort, hoarseness or change in voice, irregular heart beat (arrhythmia), metallic taste, nausea, shortness of breath (dyspnea)

The principle investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may arise at any time. As a result, the patient will be evaluated directly after each stimulation. The neurointensivist in charge will determine the frequency of vital signs and neurologic examination checks.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity and relatedness to the study device, and time of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of the relationship to the device. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

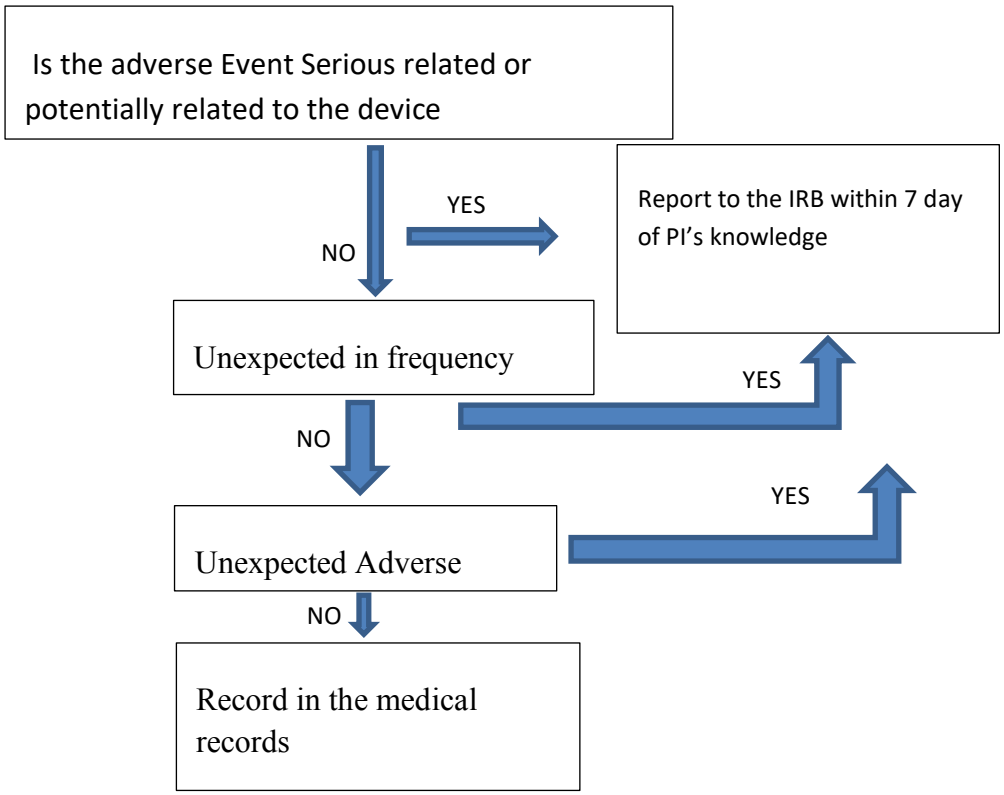
The principal investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 3 days after the last day of study participation (Vagus nerve is stimulated), or until discharge from hospital (whatever comes first) . Events will be followed for outcome information until resolution or stabilization.

8.3.4 ADVERSE EVENT REPORTING

Given that patients with SAH experience many known complications, like hydrocephalus, strokes, delayed cerebral ischemia, cerebral vasospasm, fever, electrolyte disturbance, post-operative complications, only adverse effects that are thought to be related to the study device or are unexpected as part of the natural course of subarachnoid hemorrhage will be reported. The Neurointensivist in charge of the patient will evaluate all side effects and deem its seriousness and relatedness to the device.

All adverse effects thought to be part of the natural history of SAH, or mild side effects that are expected to occur during the VNS such as skin irritation, muscle twitch, transient dyspnea during stimulation, transient hoarseness during stimulation, mild pain at the stimulation site will be recorded in the participant's medical record and will be collected as secondary endpoints. All serious or severe or unexpected side effects related to the device will be reported to the IRB within 7 days of the PI's knowledge. Any unknown adverse event thought to be related to the device will also be reported to the IRB.

Adverse Events reporting:



8.3.5 SERIOUS ADVERSE EVENT REPORTING

The study clinician will report to the IRB any serious adverse event related or potentially related to the study intervention. All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

POTENTIAL SERIOUS ADVERSE EVENT mentioned in section 8.3.2

Monitoring: Participants will be on continuous telemetry recording continuously the EKG, respiratory rate, oxygen saturation, Blood pressure will be recorded one-hour post-stimulation and 1-4 hours afterwards. Vital signs will be recorded before and directly after stimulation, the medical professional will be at bedside during the stimulation monitoring any side effect. Vital signs and neurologic examination are evaluated every 1-4 hours and as needed afterwards. The VNS will be performed in the intensive care unit setting, where personnel are trained in cardiopulmonary resuscitation and treating hemodynamically unstable patients.

Actions:

- Participants must have stable vital signs (SBP> 100mmHg, MAP>60 mmHg, HR> 60 beats/minute, oxygen saturation > 90%, not on mechanical ventilation) before the vagus nerve is stimulated. If unstable vital signs, the stimulation will be skipped, until the patient is more stable.
- If the participants develop a life-threatening arrhythmia thought to be due to the VNS, subject will be taken off therapy, but will continue to be followed until end of study.
- If the participants get intubated or develops hemodynamic shock due to the natural history of the disease, the subject will be taken off the therapy.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 7 working days after the investigator first learns of the effect. The principle investigator is responsible for conducting and evaluating any unanticipated adverse device effect and shall report the results of such evaluation to the reviewing IRB and participating investigators within 7 working days of the event.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

Participants will be directly informed of side effects considered to be related to the VNS.

8.3.7 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.8 REPORTING OF PREGNANCY

Not applicable, only woman with negative pregnancy test will be enrolled in this inpatient trial

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 2 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 7 days of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The participant will be individually informed of any UP. Given that the patients are in the intensive care unit and that most side effects occur during stimulation, the individual will be informed directly (within 3 days) of the unanticipated problems. 3 days in order to make sure that the UP is due to the VNS.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There are no statistical hypotheses in this study. This is a feasibility pilot study that will allow us to better calculate the sample size for a large randomized control study comparing VNS to sham device.

The primary outcome measurements for effectiveness will be:

-The difference between the active and sham treatment groups in mean daily morphine equivalence dosage during the study period

Secondary endpoints include descriptive comparisons between the active and sham treatment groups in:

- The difference between the active and sham treatment groups in mean daily headache intensity during the study period
- The difference between total overall morphine equivalence dosage between the active and sham group per subject during study
-Opiate related adverse events (such as urinary retention, constipation, sedation, nausea, vomiting and pruritis)

Exploratory analyses will include comparisons of the rates of stroke, vasospasm, DCI, seizure, central fever and severity of vasospasm between the active and sham treatment groups.

9.2 SAMPLE SIZE DETERMINATION

There are no statistical hypotheses in this study, and therefore there is no sample size justification for this study. This is a feasibility pilot study that will allow us to better calculate the sample size for a large randomized control study comparing VNS to sham device.

9.3 POPULATIONS FOR ANALYSES

Participants who received at least 1 stimulation will be included in the Intent To Treat (ITT) population. Opiate usage and pain intensity during the days of procedures in which patients are intubated and unconscious will be excluded from the analysis. The days of EDV weaning will be noted, given that hydrocephalus can cause headache due to high ICP. A modified Intent-to-treat (mITT) population inclusive of all subjects who treat at least 7 days with at least 3 stimulations of the study device; and a per-protocol (PP) population of people who are compliant with the treatment regimen for the duration of the study will be analyzed.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

Discrete variables will be tabulated by frequency and proportion of subjects falling in each category.

Continuous variables will be summarized using mean, standard deviation, median, minimum and maximum values.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

-The difference between the active and sham treatment groups in daily mean morphine equivalence dosage during the study

Repeated measures mixed models will be used to describe the difference between the active and sham treatment groups in morphine equivalence dosage during NSCU length of stay. Morphine equivalence dosage will be modeled as a function of treatment group and measurement time. Subject will be included as a random effect. Least squared means will be used to estimate the treatment effect.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- The difference between the active and sham treatment groups in mean headache intensity during study period

Repeated measures mixed models will be used to describe the difference between the active and sham treatment groups in mean headache intensity during NSCU length of stay. Pain will be modeled as a function of treatment group and measurement time. Subject will be included as a random effect. Least squared means will be used to estimate the treatment effect.

- The difference between total overall morphine equivalence dosage between the active and sham group per subject during study

Total overall morphine equivalence dosage in the active and sham treatment groups will be compared using analysis of covariance (ANCOVA) with adjustment for number of days in study.

-Opiate related adverse events (such as urinary retention, constipation, sedation, nausea, vomiting and pruritis)

9.4.4 SAFETY ANALYSES

The primary safety endpoint of this clinical investigation is the overall incidence of device-related serious AEs. The primary safety analysis will be summarized and presented as proportions and respective 95% exact binomial confidence intervals (CIs). The rate of opiate

related adverse events will similarly be presented as proportions and respective 95% exact binomial confidence intervals.

Frequency and percentage of subjects experiencing a specific adverse event will be tabulated by system organ class, preferred term, and treatment group. Summary tables and subject data listings will be provided.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

NA

9.4.6 PLANNED INTERIM ANALYSES

A safety interim analysis may be considered if deemed necessary by the principal investigator

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
If the patient is physical disabled and is unable to sign the informed consent, oral consent process for more than minimal risk research will be followed as stated in the HRPP Policy and Procedures Manual. If patient decision capacity is in doubt, a mini mental state examination will be performed, and if the score is <24, the signature of a healthcare Agent, guardian or next of kin will be required with an assent of the patient.

Via Telephone/Email/Mail (one or in combination) for LAR's that are off-site:

Investigator may contact (or be contacted by) a potential LAR by telephone or email to discuss participation in a research study. Investigator must provide LAR with all the information contained in the consent form. Investigator will answer any questions regarding the research study and giveLAR ample time to consider participation in the study. (May require follow-up email/phone conversation). IfLAR indicates interest in participating in the research study, the LAR will be informed of the next steps necessary to provide informed consent

a. A consent form will be sent to the LAR by regular mail (if no email access), an email attachment
b. The LAR must read the consent form and call or email the investigator if he/she wishes to discuss the research and resolve issues/questions

If LAR agrees to participate in research, he/she should sign the consent form and return it to the investigator by one the following methods:

c. Mail or fax hard copy to the site
d. Return a picture/image of signed consent form
e. Scan the signed consent form and return it to the investigator as an email attachment.
f. If the LAR received the consent electronically but does not have access to printing, the following will apply
    i. The LAR will verbally consent (with a witness on the phone) and respond via email documenting the confirmation he/she consents.
    ii. A copy of the email confirming consent will be filed in the subject's binder.
    iii. LAR may sign and return the ICF on a future date.

An enrollment note must be written by the investigator documenting all phone conversations with the subject. Printouts of any email correspondence must be placed in the subject's file. After the signed consent form is received, investigator will sign the consent form and date the signature with the current date. The investigator should add a note detailing the date discrepancy of the signatures. A copy will be made and sent to the LAR for his/her records.

If a consent form is returned missing a signature, the participant will be notified by phone or email. A copy will be made and kept in the participant's file and the original will be sent back to the participant for completion and resubmission to the investigator.

1. Documentation required
    a. How was the ICF transmitted to the LAR (email, mail, fax)
    b. How was the LAR signature obtained (e-signature, scanned and email back, mailed back, took a picture of signature page emailed/text back, verbal assent with witness present and subsequent email confirmation)
    c. Enrollment note written by investigator documenting consent discussions by phone with the LAR
    d. Statement describing how fully signed consent copy was given to LAR

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Verbal notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the primary investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in Northwell database This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Northwell research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Northwell data base

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

NA

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator and medical monitor
Tania Rebeiz, MD, Assistant professor
Northshore University Hopsital
3126228808
trebeiz@northwell.edu

10.1.6 SAFETY OVERSIGHT

The principle investigator will be responsible in collecting any adverse event and reporting it to the IRB. An un-blinded co-investigator not involved in the study procedure will review aggregate safety data on a weekly basis.

10.1.7 CLINICAL MONITORING HEALTHCARE PROVIDER

The principle investigator will ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s)

- Monitoring for this study will be performed by the principle investigator, co-investigators the research coordinator and research assistants.

- At the start of the intervention, the principle investigator or co-investigators will be performing the vagus nerve stimulation and teaching the patients andIRB approved personnel on how to use the device. This will be done for the first 3 episodes of headache. On site assessment will be performed daily by the research team.
- An unblinded investigator not involved in the study will be review unexpected adverse events or serious adverse events
- u**Physical examination** Neurologic examination will be recorded, including the NIHS scale as part of standard of care.
- **Vital signs** (e.g., temperature, pulse, respirations, blood pressure, oxygen saturation) every hour or as ordered by the physician, and before and after each stimulation.
- **Electrocardiograms (EKGs)**: EKG will be performed at baseline. Patients will be on continuous cardiac monitoring, (telemetry) during the study. If any changes detected on telemetry (arrhythmia) or chest pain or dyspnea during the stimulation, an emergent EKG will be done. The EKG will be printed on a paper and stored in SUNRISE and will be read directly. EKG will also be done as needed per physician's request.
- **Radiographic or other imaging assessments.** Reports of CT scan, MRI brain, CT angiogram, CT perfusion, conventional angiogram, transcranial dopplers done as standard of care diagnosis will be collected.
- **Biological specimen collection and laboratory evaluations**. Standard of care blood tests including CBC, BMP, LFT, cultures, procalcitonin when done will be evaluated.

Assessment of study intervention adherence or see Study Intervention Compliance, section 6.4 Headache: headache intensity and quality will be evaluated as part of the standard of care every 4 hours.

Assessment of adverse events. Side effects are evaluated during the stimulation, directly afterwards until resolution as appropriate. The neurointensivist will evaluate the need for more frequent vital signs assessment.

- **Patient's satisfaction with using the VNS in managing the headache intensity** will be evaluated: Satisfaction will be rated on a 5-point scale: 1- very unsatisfied, 2- mild unsatisfied, 3- indifferent, 4- satisfied, 5 very satisfied.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct and data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be evaluated by the principle investigator.

The primary investigator, and research coordinator will verify that the clinical trial is conducted and data are generated and documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and

applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

A protocol on when to use the VNS and abortive medications will be given to all healthcare providers taking care of the patients.
All study personnel will be trained on how to collect the data. The principle investigator will check the data on a weekly basis. The principle investigator and the electrocore company will train the healthcare providers on how to use the device. Data will be recorded in redcap. Most of the information is pulled from our electronic medical records, SUNRISE.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study work sheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be recorded in paper CRFs and transcribed into the redcap database for statistical analysis purposes. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for 10 years after completion of the study. These documents should be retained for a longer period, however, if required by local regulations. Permission is not required prior to destruction of records.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest

10.2 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

1. Swope R, Glover K, Gokun Y, Fraser JF, Cook AM. Evaluation of headache severity after aneurysmal subarachnoid hemorrhage. Interdisciplinary Neurosurgery. 2014;1(4):119-22.

2. Magalhães JE, Azevedo-Filho HR, Rocha-Filho PA. The risk of headache attributed to surgical treatment of intracranial aneurysms: a cohort study. Headache. 2013;53(10):1613-23.

3. Rumalla K, Smith KA, Arnold PM, Mittal MK. Subarachnoid Hemorrhage and Readmissions: National Rates, Causes, Risk Factors, and Outcomes in 16,001 Hospitalized Patients. World Neurosurg. 2018;110:e100-e11.

4. Glisic EK, Gardiner L, Josti L, Dermanelian E, Ridel S, Dziodzio J, et al. Inadequacy of Headache Management After Subarachnoid Hemorrhage. Am J Crit Care. 2016;25(2):136-43.

5. Morad AH, Tamargo RJ, Gottschalk A. The Longitudinal Course of Pain and Analgesic Therapy Following Aneurysmal Subarachnoid Hemorrhage: A Cohort Study. Headache. 2016;56(10):1617-25.

6. Dorhout Mees SM, Bertens D, van der Worp HB, Rinkel GJ, van den Bergh WM. Magnesium and headache after aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2010;81(5):490-3.

7. Oshinsky ML, Murphy AL, Hekierski H, Jr., Cooper M, Simon BJ. Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain. 2014;155(5):1037-42.

8. Akerman S, Simon B, Romero-Reyes M. Vagus nerve stimulation suppresses acute noxious activation of trigeminocervical neurons in animal models of primary headache. Neurobiol Dis. 2017;102:96-104.

9. Frangos E, Komisaruk BR. Access to Vagal Projections via Cutaneous Electrical Stimulation of the Neck: fMRI Evidence in Healthy Humans. Brain Stimul. 2017;10(1):19-27.

10. Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol. 2010;67(5):607-17.

11. Chen SP, Ay I, de Morais AL, Qin T, Zheng Y, Sadeghian H, et al. Vagus nerve stimulation inhibits cortical spreading depression. Pain. 2016;157(4):797-805.

12. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol Med. 2003;9(5-8):125-34.

13. Suzuki T, Takizawa T, Kamio Y, Qin T, Hashimoto T, Fujii Y, et al. Noninvasive Vagus Nerve Stimulation Prevents Ruptures and Improves Outcomes in a Model of Intracranial Aneurysm in Mice. Stroke. 2019:STROKEAHA118023928.

14. George MS, Ward HE, Ninan PT, Pollack M, Nahas Z, Anderson B, et al. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul. 2008;1(2):112-21.

15. Pascal G. Transcutaneous Vagus Nerve Stimulation in Private Healthcare Center [

16. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders. Front Psychiatry. 2018;9:44.

17. Lendvai IS, Maier A, Scheele D, Hurlemann R, Kinfe TM. Spotlight on cervical vagus nerve stimulation for the treatment of primary headache disorders: a review. J Pain Res. 2018;11:1613-25.

18. Reuter U, McClure C, Liebler E, Pozo-Rosich P. Non-invasive neuromodulation for migraine and cluster headache: a systematic review of clinical trials. J Neurol Neurosurg Psychiatry. 90. England: Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.; 2019. p. 796-804.

19. Gammacore. *https://gammacorecom/wp-content/themes/gammacore-p2/pdf/gammacore_IFUpdf*.

20. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, et al. Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review. Brain Stimul. 2018.

21. Burgman T, Samadani U. Vagus Nerve Stimulation to Treat Moderate Traumatic Brain Injury 2016 [*https://clinicaltrials.gov/ct2/show/NCT02974959*].

22. Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Tarver B, et al. Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Ischemic Stroke. Stroke. 2016;47(1):143-50.

23. Steinberg BE, Sundman E, Terrando N, Eriksson LI, Olofsson PS. Neural Control of Inflammation: Implications for Perioperative and Critical Care. Anesthesiology. 2016;124(5):1174-89.

24. Duris K, Manaenko A, Suzuki H, Rolland WB, Krafft PR, Zhang JH. alpha7 nicotinic acetylcholine receptor agonist PNU-282987 attenuates early brain injury in a perforation model of subarachnoid hemorrhage in rats. Stroke. 2011;42(12):3530-6.

25. Hays SA, Khodaparast N, Hulsey DR, Ruiz A, Sloan AM, Rennaker RL, 2nd, et al. Vagus nerve stimulation during rehabilitative training improves functional recovery after intracerebral hemorrhage. Stroke. 2014;45(10):3097-100.

26. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968;28(1):14-20.

27. Hunt WE, Meagher JN, Hess RM. Intracranial aneurysm. A nine-year study. Ohio State Med J. 1966;62(11):1168-71.

28. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21-7; discussion -7.

POSSIBLE ALTERNATIVE AE SECTION

11.1 ADVERSE EVENTS/ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

The definitions and procedures for reporting adverse events (AE), adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE) and are presented in the sections below. It is of utmost importance that all staff involved in the investigation are familiar with the definitions and procedures and it is the responsibility of the Clinical Investigator to ensure this.

11.1.1 ADVERSE EVENT/ADVERSE DEVICE EFFECT DEFINITIONS

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal findings) in subjects, users or other persons, whether or not related to the study device.

Note1: This definition includes events related to the investigational medical device or comparator.

Note 2: This definition includes events related to the procedures involved

Note 3: For users or other persons, this definition is restricted to events related to investigational medical device

Adverse Device Effect

Adverse event related to the use of an investigational medical device

Note 1: This definition includes any event resulting from insufficiencies or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event that is a resulting from a user error or from intentional misuse of the investigational medical device.

11.1.2 SERIOUS ADVERSE EVENT/SERIOUS ADVERSE DEVICE EFFECT/UNANTICIPATED ADVERSE DEVICE EFFECT DEFINITIONS

Serious Adverse Event

Adverse event that:

a) Leads to a death

b) Led to a serious deterioration in the health of the subject that either resulted in:

1. a life-threatening illness or injury or
2. a permanent impairment of a body structure or a body function, or
3. in-patient hospitalisation or prolonged hospitalisation,
4. medical or surgical intervention to prevent life-threatening illness or permanent impairment to a body structure or a body function

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

Serious Adverse Device Effect

A SADE is an ADE that results in any of the consequences characteristic of an SAE or that might lead to any of these consequences if suitable action is not taken, if intervention is not made or if circumstances are less opportune.

11.1.3 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.

11.1.4 REPORTING OF ADVERSE EVENTS/ADVERSE DEVICE EFFECTS

11.1.4.1 METHODS FOR ELICITING ADVERSE EVENTS/ADVERSE DEVICE EFFECTS

All subjects will be carefully monitored for the occurrence of AEs during the investigation period from the run-in to the completion of follow up. The Clinical Investigator will collect AE information using non-leading questions such as “have you experienced any new health problems or worsening of existing conditions”. Events directly observed or spontaneously volunteered by subjects will also be recorded.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject or reported in response to an open question by the Clinical Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the CRF and should include the following information.

- Brief description of the event (diagnosis)

- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding the medical device
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event and will be assessed as:

Mild

The AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.

Moderate

The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe

The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description.

Causality (Adverse Device Effects/ADE)

Causality will be assessed as:

Related (definitely, possible or probable)

A causal relationship between the clinical investigational medical device and the AE is at least a reasonable possibility, i.e. there is evidence or argument suggesting a causal relationship.

Not related

There is no indication that the AE was caused by the clinical investigational medical device.

ADEs will be reported by ticking the “yes” box for ADEs on the CRF page for AEs/ADEs.

The procedures described for AEs above will be followed for documenting ADEs.

11.1.4.2 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

Any AE that is ongoing when the subject is withdrawn from the investigation should be followed-up until the AE is resolved or the Clinical Investigator decides that the AE is stable and needs no further follow-up. The date when the Clinical Investigator considers one of these outcomes to have occurred for the last ongoing AE for a subject will be considered the last visit for this subject, and the outcome should be recorded in the CRF.