Title: Transauricular Vagus Nerve Stimulation (taVNS) for Delirium

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PROTOCOL TITLE:

Response: Transauricular Vagus Nerve Stimulation (taVNS) for Delirium

PROTOCOL VERSION/AMENDMENT # AND DATE

Response: 4.0

PRINCIPAL INVESTIGATOR:

Response: Isadora Botwinick

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research. Specifically, explain why it is important to do the study.

Response:

Delirium, an acute confusional state, often associated with illness or injury, affects >30% of hospitalized patients[1]. Delirium increases the risk of morbidity, mortality and institutionalization.[2] At present, there is no FDA-approved therapy for delirium. Although exact mechanism is complex and poorly understood, some data suggests that delirium may result from neuroinflammation interfering with functional connectivity of brain networks supporting attention and consciousness, especially in the dorsolateral prefrontal cortex (DLPFC).[1] A possible intervention for delirium would therefore decrease neuroinflammation and modulate DLPFC functional connectivity. For these reasons, neuromodulation of the vagus nerve represents a promising approach to treat delirium. Vagus nerve stimulation (VNS) is a treatment modality in which a small device stimulates the vagus nerve. VNS is part of the standard of care in treatment-resistant epilepsy and is currently being investigated as a treatment for depression.[3,4] Trans-auricular vagus nerve stimulation (taVNS), in which a wearable device on the ear delivers transcutaneous stimulation to vagal afferents, is reported to decrease neuroinflammation[5] as well as to modulate neural activity in the dorsolateral prefrontal cortex (DLPFC).[6] We therefore hypothesize that taVNS will reduce clinical symptoms of delirium by reducing vagally-mediated neuroinflammatory changes that result in aberrant functional connectivity. We propose a two-part pilot study to test our hypotheses - firstly that brain blood flow and connectivity is altered in delirium, and we can detect these changes using noninvasive point of care monitoring, and secondly, that taVNS is a feasible therapy in delirious inpatients.

<u>Specific aim 1</u>. Evaluate brain blood oximetry (oxygen saturation) and EEG in delirious patients using point-of-care noninvasive monitors.

<u>Specific aim 2.</u> Evaluate the feasibility of treating delirious hospitalized patients with non-invasive transauricular vagus nerve stimulation (taVNS).

We will recruit inpatients who screen positive on the ICDSC, a widely-used and well-validated delirium-assessment instrument.

Subjects will undergo one session of non-invasive brain monitoring, measuring oximetry and EEG using point of care noninvasive monitors. Subjects will undergo noninvasive transauricular vagus nerve stimulation for a total of 1 week until either delirium resolves, or the patient is discharged from the hospital.

2.0 Background

2.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute/fill in gaps to existing knowledge.

Response:

The pathophysiology of delirium is still under investigation, but accumulating evidence suggests that disordered brain connectivity may play a significant role. According to a recent report, neuroinflammation leads to dysconnectivity of the dorsolateral prefrontal cortex (DLPFC) with the rest of the frontoparietal executive network[8]. This finding replicated a prior report of aberrant DLPFC connectivity during delirium, which reversed when delirium improved[9]. Disordered functional connectivity in delirium has been demonstrated utilizing several different modalities, including functional MRI (fMRI) and EEG connectivity analysis.[10] Brain dysconnectivity has been associated with neuroinflammation and disordered cholinergic neurotransmission.[11] Of note, the vagus nerve is a major mediator of of the so-called "cholinergic anti-inflammatory pathway in the brain.[12] Thus, vagus nerve transmission in the brain is a potential target for modulating the underlying pathophysiology of delirium.

Several pharmacologic treatments have been studied for delirium without success. In particular, there is no proven benefit in antipsychotics, cholinesterase inhibitors or opioid-sparing pain medications such as gabapentin.[131415] Benzodiazepines, particularly midazolam, are associated with increased delirium.[16] A large meta-analysis suggests that dexmedetomidine, an alpha-2 agonist, reduces delirium, but it is only available as an intravenous drip and has significant side effects of hypotension and bradycardia[17] which can limit its use in patients. Corticosteroids, which act as potent anti-inflammatories, are reported to worsen delirium,[18] yet nonsteroidal anti-inflammatory agents appear to have a protective effect.[19] Because of the significant off-target effects by these medications, it is still unclear how their effects are mediated. A randomized controlled trial of minocycline, which is known to reduce neuroinflammation, for postoperative cognitive dysfunction, explored a secondary endpoint of effect of ICU delirium and found no significant effect, although the study may have been underpowered.[20] In short, there are currently no good pharmacologic therapies for delirium - the only possibly effective drug (dexmedetomidine) has significant untoward effects. This has prompted the exploration of non-pharmacologic treatments. Holistic "delirium bundles" target modifiable risk factors such as optimizing sleep, providing visual and hearing aids, frequent reorientation and early mobilization. These bundles have shown some success but do not directly target the underlying pathophysiology.[21]

Meanwhile, some animal and human work has begun to try and directly modulate the hypothesized underlying pathophysiology. Vagus nerve stimulation appears to reduce brain inflammation and improve cognitive function in septic mice.[5] TaVNS in humans has shown some promising results in modulating outcomes closely related to delirium: cognition and inflammation. A meta-analysis of cognition in healthy individuals demonstrated improvements in cognitive and

executive function.[22] Other small studies have demonstrated that taVNS may have an anti-inflammatory effect.[23] Reassuringly, human studies of transcutaneous vagus nerve stimulation for epilepsy demonstrate extremely mild side effects, mostly headache and skin irritation.[24] Overall existing data suggests that, not only does vagus nerve transmission play a key role in the pathophysiology of delirium, but vagus nerve stimulation seems to modulate clinical outcomes of interest in delirium, such as reducing neuroinflammation and improving cognition.

Innovation This project has the potential to advance the field in delirium. We will assess the feasibility of using noninvasive point-of-care brain monitors in hospitalized patients with delirium which potentially can allow scientists and clinicians to appreciate subclinical changes in the brains of delirious patients. We will also assess the feasibility of using a novel therapeutic modality, taVNS, in delirium, a common pathology with limited treatment options.

2.2 Include complete citations or references:

References

1. Wilson, J. E. *et al.* Delirium. *Nat Rev Dis Primers* **6**, 90 (2020).
2. Witlox, J. *et al.* Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* **304**, 443–451 (2010).
3. Toffa, D. H., Touma, L., El Meskine, T., Bouthillier, A. & Nguyen, D. K. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. *Seizure* **83**, 104–123 (2020).
4. Conway, C. R. *et al.* A prospective, multi-center randomized, controlled, blinded trial of vagus nerve stimulation for difficult to treat depression: A novel design for a novel treatment. *Contemp. Clin. Trials* **95**, 106066 (2020).
5. Huffman, W. J. *et al.* Modulation of neuroinflammation and memory dysfunction using percutaneous vagus nerve stimulation in mice. *Brain Stimul.* **12**, 19–29 (2019).
6. Badran, B. W. *et al.* Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review. *Brain Stimul.* **11**, 492–500 (2018).
7. Gusmao-Flores, D., Salluh, J. I. F., Chalhub, R. Á. & Quarantini, L. C. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit. Care* **16**, R115 (2012).
8. Zhu, Y. *et al.* Inflammation Disrupts the Brain Network of Executive Function after Cardiac Surgery. *Ann. Surg.*

277, e689–e698 (2023).

9. Choi, S.-H. *et al.* Neural network functional connectivity during and after an episode of delirium. *Am. J. Psychiatry* **169**, 498–507 (2012).
10. Numan, T. *et al.* Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. *Clin. Neurophysiol.* **128**, 914–924 (2017).
11. Hshieh, T. T., Fong, T. G., Marcantonio, E. R. & Inouye, S. K. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J. Gerontol. A Biol. Sci. Med. Sci.* **63**, 764–772 (2008).
12. Pavlov, V. A. & Tracey, K. J. The cholinergic anti-inflammatory pathway. *Brain Behav. Immun.* **19**, 493–499 (2005).
13. Nikooie, R. *et al.* Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. *Ann. Intern. Med.* **171**, 485–495 (2019).
14. van Eijk, M. M. J. *et al.* Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* **376**, 1829–1837 (2010).
15. Leung, J. M. *et al.* Perioperative Gabapentin Does Not Reduce Postoperative Delirium in Older Surgical Patients: A Randomized Clinical Trial. *Anesthesiology* **127**, 633–644 (2017).
16. Riker, R. R. *et al.* Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* **301**, 489–499 (2009).
17. Ng, K. T., Shubash, C. J. & Chong, J. S. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* **74**, 380–392 (2019).
18. Schreiber, M. P. *et al.* Corticosteroids and transition to delirium in patients with acute lung injury. *Crit. Care Med.* **42**, 1480–1486 (2014).
19. Yamanashi, T. *et al.* Anti-inflammatory medication use associated with reduced delirium risk and all-cause mortality: A retrospective cohort study. *J. Psychosom. Res.* **168**, 111212 (2023).

20. Takazawa, T. *et al.* Prevention of Postoperative Cognitive Dysfunction by Minocycline in Elderly Patients after Total Knee Arthroplasty: A Randomized, Double-blind, Placebo-controlled Clinical Trial. *Anesthesiology* **138**, 172–183 (2023).
21. Sosnowski, K. *et al.* The effect of the ABCDE/ABCDEF bundle on delirium, functional outcomes, and quality of life in critically ill patients: A systematic review and meta-analysis. *Int. J. Nurs. Stud.* **138**, 104410 (2023).
22. Ridgewell, C. *et al.* The effects of transcutaneous auricular vagal nerve stimulation on cognition in healthy individuals: A meta-analysis. *Neuropsychology* **35**, 352–365 (2021).
23. Uehara, L. *et al.* Transcutaneous auricular vagus nerve stimulation effects on inflammatory markers and clinical evolution of patients with COVID-19: a pilot randomized clinical trial. *Expert Rev. Med. Devices* **19**, 915–920 (2022).
24. Lampros, M., Vlachos, N., Zigouris, A., Voulgaris, S. & Alexiou, G. A. Transcutaneous Vagus Nerve Stimulation (t-VNS) and epilepsy: A systematic review of the literature. *Seizure* **91**, 40–48 (2021).

3.0 Study Design

3.1 Describe and explain the study design (e.g., case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, and observational). Indicate if there is randomization, blinding, control group, etc. If randomizing, explain how this will be achieved.

This will be a **single-arm, open-label study**, carried out in delirious patients to assess brain blood oxygen saturation and EEG using noninvasive point-of-care monitoring in hospitalized patients with delirium, and to assess feasibility of taVNS in this population. We will be using the Masimo O3/brain monitoring system, a noninvasive, commercially-available, FDA 510k approved noninvasive brain monitor that measures brain oxygen saturation. We will also be using the CGX Patch EEG system for research EEG acquisition.

We will be using the Soterix transcutaneous auricular vagus nerve stimulator, a noninvasive taVNS device, for which **we have submitted an IDE to the FDA and received nonsiginficant risk designation (NSR.)** Relevant regulatory documents have been attached.

3.2 Include the number of subjects and the power analysis. If applicable, indicate your screen failure rate, i.e., how many subjects you expect to screen to reach your target sample.

We aim to recruit **10 subjects**. This is a novel pilot study and the changes in brain blood oximetry and EEG, and the use of taVNS in delirium have not been clearly delineated in the literature. We plan to use the data from this study to power a larger study of delirium in the future.

3.3 Indicate the duration of the subject participation including long-term follow-up.

Subjects will undergo twice daily taVNS stimulation for a maximum of **1 week** until either delirium resolves, or the patient is discharged from the hospital.

3.4 Indicate whether you are specifically recruiting or targeting any of the following special populations in your study using the checkboxes below.

Response:

☐ Minors (under 18 years old)

☒ Adults unable to consent

☐ Pregnant women

☐ Prisoners

3.5 Indicate if you will include minorities (American Indians, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, Black [not of Hispanic origin] and Hispanic) as Federal mandates require that you include minorities unless you can justify their exclusion.

Response:

☒ Yes

☐ No, Justify:

3.6 Indicate whether you will include non-English speaking individuals in your study. Provide justification if you will specifically exclude non-English speaking individuals. Review https://www.stonybrook.edu/research-compliance/Human-Subjects/sops for the SBU policy on inclusion of non-English speakers (section 17.8). Following approval of the English version, you must submit the translated version of the materials with the attestation of the translation.

For this pilot study, given the difficulty of ensuring staff proficient in non-English languages and completing formal daily delirium assessments, we will limit the cohort to English speakers.

3.7 Describe the data analysis plan, including any statistical procedures.

NOTE: If we are a lead site for a multi-site study include the total number of subjects that will be enrolled or records that will be reviewed across all sites. This section applies to both quantitative and qualitative analysis.

We will assess brain blood oxygen saturation and EEG findings in delirious patients. Changes in brain oxygen saturation over time will be compared. Changes in EEG will be evaluated by a neuroscientist with experience in EEG analysis. A trial-based analysis will be used for EEG using 4-10 s blocks of artifact-free data sampled at 256 Hz. Statistics will consist of two-sample nonparametric tests given the nonstationarity of the data. We will account for multiple comparisons across EEG sensors with the false discovery rate approach. Brain oxygen saturation data will be analyzed in analogous fashion, except that the sampling rate is lower.

We will assess feasibility of taVNS as follows:
The proportion of stimulation delivered relative to the stimulation prescribed, calculated as:

$$\frac{\textbf{Stimulation delivered (minutes)}}{\textbf{Stimulation prescribed (minutes)}}$$

- **Secondary Descriptive Metrics**:
    - Summary statistics for the proportion of stimulation delivered (e.g., mean, median, standard deviation, and range).
    - Proportion of patients achieving ≥10% of prescribed stimulation (indicating feasibility).

Analysis Population

All enrolled patients (N=10) who receive at least one session of vagus nerve stimulation will be included in the analysis (intent-to-treat population). Patients with incomplete data will be analyzed using available data only, without imputation.

Statistical Methods

1. **Descriptive Statistics**:
    - Individual patient proportions will be summarized as means, medians, ranges, and standard deviations for the entire cohort.
    - Tabulation of the number and percentage of patients meeting predefined feasibility thresholds (e.g., ≥10% stimulation delivered).

2. **Graphical Analysis**:
    - Bar graphs or boxplots will be used to visually represent the distribution of the proportions across patients.
3. **Handling of Missing Data**:
    - Missing data will be reported, but no imputation will be performed due to the small sample size.

Feasibility Criteria

Feasibility will be demonstrated if:

1. The mean proportion of stimulation delivered across the cohort is ≥10%.

    Previous taVNS studies in adults have demonstrated that as little as 6 minutes of stimulation is adequate to demonstrate neuromodulatory effect as detected by fMRI.

    In our protocol, patients will be prescribed a total of 60 minutes of stimulation per day of study → 6 minutes of stimulation (a known minimum effective dose) is thus 10% of prescribed stimulation time.

2. At least 80% of patients achieve ≥10% of prescribed stimulation.

4.0 Inclusion and Exclusion Criteria

NOTE: If your study is more than minimal risk, you must also upload (in the myResearch IRB smartform) a copy of your inclusion/exclusion checklist to be completed at time of enrollment of each subject.

4.1 Describe, in bullet points, the criteria that define who will be included in this study.

- Stony Brook University Hospital inpatient, Age ≥ 22
- Right- handed
- Screen positive for delirium on ICDSC ≥3

4.2 Describe, in bullet points, the criteria that define who will be excluded from this study.

- Severe neurologic disability including severe traumatic brain injury, severe permanent cognitive impairment
- Pacemaker present
- Implanted VNS stimulator present
- Personal history of epilepsy

- Facial or ear pain or trauma
- Recent history of substance abuse
- Any other medical condition that, in the judgment of the investigator, makes participation in the study unsafe.
- Weight < 40kg
- Pregnant females
- Intubated patient
- Patients with open forehead wounds or forehead skin breakdown will be excluded from EEG component
- Patients will be excluded from EEG component if they are in an oxygen-enriched environment (concentration >25% a atm) (e.g., hyperbaric oxygen settings or other environments with elevated ambient oxygen concentration.)

4.3 Describe how individuals will be screened for eligibility. Upload all relevant screening documents with your submission (screening protocol, script, questionnaire). Identify who will certify that subjects meet eligibility requirements. (Upload these documents in the myResearch IRB smartform.)

●Candidate inpatients will be identified on daily rounds by the primary medical team in the ICU or hospital unit. Evaluation for delirium is part of the usual standard of care for hospitalized patients.

●If the primary clinical team has not already consulted psychiatry or neurology for assistance with the diagnosis and management of delirium then a hospital psychiatrist, neurologist or neurointensivist will confirm the diagnosis of delirium prior to enrollment in the study. A baseline ICDSC ≥3 (see attached) will be used as screening cutoff based on clinical assessment by bedside nursing staff. If a clinical ICDSC is not available at the time of screening, the study team may complete an ICDSC assessment in coordination with the clinical team. In cases of discrepancy between clinical documentation and study team assessment, the PI will adjudicate to determine eligibility.

●Potential subjects will be evaluated to ensure they meet inclusion and exclusion criteria (see above) Any questions about eligibility will be referred to the PI.

●No compensation will be offered to participants.

Screen Failures

We anticipate that a small minority of patients who initially meet criteria for participation may, during their hospital stay become ineligible for further partipation due to change in clinical status. It is not unusual for patients in the ICU to have changes to their medical condition during the course of their admission to the hospital. For example, if a patient were to suffer a stroke, or require intubation after entering the study, he or she would meet exclusion criteria. All data previously collected on such patients would be utilized prior to the event which rendered the patient no longer eligible for further participation.

5.0 Vulnerable Populations

5.1 For research that specifically recruits/targets minors (under 18 years), review, complete and upload Supplemental Form F: Minors.

☐ Confirmed

☒ N/A: This research does not involve persons who have not attained the legal age for consent to treatments or procedures (“children”).

5.2 For research that specifically recruits/targets adults who cannot consent for themselves, you will be asked additional information in Section 25 (“Informed Consent”).

☒ Confirmed

☐ N/A: This research does not involve this population.

5.3 For research that specifically recruits/targets pregnant women, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed

☒ N/A: This research does not involve pregnant women.

5.4 For research that specifically recruits/targets neonates of uncertain viability or non-viable neonates, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed

☒ N/A: This research does not involve non-viable neonates or neonates of uncertain viability.

5.5 For research that specifically recruits/targets prisoners, review, complete and upload Supplemental Form B: Prisoners.

☐ Confirmed

☒ N/A: This research does not involve prisoners.

5.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.

Students and trainees in the community may elect to participate **as research subjects**. Whenever possible, **consent from students** will be obtained by study staff who do not have a direct supervisory relationship with the **student or trainee who is a potential research subject** to safeguard against coercion or undue influence.

☐ N/A: This research does not involve these populations.

6.0 Recruitment Methods

☐ N/A: This is a records review only, and subjects will not be recruited.

NOTE: If you select this option, please make sure that all record review procedures and inclusion/exclusion screening are adequately described in other sections, including date range for records that will be reviewed.

6.1 Describe source of subjects: When, where, and how potential subjects will be recruited. In order to approach patients in the clinic/hospital setting you must have a treatment relationship with these individuals.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study.

Inpatients suffering from delirium will be identified as potential subjects by members of the treating clinical team. After identification, the study team will attempt to recruit eligible patients. Patients (or their legally authorized representative (LAR) if the patient lacks capacity) will be informed that involvement in the study is optional and that should they decline to participate, it will not impact current or future clinical care. **We anticipate that in most situations, the LAR will be the initial contact for the study as well as the individual providing consent.**

6.2 Describe how you will protect the privacy of prospective subjects during the recruitment process.

NOTE: Examples of appropriate responses may include: “participant only meets with a study coordinator in a private office setting where no one can overhear”, “the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering.”

In-person discussions during the recruitment process will be conducted in a private setting in the hospital or university. Telephone discussions with participants or legally authorized representatives (LAR) will be conducted with the study team member in a private room. Before discussions are conducted, the participant or LAR will be asked if any family or friends present can remain in the room for the discussion. If the participant or LAR is communicating with the study team by telephone, the study team will inquire if the LAR is in a private place where they are comfortable discussing protected health information. Participant or LAR will be notified that they can refuse to answer any questions they do not feel comfortable answering.

7.0 Research Procedures

7.1 Provide a detailed description of all research procedures or activities being performed on the research subjects. **This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research.** For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in your response. Be sure to include:

· Procedures being performed to monitor subjects for safety or to minimize risks.

· All drugs and devices used in the research and the purpose of their use, and their regulatory status

Response:

1 Research Activities

Screening Procedures

- Candidate inpatients will be identified on daily rounds by the primary medical team in the ICU or hospital unit. Evaluation for delirium is part of the usual standard of care for hospitalized patients.
- If the primary clinical team has not already consulted psychiatry or neurology for assistance with the diagnosis and management of delirium then a hospital psychiatrist neurologist or neurointensivist will confirm the diagnosis of delirium prior to enrollment in the study.
- Inclusion and exclusion criteria will be reviewed to confirm eligibility. Any questions about eligibility will be referred to the PI.
- Baseline assessment of delirium (e.g., using ICDSC, see attached) will be documented
- Vitals, physical exam, medical history, medication review data will be collected from the chart. These are results from the standard of care procedures will be collected from the medical record; these procedures are not being performed solely for research purposes.
- Written informed consent will be obtained from the participant or their legally authorized representative. Please attached consent form.

- After screening and informed consent, the patient will be considered as entered into the study.
- After screening and consent, the patient will begin taVNS within 24 hours.
- Patients who are consented but do not begin taVNS within 24 hours will require repeat screen to evaluate updates to clinical condition, and repeat ICDSC score to ensure they continue to meet inclusion criteria.

Randomization/Study Entry Procedures

As this is a feasibility trial, there will be no randomization. After consent is obtained, patients will be considered as entered into the study.

Study Device – we will be utilizing the Soterix Medical Transcutaneous auricular Vagus Nerve Stimulator. This is an experimental device. We submitted an IDE for our study and received NSR designation from the FDA. Please see attached documentation.

Study Device Intervention.

- The Soterix Medical Transcutaneous auricular Vagus Nerve Stimulator device will be configured to deliver stimulation to the auricular branch of the vagus nerve in the left ear.
- Stimulation parameters will be set as follows:
  Location: tragus of left ear
  Pulse width: 500 μs
  Frequency: 25Hz
  Train duration: 30 seconds
  Intertrain interval: 30 seconds
  Duration of therapy: 30 minute session, twice a day (morning and evening- with a minimum of 6 hours between sessions) for a maximum of 7 days.
  Electrodes: Soterix Medical RELIfit tragus
  Current intensity: titrated to perceptual threshold using the titration mode on the device (see **Determination of Perceptual Threshold**, below):
  Current intensity will range from min 0.5mA - max of 5.0mA and will be titrated as per the below protocol

  (from Badran, Bashar W., et al. "Laboratory administration of transcutaneous auricular vagus nerve stimulation (taVNS): technique, targeting, and considerations." *JoVE (Journal of Visualized Experiments)* 143 (2019): e58984.)

Determination of Perceptual Threshold (PT)

1. Turn on the stimulator and set the output to 3 mA. Deliver a 1 second train of taVNS stimulation at 500 μs and frequency 25 Hz.
2. Ask the subject whether they felt the stimulation (a “tickle” or “pricking.”)
    1. If YES, turn down stimulation intensity by 50% and repeat step 2.
    2. If NO, increase stimulation intensity by 50% and repeat step 2.

3. Repeat the process described in step 2 until recording a minimum of 4 “YES” responses in which the 4th YES response must come after a NO. The intensity (in mA) of the PT will the value at which the subject says their fourth YES response to.

Table shows an example sequence of Yes/No responses used to determine PT.

Stimulation Current Setting	3 mA	1.5 mA	0.75 mA	1.1 mA	0.55 mA	0.825 mA
Response	Yes	Yes	No	Yes	No	Yes

For patients unable to cooperate with the Perceptual Threshold determination: stimulation amplitude will be set at 0.6 mA.

2.3 Study Interventions; see attached, “Schedule of Research Activities”

Participants will undergo:

1. **Prestimulation review** – this data is drawn from the standard of care procedures and will be collected from the medical record; these procedures are not being performed solely for research purposes.
    - Review updates to clinical condition, physical exam, vital signs and concomitant medication review.

2. **ICDSC assessment (see attached) for presence of delirium**

3. **Transauricular vagus nerve stimulation – 30 minutes**:
    - Administered twice daily, 30 minutes per session, with parameters as described above, with at least a 6-hour interval between sessions.
        - If the first stimulation session of the day is before 12pm, the second stimulation session will be after 12pm of that day.
    - A research staff member familiar with the operation of the device will ensure proper device placement, perceptual threshold determination and monitor stimulation sessions.

4. **Post-stimulation evaluation - immediately upon completion of stimulation**
    - Review updates to clinical condition, physical exam, vital signs. This data is drawn from standard of care procedures.
    - Post-stimulation assessment – the patient’s ear will be inspected for redness or irritation. The patient will be asked if they experienced any discomfort or ill effects from stimulation. Post-stimulation assessment will be documented (see attached.)

5.1 Neurophysiological Monitoring (on the first day of stimulation):

- **Pre-Stimulation Baseline recording - 10 minutes**:
    - Record baseline cerebral oxygenation and hemodynamics using a commercially-available FDA-approved Massimo brain oximetry device

- **Active Stimulation Assessment -10 minutes:**

  With transauricular vagus nerve stimulation ongoing:
    - Record cerebral oxygenation and hemodynamics using a commercially-available FDA-approved Massimo brain oximetry device
    -

5.2 Research EEG signal collection for each taVNS session:

10 minutes of pre-stimulation baseline EEG will be collected, followed by 30 minutes of EEG recording while taVNS is ongoing, using the CGX Patch device.

5. **Note regarding compliance with frequency and timing of study interventions:**

   Patients will participate in the study for a maximum of 7 days, with up to 2 stimulation sessions scheduled per day. However, due to the nature of ICU care, which includes frequent off-unit studies, procedures, and changes in clinical status, it is acknowledged that administering both stimulation sessions each day for the full 7-day period may not always be feasible.

   Compliance with the protocol will be defined as completing at least 1 stimulation session during the 7-day study period. Patients meeting this criterion will be considered compliant with the study protocol.

   Missed stimulation sessions on one or more days during the 7-day study period will not be considered protocol violations, recognizing the inherent variability in ICU patient care and scheduling.

References

https://professional.masimo.com/technology/brain-monitoring/cerebral-oximetry/

https://professional.masimo.com/products/sensors/brain-monitoring/sedline/

7.2 Describe what data, including long-term follow-up data, will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

We will collect demographic and clinical data, relevant to the study procedures, including demographics, labs, vital signs and medication usage. Please see attached data collection forms.

7.3 List any instruments or measurement tools used to collect data (e.g., surveys, scripts, questionnaires, interview guides, validated instruments, data collection forms). Upload these materials in the myResearch IRB smartform.

Response:

The validated ICDSC instrument will be used to assess delirium (uploaded).

Additional data collection forms are uploaded separately.

7.4 Describe any source records that will be used to collect data about subjects (e.g., school records, electronic medical records) and include the date range for records that will be accessed.

Response:

Data will be collected from the Stony Brook University Hospital electronic medical record. The date range will be from the subject's current admission to the hospital up until discharge from the hospital.

7.5 Indicate whether or not the results for individual subjects, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.

Results will not be shared with subjects.

8.0 Research Setting

8.1 Describe all facilities/sites/locations where you will be screening and conducting research procedures.

Example: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Stony Brook University Hospital, a fully accredited tertiary care institution within New York State with badge access," etc.

Research procedures will be carried out in patient rooms on the adult inpatient units at Stony Brook University Hospital, a fully accredited tertiary care institution within New York State with badge access.

8.2 For research procedures being conducted internationally), Supplemental Form C must be completed and uploaded.

Response:

☒ N/A: This study is not conducted outside of SBU or its affiliates.

8.3 For research procedures conducted externally to Stony Brook University (e.g. other institutions, schools, other states), attach applicable approval letter(s) in the myResearch IRB smartform.

Response: N/A

9.0 Resources and Qualifications

9.1 The Principal Investigator (PI) must confirm, in consultation with Chair and Dean as applicable, that adequate resources are present to conduct and complete the study compliantly and safely. Specifically:

☐ NO ☒YES The proposed subject population(s) are available in sufficient numbers to meet the study requirements.

☐ NO ☒YES Sufficient funds are available to conduct and complete the study compliantly and safely.

☐ NO ☒YES The PI and study team have sufficient time to conduct and complete the study compliantly and safely.

☐ NO ☒YES The PI has determined that the named study team is qualified to conduct the research compliantly and to monitor the safety and welfare of the enrolled research subjects effectively.

☐ NO ☒YES The PI ensures that the study team is fully aware of his/her involvement in this study and the details of the study protocol.

☐ NO ☒YES The PI ensures that the study teams will only be involved in research procedures for which they have been trained, and are currently certified and/or licensed, if required.

☐ NO ☒YES The PI ensures that all study team members are updated on the progress of the research and the regulatory requirements (including enrolled subjects, unanticipated problems, etc.).

Response:

10.0 Other Approvals

10.1 List approvals that will be obtained prior to commencing the research (e.g., University Hospital sign-offs per the UH Application, Cancer Center Scientific review, external site, funding agency, laboratory, Radiation Safety, IBC, SCRO, IACUC, RDRC).

Response: UH Application

FDA IDE submission – please see FDA NSR letter uploaded separately

☐ N/A: This study does not require any other approvals.

11.0 Provisions to Protect the Privacy Interests of Subjects

11.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's desire/right to control access to or to place limits on whom they interact with or whom they provide personal information. Privacy applies to the person. Examples of appropriate responses include: "participant only meets with a study coordinator in a private office setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response:

In-person discussions during the course of the research will be conducted in a private setting in the hospital or university. Telephone discussions with participants or legally authorized representatives (LAR) will be conducted with the study team member in a private room. Before discussions are conducted, the participant or LAR will be asked if any family or friends present can remain in the room for the discussion. If the participant or LAR is communicating with the study team by telephone, the study team will inquire if the LAR is in a private place where they are comfortable discussing protected health information. Participant or LAR will be notified that they can refuse to answer any questions they do not feel comfortable answering.

12.0 Confidentiality

A. Confidentiality/Security of Study Data

Describe the local procedures for maintenance of security and confidentiality of study data and any records that will be reviewed for data collection.

NOTE: Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

12.1 Where and how will all data and records be stored? Include information about: locked cabinet/locked office, authorization of access, certificates of confidentiality, and separation of identifiers and data, as applicable. Include physical (e.g., paper) and electronic files (e.g., storage of data in REDCap) password protection, encryption.

Response:

Protected health information will be accessed electronically by the EMR or by a direct discussion with the study subject or LAR after they have agreed to participation in the study and signed the IRB-approved informed consent document. All data for subjects will be collected in a coded manner. Each subject will be assigned a subject identifier. The link between the subject identifier and subject's name will be kept in a locked office of the PI or study team member. For data security, data will be kept on an encrypted server which is only accessible by the study PI and her designates. Data on paper are kept in locked drawers to which only the study PI has the key.

12.2 Who will have access to the data?

Response:

Study team members listed on this IRB will have access to the data only as needed for the purposes of this study.

12.3 How will the data be transported/transmitted (if applicable)?

Data will be logged into REDCap or password protected excel spreadsheets.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of study specimens.

☒ N/A: No specimens will be collected or analyzed in this research.

12.4 Where and how will all specimens be stored? Include information about: locked freezers, locked laboratory, authorization of access, and labeling of specimens, as applicable.

Response: N/A

12.5 How long will the specimens be stored for future/unspecified research (including genetic research)?

Response: N/A

12.6 Who is responsible for receipt or transmission of the specimens (if applicable)? If you are transporting specimens to another location not affiliated with Stony Brook University, you must have a Material Transfer Agreement.

Response: N/A

12.7 Banking Data or Specimens for Future Unspecified Use

☒ N/A: This study is not storing data or specimens for research outside the scope of the present protocol. This section does not apply.

NOTE: If you are proposing to bank specimens for future use, you may be subject to licensure requirements under the NYS Department of Health and must be covered under the SBU license. See SOPs section 17.2 at https://www.stonybrook.edu/research-compliance/Human-Subjects/sops.

12.8 If data will be banked for research outside of the scope of the present protocol, describe where the data will be stored, how long they will be stored, and who will have access to the data

NOTE: Your response here must be consistent with the information provided to subjects in your Consent Documents

Response: N/A

13.0 Withdrawal of Subjects

☐ N/A: This study is not enrolling subjects. This section does not apply.

13.1 Describe anticipated circumstances under which subjects may be withdrawn from the research without their consent.

Response:

Adverse Events Requiring Discontinuation

Serious adverse events (SAEs) which are deemed by the PI to be “definitely” or “probably” related to the device will require the discontinuation of the participant from the study.

- End of study assessments (see attached) will be completed promptly upon discontinuation from the study.

5.3 Other Criteria Requiring Discontinuation

Any participant developing severe clinical instability unrelated to the device, that in the opinion of the of the PI makes further participation unsafe, will be discontinued from the study.

13.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Please see attached schedule of research activities.

When the final taVNS session is completed, we will query the subject to assess for any sensory changes, discomfort, or adverse events after monitoring. Responses will be recorded on a numeric scale.

ICDSC delirium screen will be performed.

Current medication list, updated vitals and labs will be recorded.

The subject will then be considered discharged from the study. As there is minimal risk involved in this study, additional follow-up is not planned.

13.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

For subjects who withdraw from research prior to completion of the study, we will retain already collected data.

13.4 Describe what will happen to data already collected.

Response:

Data already collected will be stored in REDCap or a password protected Excel spreadsheet accessible only to study personnel.

14.0 Risks to Subjects

14.1 Describe if any subjects will be withdrawn from therapeutic procedures or drugs (e.g., washout periods) prior to, or during, their participation in the study.

Response: N/A

14.2 List the reasonably foreseeable risks, discomforts, to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

For participation in research: Breach of confidentiality is always a potential risk when identifiable subject data are collected.

For the Masimo brain monitoring system and CGX Patch EEG device:
The Masimo O3 monitoring system is a noninvasive, FDA-cleared device with minimal risk. The CGX Patch EEG device is a noninvasive research EEG acquisition system with minimal risk.

There is a small risk of forehead discomfort and/or minor skin irritation from the Masimo sensors or CGX Patch EEG electrodes. We anticipate that any adverse effects, such as mild discomfort or skin irritation, would resolve after removal of the sensors. Subjects' foreheads and scalp will be inspected before and after placement of the Masimo O3 sensors and CGX Patch EEG electrodes to ensure appropriate placement and a comfortable fit.

For the experimental Soterix taVNS device:

1. Risk Assessment Methodology

The risk analysis for this submission follows a structured approach in accordance with ISO 14971:2019 (Medical devices — Application of risk management to medical devices), focusing on identifying hazards, assessing risks, and mitigating risks associated with the use of **Soterix Medical transcutaneous auricular vagus nerve stimulator** in the targeted patient population.

2. Risk Evaluation

Each identified risk will be evaluated for its likelihood of occurrence and severity of impact. This will be done applying a risk matrix where:

severity/likelihood	1 (Very Unlikely)	2(Unlikely)	3 (Possible)	4 (Likely)	5 (Almost Certain)
5 (Catastrophic)	medium	high	high	high	high
4 (Severe)	medium	medium	high	high	high
3 (Moderate)	low	medium	medium	high	high
2 (Minor)	low	low	medium	medium	high
1 (No Harm)	low	low	low	medium	medium

Risk	Likelihood	Severity	Risk level
Electrical Safety/device malfunction	very unlikely	moderate	low
Skin Irritation or Injury	unlikely	minor	low
Pain or Discomfort from Stimulation	unlikely	minor	low
Adverse effects on neurologic function	very unlikely	severe	medium
Failure to deliver stimulation	possible	no harm	low
Patient Confusion or lack of compliance with stimulation	possible	no harm	low
Adverse Effects on Cardiac Function	very unlikely	severe	medium

3. Identified Hazards and Risks

Here are the key identified hazards and the associated risks:

Electrical Safety

- **Hazard:** Electrical malfunction.
- **Risk:** Electrocution or burns.
- **Risk Mitigation:** FDA review of electrical safety of the device. See attached documentation.

Skin Irritation or Injury

- **Hazard:** Skin irritation or skin reaction at the electrode site.
- **Risk:** Mild to severe skin reactions, which may cause discomfort or minor harm.
- **Risk Mitigation:** Use of biocompatible materials for electrode contact. FDA review of the biocompatibility of the device. See attached documentation.

1. We ensure patients use the device only under supervision by the research team, with proper application, and **ensure regular skin inspections** (see protocol) after each stimulation section as described in the research protocol.

Pain or Discomfort from Stimulation

- **Hazard:** Uncomfortable or painful electrical stimulation during use on the ear.
- **Risk:** Patient discomfort, refusal to continue treatment.
- **Risk Mitigation:** We will be utilizing a standardized current intensity protocol to titrate stimulation to ensure it is barely perceptible to the patients. Please see the research protocol for the titration protocol.

- We will be utilizing stimulation parameters that have previously been demonstrated to be effective and low-risk. If a patient complains of severe discomfort despite appropriate current titration the device will be removed from the patient.

Adverse effects on neurologic function

- **Hazard:** Potential for adverse neurological effects.
- **Risk:** Unwanted neurological effects.
- **Risk Mitigation:** Patients will be screened carefully. As previously described in the study protocol, patients with a history of epilepsy or severe permanent neurologic deficits will be excluded from the study. Patients are monitored closely for any acute neurologic changes during treatment in the ICU as part of usual standard of care.

Device Malfunction (Failure to Deliver Stimulation)

- **Hazard:** Failure in delivering appropriate electrical stimulation.
- **Risk:** No known risk to patient; risk of inability to collect study data.
- **Risk Mitigation:** The device has a built-in feed-back mechanism that tracks and quantifies delivery of stimulation. FDA reviewed the of electrical safety of the stimulation delivery by the device. See attached documentation.
- We will ensure all research staff who have contact with patients are are well-versed in the proper setup and function of the device.

Patient Confusion or lack of compliance with stimulation

- **Hazard:** Difficulty in complying with stimulation due to confusion associated with delirium.
- **Risk:** Incorrect use of the device, leading to failure in delivering stimulation if the patient chooses to remove the device before stimulation is complete.
- **Risk Mitigation:** We will frequently reorient patients about the nature of the device and ensure close supervision by the research team during the stimulation period to help maximize patient cooperation.

Adverse Effects on Cardiac Function

- **Hazard:** Unintended vagus nerve stimulation effects on cardiac function
- **Risk:** Potential for cardiac arrhythmias.
- **Risk Mitigation:**
    1. Patients will be screened for cardiovascular contraindications before enrollment; specifically, patients with cardiac pacemakers will be excluded.

2. Additionally, patients with severe ongoing hemodynamic instability, at the discretion of the PI, will be excluded.

3. Research suggests that the right vagus nerve appears to have greater input to the sinoatrial node (cardiac pacemaker) when compared to the left vagus nerve. [1] Right vagus nerve stimulation is associated with more significant cardiac effects.[2] Of note, in a large systematic review of transcutaneous vagus nerve stimulation, encompassing 51 studies and over 1000 subjects, there was was only a single report of symptomatic bradycardia - and the causal relationship of the stimulation to the bradycardia was unclear.[3] To minimize the already negligible risk, we will only be utilizing left-sided stimulation to avoid any increased chance for inadvertent cardiac effects.

4. ICU patients are monitored closely with continuous EKG monitoring/ cardiac telemetry as part of usual standard of care.

Conclusion

The overall risk for the proposed taVNS intervention in adult hospitalized patients with delirium is low, and manageable with proper mitigations in place. Patients will undergo frequent safety assessments during study participation, with plans for escalation if any serious risks arise. The proposed controls, including screening, patient education, device monitoring, and clinical oversight, aim to ensure patient safety while evaluating the feasibility benefit of taVNS for delirium management.

References

1. Garamendi-Ruiz, I. & Gómez-Esteban, J. C. Cardiovascular autonomic effects of vagus nerve stimulation. *Clin Auton Res* **29**, 183–194 (2019).

2. Ardell, J. L. & Randall, W. C. Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart. *Am J Physiol* **251**, H764–73 (1986).

3. Redgrave, J. *et al.* Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review. *Brain Stimul* **11**, 1225–1238 (2018).

14.3 Describe the probability, magnitude, duration, and reversibility of the risks and the procedures to minimize these risks.

See above discussion in 14.2.

14.4 Describe procedures being performed to monitor subjects for safety.

See above discussion in 14.2.

Subjects will be supervised during monitoring by study personnel who will observe for any evidence of subject discomfort from monitoring. **A member of the study team who is a Stony Brook University Hospital Surgical ICU attending intensivist will be present throughout each stimulation session, as well as for the initial device titration. The surgical ICU attendings frequently manage both hyperactive and hypoactive delirium as part of usual ICU care.**

Additionally, the primary team will have 24/7 access to the PI if any concerns about patient safety should arise during the subject's admission to the hospital.

14.5 If the study poses risks to an embryo or fetus should the subject be or become pregnant, how will you minimize the risk of a pregnancy occurring during the course of the study? (Select all that apply.)

☐ Counseling on birth control and /or abstinence

☐ Pregnancy test during the study

☒ Pregnancy test prior to initiation of the study for subjects capable of pregnancy

☐ Other

14.6 If applicable, describe possible risks to others who are not subjects (e.g., partner of a subject who is administered a study drug).

Response: N/A

14.7 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ N/A: This study is not enrolling subjects OR is limited to records review procedures only OR is a minimal risk study. See SBU SOPs section 3.6 for a list of the procedures that are generally considered to be minimal risk: https://www.stonybrook.edu/research-compliance/Human-Subjects/sops).

Response:

14.8 Provide information about the Data and Safety Monitoring Plan.

Please see AE and SAE CRF attached separately.

The clinical and study team will monitor all subjects closely during and after study procedures for the existence of adverse events (AEs) and/or serious adverse events (SAEs) related to the study procedures. Our study utilizes an experimental device that has been FDA designated as minimal risk (please see FDA documentation uploaded separately.) The study will be monitored by a Data Safety Monitor (DSM), Dr. James Vosswinkel, an attending physician specializing in critical care and neurocritical care with specific expertise relating to this protocol. All unanticipated SAE's are reported within 24 hours to the DSM and within 5 working days of occurrence to Stony Brook IRB. In case of the occurrence of an SAE or AE which in the opinion of the principal investigator (PI) may potentially stop enrollment, the DSM will be immediately contacted. The PI will assess the severity of each event, and provide interpretation as to the likelihood of relatedness to study procedures to the DSM. The DSM will also assess the conduct and study procedures as enrollment continues, and provide recommendations to the study team, as necessary. If a subject develops any adverse event from the study procedures that the principal investigator feels it is in the best interest to discontinue the study, study participation will end. The subject will be followed for resolution and/or any new adverse events following departure from the study. A summary of all unanticipated adverse events that are found to be related to study procedures after review and adjudication by the DSM will be reported to the IRB at the time of continuing review in accordance with the standard operating procedures set forth by the office of research compliance here at Stony Brook University. A summary list of subject IDs will be tabulated and contain descriptive details for all AEs (and SAEs) documenting the AE (in clinical terms), data of onset, ending date, severity (mild, moderate severe), relatedness (unrelated, unlikely, possible, probable, definite) and action taken (if any) to resolve the problem.

14.9 Provide information if a medical monitor will be used to monitor the safety of the study.

The study will be conducted under the supervision of a Data Safety Monitor, Dr. James Vosswinkel, who is a physician with expertise relating to this protocol.

14.10 Provide information if a Data and Safety Monitoring Committee/Board will be used to monitor the safety of a study that is greater than minimal risk. Provide justification if a Data and Safety Monitoring Committee/Board will not be used.

☒ N/A:

14.11 Describe what data are reviewed, including safety data, and efficacy data.

Adverse Events (AE) and Serious Adverse Events (SAE) will be reviewed.

1.1 Management of device related adverse effects

The management of device-related adverse effects (AEs) will be handled with systematic approach to ensure participant safety and compliance with FDA regulations. The following steps will be implemented:

1. Identification and Reporting of Adverse Effects:
    - All investigators and study staff will be trained to recognize potential device-related AEs.
    - Participants will be instructed to report any adverse symptoms, issues, or concerns immediately.
2. Documentation of Adverse Effects:
    - All reported AEs will be documented in detail, including date and time of onset, severity, duration, resolution status, and potential relationship to the device.
    - The information will be recorded in case report forms (CRFs) and the study database.
3. Immediate Mitigation and Medical Management:
    - Upon identification of a device-related AE, the investigator will take immediate steps to manage the participant's condition.
    - This may include discontinuation of device use, administration of appropriate medical treatment, or referral for further clinical care.

1.2 Management of research related risks

All study team members will be properly trained on protocol requirements. Research procedures performed for study purposes will be performed by qualified individuals as evidenced by education, experience, and/or training. All members of the study team will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding CRFs by study identification numbers rather than any personal identifying information to avoid revealing

the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers.

2 Adverse Device Effects

The proposed clinical trial will use the following definitions:

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Note: Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s).

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse effects will be assessed on each participant at regular intervals throughout participation. When an adverse effect is discovered, the event will be assessed for severity, relatedness and expectedness. All adverse events will be documented in the research records and followed until resolved or back to baseline state.

2.1 Assessment of Severity

For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

Abnormal test findings: ICU patients, as part of usual clinical practice undergo many tests and and often have abnormal test findings. An abnormal test finding will be classified as an adverse effect if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

AND

- The test finding is deemed to be probably or definitely related to the study device. (See causality definitions below.)

Causality and severity assessment: The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as associated with the use of the investigational device or study treatment or diagnostic drug product(s) for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the

investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

2.2 Relatedness

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The adverse effect, 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.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The adverse effect, including an abnormal laboratory test result, occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the adverse effect occurred within a reasonable time after the study intervention). However, other factors may have contributed to the adverse effect (e.g., the participant's clinical condition, other concomitant events). Although an adverse effect 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 – An adverse effect, 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 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 adverse effect is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

14.12 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

See attached AE and SAE CRF.

Safety information will be collected from the participant during the course of the research procedure. The study team will also review with the patient's inpatient clinical team on a daily basis if there are any safety concerns relating to study procedures.

14.13 Describe the frequency of safety data collection, including when safety data collection starts.

Safety data collection will begin being collected from the time we begin the research procedures outlined in this protocol and thereafter. Monitoring, collection and reviewing for safety will be continuous throughout the study.

14.14 Describe who will review the safety data.

The Data Safety Monitor and the PI will review the safety data.

15.0 Potential Benefits to Subjects

15.1 Describe the potential benefits that individual subjects may experience by taking part in the research.

This is a pilot study that will not benefit individual subjects.

15.2 Indicate if there is no direct benefit.

NOTE: Compensation cannot be stated as a benefit.

Response: N/A

15.3 Indicate if there is a potential benefit to others, future science, or society.

As this is a pilot study, the probable benefits for the participant and for society are unknown.

16.0 Economic Burden to Subjects

☐ N/A: This study is not enrolling subjects, or is limited to records review procedures only.

16.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking, insurance co-payments, study drugs.

No economic burden to subjects.

17.0 Compensation for Participation

☐ N/A: There is no compensation for participation. This section does not apply.

17.1 Describe the amount/nature and timing/scheduling of any compensation to subjects, including monetary, course credit, or gift card compensation. Describe any prorated payments based on participation. Add IRS tax information to the consent form per template.

No compensation for subjects.

NOTE: If using West Campus Departmental pools, participation in studies may be offered for credit in class but students MUST be given other options for fulfilling the research component that are comparable in terms of time, effort, and education benefit. Please indicate the alternative activity/related contact information in the consent form.

18.0 Informed Consent

18.1 Will you be obtaining consent from subjects?

☒ Yes (If yes, provide responses to each question in this section, and upload your consent documents where indicated in the electronic submission system.)

☐ No (If no, skip to the next section.)

18.2 Describe how the capacity to consent will be assessed for all subjects. Review SBU SOPs section 5.5 for guidance: https://www.stonybrook.edu/research-compliance/Human-Subjects/sops).

Response:
Capacity will be assessed for each potential subject, specifically we will assess that the subject is able to understand the following, and apply the information in a rational manner to his/her individual situation:

1. That the activity is research, not standard treatment;
2. The risks and benefits of a study
3. The alternatives that are available
4. The decision not to participate will be accepted without penalty, i.e. without jeopardizing clinical care.

We will discuss with the primary clinical team to ensure they are in agreement with capacity assessments. If there are discordant views on the capacity of the subject, a psychiatry attending on this study will assess the patient for capacity.

18.3 Describe the consent process that will be conducted to ensure that the subject is fully informed regarding study details and subject rights. Include where the consent process will take place, with consideration of the need to protect the subject's right to privacy.

Response:

We anticipate that in most situations, the legally authorized representative (LAR) will be the initial contact for the study as well as the individual providing consent. In-person discussions during the consent process will be conducted in a private setting in the hospital. If the subject lacks capacity to consent, any telephone discussions with the legally authorized representative (LAR) will be conducted with the study team member in a private room. Before discussions are conducted, the participant or LAR will be asked if any family or friends present can remain in the room for the discussion. If the participant or LAR is communicating with the study team by telephone, the study team will inquire if the LAR is in a private place where they are comfortable discussing protected health information. It will be explained that the project is research and participation is voluntary. A summary of the research including the purpose, duration and procedures will be discussed, as well as any risks or discomforts. Opportunity will be provided for the subject or LAR to ask questions. The LAR will be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest. The subject or LAR will be provided with the written consent form and given time to read the form and consider the decision to participate.

Effort will be made to obtain in-person consent from the LAR. If this is not feasible, email or faxed consent will be obtained. The consent form will be emailed or faxed to the LAR and opportunity will be provided for the LAR to ask questions. The LAR will be provided time to read the form, and consider the decision to participate. The LAR, if they chose to consent, will sign and return a copy of the signed consent to the study team.

If in-person or email/fax consent is not feasible, telephone consent will be obtained. The consent form will be read to the LAR on the phone and opportunity will be provided for them to ask questions. The study personnel obtaining consent and a witness will sign the written study consent form with a statement that documents that telephone consent was obtained.

18.4 Describe how you will ensure that subjects are provided with sufficient time to consider taking part in the research study. Detail if there is any time period expected between informing the prospective subject and obtaining the consent.

NOTE: It is required that the prospective subject receive sufficient time to have their questions answered and to consider their participation

Response:

Subjects, or their LAR if the subject lacks capacity to consent, may take as long as they need to provide consent for the study. There is no time deadline in which they need to provide consent by. This will ensure subjects receive sufficient time to have their questions answered.

18.5 Describe the process to ensure the subject's ongoing willingness to continue participation for the duration of the research study.

Response:

For subjects with capacity: if the subjects express any concerns during the duration of the study they will be assessed for their ongoing willingness to continue. Any and all questions will be answered. The subject and the clinical team will have contact information for study personnel for same day discussion of any concerns.

For subjects without capacity for whom consent was given by LAR: if the LAR expresses any concerns during the duration of the study they will be assessed for their ongoing willingness to continue. Any and all questions will be answered. The LAR and the clinical team will have contact information for study personnel for same day discussion of any concerns. If the subject regains capacity to consent at any time during the course of the study, willingness to continue will be assessed as for subjects with capacity.

Non-English Speaking Subjects

☒ N/A: This study will not enroll Non-English speaking subjects.

18.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: N/A

18.7 If subjects who do not speak English will be enrolled, describe the process to consent the subjects, as well as the process to be used to ensure their understanding of research procedures throughout the conduct of the study. Review SOPs section 17.8 for important policies in this regard: https://www.stonybrook.edu/research-compliance/Human-Subjects/sops).

Response:

Adults Unable to Consent

☐ N/A: This study will not enroll adults unable to consent.

18.8 Justify why it is necessary to include adult subjects who are unable to consent.

Response:

Delirium is a fluctuating confusional state; we anticipate subjects in our delirious cohort will have limited decision-making capability by nature of the disease process we are trying to study.

18.9 Describe how you will identify Legally Authorized Representatives (LAR) for the subjects that will be consistent with the NYS Family Health Care Decisions Act (FHCDA; see SBU SOPs section 5.2 at https://www.stonybrook.edu/research-compliance/Human-Subjects/sops).

Response:

As per NY state Family Health Care Decisions Act, we will seek consent from the person in the highest category on the following surrogate list who is available, willing and competent to make decisions for the incapable patient:

1. A court-appointed guardian

2. An individual designated as a representative/agent through a health care proxy

3. The spouse, if not legally separated from the patient, or the domestic partner;

4. An adult son or daughter (eighteen years of age or older)

5. A parent

6. An adult brother or sister (eighteen years of age or older)

7. A close adult friend (eighteen years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health and beliefs).

18.10 For research conducted outside of New York State, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research.

Response: N/A

18.11 Describe the process for obtaining assent from the adult subjects

Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.

Response:

For patients without capacity to consent, for whom consent was obtained from LAR: we will not formally obtain signed assent. The study procedure will be explained to the patient in very simple language. The subject will not be forced or coerced to participate.

18.12 Describe whether assent of the adult subjects will be documented and the process to document assent.

Response:

Not applicable.

18.13 Describe how you will obtain consent from a subject to use their data if they later become capable of consent. Include information regarding how competence will be assessed.

Response:

If a subject for whom consent was previously obtained from the LAR regains capacity to consent during the course of the study, then we will obtain consent from the subject to continue with the study and use the subject's data. Competence will be assessed as described previously for the initial consent process.

19.0 Waiver or Alteration of Consent Process

☒ N/A: A waiver or alteration of consent is not being requested.

Complete this section if:

· Informed consent will not be obtained at all

· Informed consent will be obtained, but not documented, or

· Informed consent will be obtained, but not all required information will be disclosed (e.g., in deception research)

☐ A waiver is requested. Complete and upload Supplemental Form G.

19.1 If the research involves a waiver of the consent process for planned emergency research, please contact the Office of Research Compliance for guidance regarding assistance in complying with federal regulations governing this activity (see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research

20.0 Drugs and Devices

☐ N/A: This study does not involve drugs or devices. This section does not apply.

20.1 Does this study involve use of radiopharmaceuticals?

☐ Yes

☒ No

20.2 For investigational devices, provide the following information below:

Where will the device(s) be stored? Note that the storage area must be within an area under the PI's control. Describe the security of the storage unit/facility. Provide full detail regarding how the dispensing of the device(s) will be controlled (accountability of removal/return of used devices, and disposition of remaining devices at the conclusion of the investigation) and documented (accounting records/logs).

Response:

The Masimo device is stored in the Stony Brook University Hospital Surgical Intensive Care Unit in a secure closet with limited badge access. We will use a sign in/sign out device log in which study personnel will record the time when devices are taken from storage, by whom, and when they are returned.

The experimental Soterix taVNS device will be stored in the PI's locked office. We will use a sign in/sign out device log in which study personnel will record the time when devices are taken from storage, by whom, and when they are returned. To ensure proper accountability of the study device and to guarantee its use exclusively on study participants by authorized investigators, the following procedures will be implemented:

1. **Device Accountability Log**: A sign-in and sign-out log will be maintained for the taVNS device. This log will document the following details:
    - Date and time of device issuance.
    - Name and signature of the authorized investigator checking out the device.
    - Date and time of device return.
    - Name and signature of the individual verifying the return of the device.
2. **Access Control**: The study device will be stored in a secured location in the PI's office. Only authorized investigators listed in the study protocol will have permission to access the device.
3. **Authorized Use**: Investigators will be required to confirm that the device is being used solely on study participants, as specified in the protocol.
4. **Final Disposition**: Upon completion or termination of the clinical research study, the study device will be stored in a secure location. The PI will be responsible for the final disposition of the device.

20.3 For investigational drugs (including marketed drugs being used off label), will the services of the Investigational Drug Pharmacy be used for storage, dispensing, accounting the drug (required for research conducted at UH, HSC, Cancer Center, and Ambulatory Surgery Center)?

☐ Yes

☐ No → Provide the following information below:

· Where will the drugs/biologics be stored? Note that the storage area must be within an area under the PI's control

· Describe the security of the storage unit/facility:

· Provide full detail regarding dispensing of the drugs(s), how labeled, controlled (accountability, disposition of unused drug at the conclusion of the investigation) and documented (accounting records/logs):

Response: N/A

21.0 Sharing of Results with Subjects

21.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Results will not be shared with subjects.

22.0 Collaboration

☐ N/A: This study does not include any collaborations.

22.1 Internal Collaboration

The departments of surgery, neurosurgery and psychiatry will be collaborating to conduct the study.

22.2 External Collaboration

Response: N/A