Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) to Reduce Post Traumatic Stress Disorder (PTSD) Symptoms in World Trade Center (WTC) Responders

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Summary of Changes from Previous Version:

Date	Summary of Revisions Made
9/2021	Updating name from VORSO to Nesos. Updating timing of treatment arm. Adding potential COVID-19 remote options. Updated Vorso consultants to Feinstein researchers for demonstration of device.
10/2021	Updating exclusions criteria so focus group participants can take part in Aim 2
11/2021	Streamlined the assessment schedule for participants

12/2021-2/22	**Adding additional location of in person CAPS interview for ease of participants.** **Adding language around recording of CAPS interview for training purposes and interrater reliability. Using this recording to ensure validity of assessment prior to notifying patient of eligibility status.** **Adding Ms Ryniker and Ms Lierberman as a potential CAPS interviewers.** **Changing the location of the earbud to include both ears for participant comfort level.** **Adding online reimbursement option such as Amazon to accommodate the ease of reimbursement due to challenges with rising COVID cases and likelihood of online assessments.** **Streamlining the process of full consent into RCT to after the eligibility screener CAPS assessment to help with being done remotely due to rising COVID cases.** **Initial consent/HIPPAA authorization to be done in person or with verbal approval if remote.**
3/3/2022	**Added language around adding eligible patient info from** Mount Sinai WTCHP Data Center
4/7/2022	Using the suicidality screener, Columbia-Suicide Severity Rating Scale (C-SSRS), in place of the suicidality module in the Standard MINI. We are making this change in order to make the interview less cumbersome and repetitive on the participants. We will still be using the other modules in the Standard MINI to assess for psychiatric exclusion. Requesting a HIPAA waiver of authorization to receive and possess the Mt Sinai WTCHP PHI.

Northwell Health

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812).

The principal investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the principal investigator and documented approval from the institutional review board (IRB), except where necessary to eliminate immediate hazards to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Training.

The protocol, informed consent form, 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, and a determination will be made regarding whether re-consent needs to be obtained from participants who previously provided consent using a previously approved consent form.

The information for the IRB of record for this study is listed below.

Northwell Health Institutional Review Board
125 Community Drive
Manhasset, NY 11030
Phone: (516) 465-1910
Email: irb@northwell.edu

The chairman of the IRB is Martin L. Lesser, PhD, EMT-CC

FWA # 00002505
IRB Registration # IRB00000119

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) to Reduce PTSD Symptoms in WTC Responders

Study Description:

Posttraumatic Stress Disorder (PTSD) remains the most prevalent mental health (MH) diagnosis for first responders involved with responding to the 9/11 World Trade Center (WTC) terrorist attacks, with rates of PTSD much higher than that of the general population. There are a number of evidence-based treatments (EBT) for PTSD, with the strongest evidence base for trauma focused therapies, which typically require that patients engage with the index trauma and the associated fears and cognitions. This can be particularly difficult for PTSD patients for whom avoidance is a key symptom. Although these treatments are well supported, they are less effective in military and veteran populations in particular. Additionally, high dropout rates are observed across treatments for PTSD, with some studies yielding dropout rates of over 30%. Given the high rates of PTSD and the lower uptake of effective PTSD treatment among responders, there is a clear need to provide brief, easily accessible treatments to WTC responders to alleviate PTSD symptoms. There is a growing body of literature to support the use of vagus nerve stimulation (VNS) to treat a number of different disorders with promising animal model research regarding the use of VNS to address some of the features of PTSD, specifically, due to the impact that VNS has on key areas of the brain that are associated with fear extinction and hyperarousal in particular. The current study aims to determine whether the use of a novel, safe, non-invasive form of VNS, transcutaneous auricular VNS (taVNS), would be acceptable and feasible for use with WTC responders who have PTSD, and whether the methodology involved with a larger randomized controlled trial (RCT) to test taVNS efficacy would be acceptable and feasible. As such, the current study involves conducting a formative phase evaluation in the context of a focus group with WTC responders with elevated PTSD symptoms, in order to tailor the taVNS intervention and the pilot study methodology so that it's relevant and acceptable for use. The taVNS intervention will then be piloted in a randomized, double-blind placebo controlled parallel-design study with 30 WTC responders affiliated with the WTC Health Program who have PTSD. Outcomes include taVNS intervention and study methodology feasibility and acceptability. In addition, differences between baseline and post-treatment MH measures will be used to generate hypotheses for a future larger RCT aimed at evaluating taVNS efficacy in PTSD symptom reduction among a larger sample of WTC responders with PTSD. We will also use results to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural and cardiovascular changes that correlate with treatment outcomes. This pilot feasibility study is a first step toward bringing the latest advances in non-invasive, easy to use bioelectronic medicine technology to a population with high rates of

PTSD who experience barriers to treatment engagement and adherence.

Objectives:

Aim 1 seeks to conduct a formative phase evaluation in order to ensure that the taVNS intervention and the pilot study methodology are relevant and acceptable for use with WTC responders with PTSD. For the evaluation, we will recruit 10 WTC responders to participate in a focus group.

Aim 2 seeks to conduct a randomized, double-blind placebo-controlled parallel-design pilot study, to determine whether the taVNS intervention and study methodology are feasible and acceptable for use with WTC responders with PTSD. We hypothesize that the taVNS intervention will be feasible and acceptable for this population. We will also use the initial study results to understand signals that point to potential variables to include that best indicate taVNS efficacy, and potential mediators of the impact of taVNS when implemented in a future RCT involving multiple World Trade Center Health Program (WTCHP) sites. Within both the intervention and sham control groups, responders who are in any form of MH treatment will stay in their usual treatment. Information regarding any current or past treatment will be collected.

Endpoints:

The primary endpoint of this study will be the feasibility of the taVNS intervention. This will be measured at the 8-week follow-up. Feasibility will be evaluated as: (1) rates of recruitment (per month), (2) adherence to the taVNS intervention, (3) 8-week retention, and (4) duration and completion rate of study assessments. Feasibility is defined as the ability to recruit 75% of eligible participants who were approached, as well as to show adherence to the intervention and retention rates of 70% each.

The secondary endpoint of this study will be acceptability of the taVNS intervention. This will be measured at the 8-week follow-up. Acceptability will be evaluated by assessing: (1) the time to completion of questionnaires, (2) percentage of missing data from questionnaires, (3) the time to completion of the biological data and blood draw, (4) the rate of refusal of biologic measurements and blood draw, and (5) the score on the taVNS Satisfaction and Usefulness Questionnaire.

Tertiary endpoints of this study include multiple mental health and biologic potential endpoints to be measured at the baseline of the pilot feasibility trial as well as at the 8-week follow-up time point. Tertiary outcome measures include potential taVNS endpoint measures. At the baseline and 8-week follow-up visits, validated self-report mental health measures, biological measures, and the CAPS PTSD interview (at screener and follow-up) will be administered. To examine potential mechanisms of action and any acute and longer-term change in these mechanisms, all biological measures will be administered at the baseline visit 10 minutes before using the device, and then again one time at the 8 week follow-up visit. These tertiary outcome measures and potential mechanisms of action will be used to inform the design of a future RCT to evaluate taVNS efficacy. We will assess measurement quality, amount of missingness/non-response, length of measurement collection, and costs. These measures will also be used to provide parameter estimates for power calculations for a future RCT.

Study Population:

WTCHP, over the age of 18, who agreed to participate in research and has PTSD as per DSM criteria and has elevated PTSD symptoms as per PCL-3 S, PCL-5 and CAPS who do not fall into any of the exclusion criteria.

Study Type:

This work is a pilot study, since it is an initial, small-scale investigation to test new experimental designs, non-invasive physiologic monitoring equipment, and advanced analytic tools. Aim 1 consists of a one-time focus group. Aim 2 consists of a randomized pilot feasibility clinical trial.

Study Sites:

The study will be run out the Feinstein Institutes for Medical Research at 350 Community Drive.

The focus group for aim 1 will take place at Queens WTCHP. If it is not possible due to COVID-19 restrictions, the focus group will be held via a secure web-based video platform.

The CAPS Assessment will take place at Queens WTCHP or at the Office of Occupational Medicine, Epidemiology & Prevention (OMEP) located at 175 Community Drive, Great Neck. The option will be given to the participant for their convenience. Additionally, the CAPS can be completed via secure video conference, and the baseline and follow-up self-report survey through a secure REDCap email link should it be necessary due to COVID-19
restrictions
In order to ensure good interrater reliability and assist in training for the assessment, the CAPS interview will be recorded. This will not be shared with anyone outside of the study and will only be used strictly for these purposes.

the completion of the CAPS assessment, there will be time for review to ensure validity and proper inclusion into the study.

To assure proper inclusion and to minimize participants being upset for being consented and then not being able to take part in the study, consents will be sent to participant after eligibility is determined and completed in person prior to baseline fitting.

Aim 2 fittings, baseline, 8-week follow-up measurements, and all blood work will take place at the Northwell Feinstein Institutes for Medical Research.

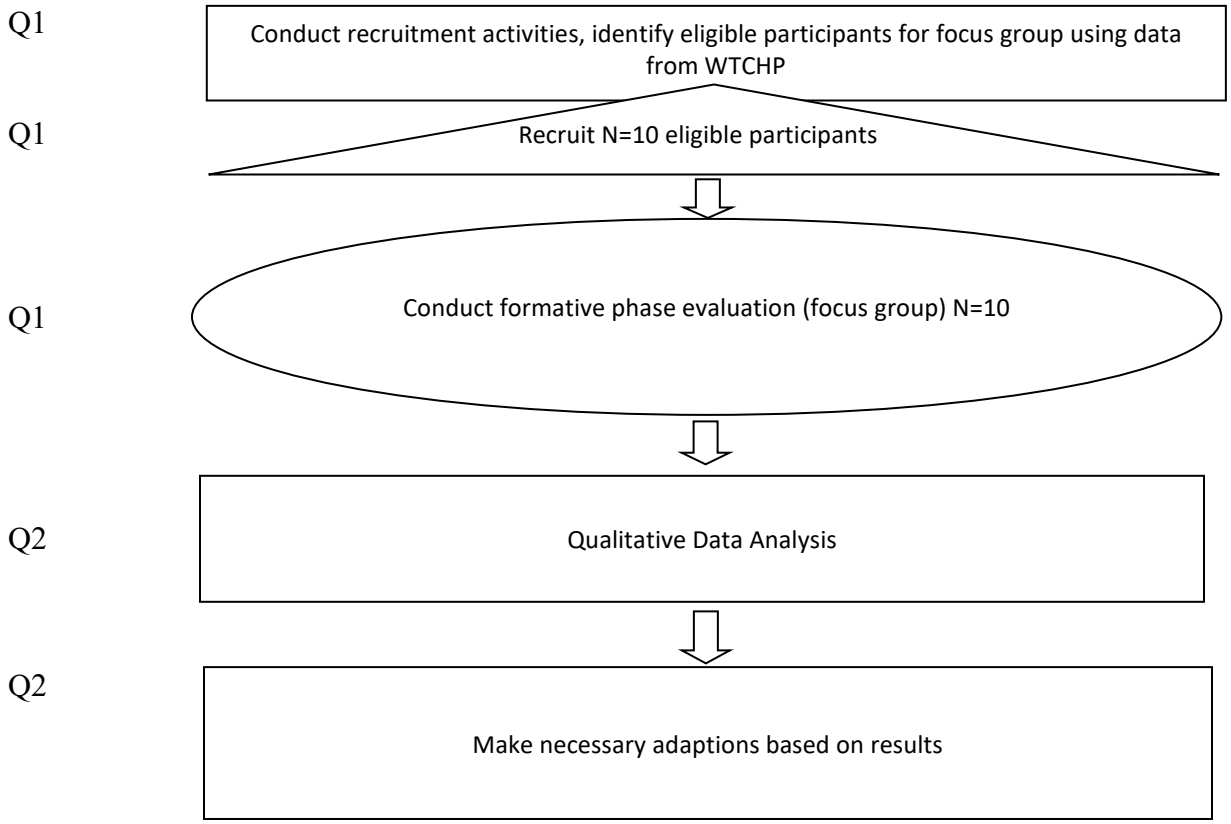
Description of Sites:

All sessions for this study will be conducted in a quiet and private setting either within the Feinstein Institutes for Medical Research . WTCHP or OMEP. All recordings will be done at a separated space such that no others can observe any procedure inside. Due to potential COVID_19 restrictions, focus group can be done remotely if necessary.

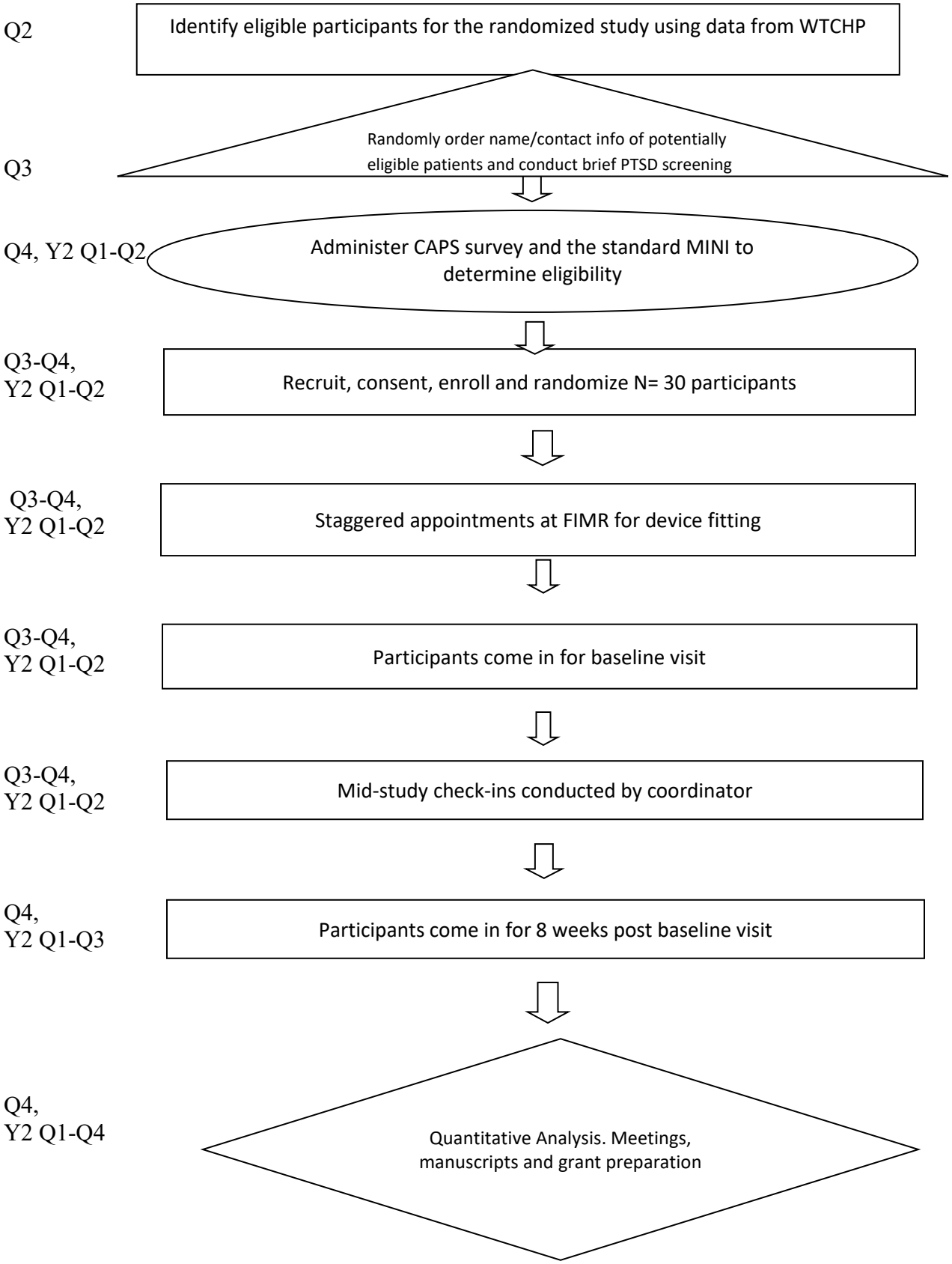
Description of Study Intervention:	The estimated duration for the focus group is ≈ 90 minutes. Dr. Zanos and/or Dr. Debnath will demonstrate the device. Individuals will have the opportunity to handle the device during this timeframe. The focus group will be transcribed for qualitative analyses to help make necessary adaptions based on info. *After each of the 30 responders are enrolled (3 per month),* they will be scheduled within that same month for an appointment at FIMR to be fitted with a custom-made taVNS device, a wearable TENS unit called the Nesos System. They will be compensated for their time/transportation. We expect to have 1 visit per month for fittings, so that all 30 participants will be enrolled and fitted over 10 months. Participant visits will be staggered in order to protect privacy.
Study Duration:	It is anticipated that it may take 24 months to complete the entire study.
Participant Duration:	The estimated duration for the focus group is roughly 90 minutes. The estimated duration of the randomized trial treatment portion is 8 weeks.

1.2 SCHEMA

Aim 1:



Aim 2:


Q2
Identify eligible participants for the randomized study using data from WTCHP
Q3
Randomly order name/contact info of potentially eligible patients and conduct brief PTSD screening
Q4, Y2 Q1-Q2
Administer CAPS survey and the standard MINI to determine eligibility
Q3-Q4, Y2 Q1-Q2
Recruit, consent, enroll and randomize N= 30 participants
Q3-Q4, Y2 Q1-Q2
Staggered appointments at FIMR for device fitting
Q3-Q4, Y2 Q1-Q2
Participants come in for baseline visit
Q3-Q4, Y2 Q1-Q2
Mid-study check-ins conducted by coordinator
Q4, Y2 Q1-Q3
Participants come in for 8 weeks post baseline visit
Q4, Y2 Q1-Q4
Quantitative Analysis. Meetings, manuscripts and grant preparation

1.3 SCHEDULE OF ACTIVITIES (SOA)

Timeline

	Year 1				Year 2			
Activities	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Administrative activities (IRB, Data Use Agreement)								
Aim 1 Conduct recruitment activities including advertising though mailings								
Aim 1 Identify eligible participants for focus group using data from WTCHP								
Aim 1 Recruit 10 eligible participants for focus group								
Aim 1 Conduct formative phase evaluation (focus group)								
Aim 1 Qualitative data analysis								
Aim 1 Make necessary adaptions based on results								
Aim 2 Identify eligible participants for the randomized study using data from the WTCHP								
Aim 2 Randomly order name/contact info of potentially eligible patients and conduct brief PTSD screening over phone								
Aim 2 Administer CAPS survey and the standard MINI & (C-SSRS) to determine eligibility								
Aim 2 Recruit, consent, enroll and randomize 30 participants								
Aim 2 Appointments at FIMR for device fitting								
Aim 2 Participants come in for baseline visit								
Aim 2 Mid-study check-ins conducted by coordinator								
Aim 2 Participants come in for 8 weeks post baseline visit								
Aim 2 Quantitative analysis								
Meetings, manuscripts, grant preparation								

Key	
	Admin Activities
	Aim 1 Activities
	Aim 2 Activities
	Dissemination

Year 1:

Administrative set up activities: Months 1-3

Aim 1: Conduct recruitment advertising activities, identify eligible participants, and recruit participants: Months 1-3

Aim 1: Conduct focus group, perform qualitative analysis, make necessary adaptations: Months 3-6

Aim 2: Identification of potential participants: Month 3-6

Aim 2: Random order, screening phone interviews: Months 7-9

Aim 2: CAPS, Recruitment, Randomize: Months 7-12

Aim 2: Device fitting: Months 7-12

Aim 2: Baseline visit: Months 7-12

Aim 2: 8-week post-visit: Months 10-12

Aim 2: Quant analysis: Months 1-12

Year 2:

Aim 2: CAPS, Recruitment, Randomize: Months 1-6

Aim 2: Device fitting: Months 1-6

Aim 2: Baseline visit: Month 1-6

Aim 2: 8-week post-visit: Months 1-9

Aim 2: Quant analysis: Months 1-12

Aim 2: Dissemination, grant prep: 11-12

2 INTRODUCTION

2.1 STUDY RATIONALE

World Trade Center (WTC) Responders Continue to Experience Significant PTSD 19 years after 9/11. The September 11, 2001 attacks on the WTC involved an estimated 40,000 to 60,000 first responders who provided emergency services at Ground Zero and were exposed to unprecedented traumatic events.[1] Posttraumatic Stress Disorder (PTSD) remains the most prevalent mental health (MH) diagnosis for first responders and clean-up workers at Ground Zero, and continues to be undoubtedly higher than in the general population.[2] One study found

that the estimated lifetime PTSD prevalence in the general United States population was 6.4%, however, 9.7% of WTC responders who were interviewed 11-13 years after 9/11 met the criteria for current PTSD.[3] In addition, a study of over 10,000 WTC responders found that, 8 years after 9/11, 7% had delayed-onset of symptoms. Studies indicate that PTSD and its correlate symptoms can potentially be chronic in this population and can cause WTC responders to be at greater risk for triggering PTSD symptoms, even when they have been previously in remission, due to new traumatic experiences.[4]

Limitations of Current Treatments for PTSD. There are a number of evidence-based treatments (EBTs) for PTSD, with the strongest evidence base for trauma-focused therapies such as Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), and Eye Movement Desensitization Reprocessing (EMDR), which involve the need for patients to engage with the index trauma and the associated fears and cognitions. Although these treatments are effective and well supported, they are less effective in the military and veteran population, and are only marginally more effective than non-trauma focused treatments in that population.[5] Given the lack of trials focused exclusively on WTC first responders, the efficacy in such a population is unclear, but there is reason to believe that first responders are similar to the military and veteran population in terms of PTSD symptomatology and, as noted above, the WTC responder population demonstrate chronic symptoms of PTSD even when receiving treatment.[6] High dropout rates are observed across treatments for PTSD, with some studies yielding a dropout rate of over 30%, and an average of 18% observed in clinical trials. The true rate of dropout is likely even higher in "real world" clinical settings.[7,8] Literature regarding the use of psychopharmaceuticals, perhaps a less taxing approach to addressing PTSD, demonstrates varying efficacy when used without psychotherapy treatments.[9] Further, among responders who have begun MH treatment, their experience with the provider may cause an additional barrier to adhere to treatment. Responders who met with providers but felt the clinician did not understand them or had limited availability, were reasons why responders were less likely to continue with or engage in consistent treatment.[10] Additionally, many treatment protocols for PTSD also require completion of 8-12 weekly 60-90 minute sessions, which can be a difficult level of engagement for clients struggling with a disorder marked by avoidance.[11] **There is a need to provide practical and easily accessible treatments to address PTSD symptoms in WTC responders. Nontraditional approaches may indeed be complimentary to EBTs currently being used.**[5,12,13]

Inconsistency among Providers and Lack of Treatment Effect. In 2002, the WTC Health Program (WTCHP) was created to address both physical and MH needs of WTC responders. Responders who enrolled in the General Responder Cohort (GRC) of the WTCHP included traditional first responder professionals, such as police, paramedics and non-FDNY firefighters, as well as non-traditional responders like construction workers and vehicle maintenance workers. The WTCHP provides no-cost MH treatment, which alleviates the issue of financial burden, a common structural barrier for MH treatment. This can serve to increase access to MH services for this population, however, among the GRC only about 40% of responders who are certified for MH treatment received any form of MH care in 2017, and rates were even lower among FDNY responders (20%). The Northwell Health Queens WTC Clinical Center of Excellence is part of the WTCHP (referred to as Queens WTCHP). The Queens WTCHP partners with both hospital systems and community practitioners to meet both the physical and MH needs of WTC responders. Our published work indicates that the Queens WTCHP responders (n=129), who are certified for MH concerns and connected to MH treatment, were most frequently diagnosed with

PTSD (74.4%), while some had primary or co-morbid diagnoses of anxiety (24.8%) and depression (34.1%).[14] The majority of those diagnosed with some MH concern (72.1%) attended individual therapy, but many (27.9%) did not consistently attend at least one appointment per week. In our group's evaluation of treatment data from community providers treating WTCHP responders, only 12.4% were assessed by independent evaluators to have received a complete EBT protocol.[14] Further, the median number of sessions per WTCHP annual monitoring data from 2018 was 27, but most EBTs, such as PE, are typically 12 sessions in total.[11] Additionally, penetration of EBTs for PTSD is challenging in many other settings as well, including in the Veterans Administration (VA) which invested heavily in a roll out of first line psychotherapies.[14] **It is clear that evidence-based psychotherapies for PTSD are being used sporadically at best, and that providers are struggling to deliver them. This points to a need to develop additional treatment options including for those already engaged in MH care to reduce PTSD symptoms.**

2.2 BACKGROUND

Vagus Nerve Stimulation (VNS) as a Viable Option to Address PTSD Symptoms.

Physiological Impact of Stress and PTSD: PTSD is categorized as a fear response to a traumatic event marked by symptoms of intrusive thoughts or memories of the event, difficulties with emotional and psychological regulation, becoming easily startled, avoiding situations which are connected to the trauma, emotional numbness, and detachment from others.[2] These symptoms have been associated with hyper-responsiveness of the hypothalamic-pituitary-adrenocortical (HPA) axis to cortisol feedback.[15] Individuals who currently have symptoms of PTSD may have abnormally low levels of cortisol compared to those who do not have current PTSD.[16,17] Research suggests that PTSD plays a role in excessive inflammation, increased plasma levels of pro-inflammatory cytokines such as TNFα, IL-1β, IL-6, IL-10, IL-12, and IL-17 as well as C Reactive Protein (CRP).[15,18,19] Further, studies indicate that alpha amylase activity (as well as heart rate variability) is associated with aspects of PTSD including sympathetic arousal and experiencing intrusive memories, in particular.[20,21] There may be an increase in glucocorticoid activity as well.[22,23] Neurotransmitter systems can be dysregulated, such as the noradrenergic system which is responsible for arousal-promoting effects that modify elevated arousal in stress.[24] There is some evidence that further connects the symptoms of PTSD, such as avoidance and re-experiencing, to the body's reaction to hyperarousal. These physiological symptoms of hyperarousal and stress can be detected through changes in facial electromyography (EMG), heart rate (HR), galvanic skin response (GRS), respiratory rate (RR), pupil diameter (PD), blood pressure (BP) and electroencephalography (EEG) features.[25,26] In addition, PTSD patients, in particular, demonstrate extinction learning impairments whereby they are unable to effectively mitigate their fear response even in non-threatening situations.[27–29] Studies have indicated that extinction learning is dependent on specific receptors in the amygdala that impact plasticity in neural synapses, as well as plasticity that occurs in the medial prefrontal cortex. Studies examining lesions in the medial prefrontal cortex, as well as using direct electrophysiological recordings, indicate medial prefrontal cortex involvement in extinction learning.[27–29]

VNS Mechanisms and Application to Treatment of PTSD: Neurostimulation techniques such as electroconvulsive therapy (ECT), repetitive transcranial magnetic simulation (rTMS), and vagus nerve stimulation (VNS) have been utilized to address various MH difficulties with varying levels of invasiveness and potential side effects.[30] VNS, in particular, has been shown to

be effective in treating different disease states. VNS (delivered either transcutaneously or using implanted devices) has been used on more than 100,000 patients for treating diseases such as epilepsy,[31] depression,[32] headache disorders,[33,34] rheumatoid arthritis[35] and Crohn's disease,[36] among others. We have recently demonstrated in a randomized, double-blind, sham-controlled pilot trial, that transcutaneous auricular VNS (taVNS) in lupus patients, resulted in significant reduction of pain, fatigue and joint swelling scores.[37] Further, patients with sleep disturbance,[38] a common symptom of PTSD, are found to benefit from VNS.[39]

VNS can potentially benefit treatment of psychiatric disorders partly due to its projections to brain areas that have been linked to the psychosomatic origins of anxiety.[40] Neural structures such as the amygdala and hippocampus that have been reported to be involved in the hardwired fear and stress response[41] are also anatomically connected to the vagus nerve.[42] Functionally, they are also strongly connected, since modulation of the vagus nerve has been shown to strengthen hippocampal-brainstem connectivity[43] and VNS has been shown to improve working memory performance, related to hippocampal activity.[44] Thus, VNS could potentially benefit psychiatric disorders by downregulating activity in these areas related to stress responses and hyperarousal. In addition, the aforementioned brain areas also play a major role in inflammation, both in the brain and periphery,[39,45] mainly due to their direct and indirect connections to the vagus nerve. Inflammation (both in the body and brain) has been shown to evoke neural responses in the vagus nerve,[46,47] and is believed to elicit neural changes leading to various psychological difficulties such as depression and anxiety, in addition to inflammatory diseases of the body[48,49] as well as neurodegenerative disease.[50,51] Finally, various studies have established a relationship between PTSD and systemic inflammation,[52,53] suggesting that PTSD is underpinned by the presence of a systemic low-grade inflammatory state.

Early animal studies examining the impact of VNS on PTSD-associated symptoms, demonstrated significant increases in extinction (i.e., fear shown to a fear-inducing stimulus) when VNS was utilized as compared to a sham simulation alone.[54] As such, VNS has been deemed a promising additional therapy for treatment of severe anxiety disorders and PTSD.[54] Multiple studies utilizing animal models explored this novel approach specifically with PTSD. Noble et al.[55] found that, among rats that were subjected to a single prolonged stressor, impairment in the fear extinction response was reduced, as was the subsequent conditioned fear response, when VNS was administered as compared to a sham. Further, PTSD-like symptoms, such as anxiety, hyperarousal and social avoidance, were reduced in the VNS animals in the short term and for more than 1 week post-VNS. In a more recent study that used combined procedures that were 30 times more intense than the conditioning procedures in previous VNS studies, the VNS rats exhibited half as much fear as the sham rats which demonstrated significantly more anxiety.[56] The wide-ranging effectiveness of VNS in improving extinction learning, reducing hyperarousal, reducing inflammation, and improving sympathetic tone in these animal studies, and the robust clinical safety record of VNS, indicates that VNS holds promise as an additional therapy that could be applied in people with PTSD and other complicated systems of MH difficulties.[56–58] A review conducted by Noble et al.[55] suggested that VNS may be beneficial in the treatment of PTSD due to the fact that VNS aids in both reducing anxiety while simultaneously increasing the consolidation of extinction of memories.

Although studies are limited, research involving human subjects have found support for the use of VNS as adjunct therapy to address treatment-resistant depression and anxiety with no adverse events.[40,59] Clinically meaningful improvements in depression symptom scores and quality of life have been observed in treatment-resistant depression patients,[59] as well as both short and long-term improvements in treatment-resistant anxiety patients.[40] In fact, one study indicated that four years after the initial VNS implantation, 4 treatment-resistant anxiety patients

were still utilizing VNS and seeing improvements in their anxiety scores compared to their baseline levels on psychotropic medication alone.[40] In terms of PTSD, specifically, recent studies[60] involving humans showed significant impacts of VNS in facilitating fear extinction among healthy subjects,[61] as well as significant impacts of VNS on both central and peripheral stress response systems in individuals with a history of psychological trauma.[62] Bremner et al.[62] found decreased inflammatory markers, decreased sympathetic tone (increased tone is associated with increased stress), and increased medial prefrontal function with VNS as compared to sham controls. These findings were replicated in double-blind, randomized, sham-controlled trials involving the application of transcutaneous cervical VNS (tcVNS) in patients with PTSD. In these studies, stimulation blocked stress-induced increases in IL-6 and IFNγ biomarkers of inflammation,[63] decreased activity of multiple brain regions in response to trauma scripts[64] and decreased sympathetic function.[65] **These results point to the potential efficacy and safety of VNS to address PTSD symptoms in individuals who have not accessed or engaged with traditional EBTs, such as WTC responders. As such, it is necessary to understand the acceptability and feasibility of using VNS to address PTSD symptoms in WTC responders with PTSD in order to then robustly test VNS efficacy in a future RCT.**

Most of the aforementioned studies (both animal and human studies) utilized VNS devices that are surgically implanted at the cervical level of the vagus nerve. Although found to be safe, the implantation requires an invasive procedure. Studies that utilize a non-invasive, transcutaneous cervical VNS (tcVNS) device[60,62,63] have several limitations, including the lack of ability to target exclusively afferent vagus nerve fibers, lack of control over proper placement of the device on the neck by a participant to optimize nerve stimulation, and no reported changes in clinically relevant endpoints related to PTSD. New studies have indicated that transcutaneous auricular vagus nerve stimulation (taVNS) offers another means of non-invasive vagus nerve stimulation without surgical intervention. The auricular branch of the vagus nerve comes from the vagus and innervates cutaneous areas of the outer ear (Figure 1).[39,66,67] Our study proposes to use this novel, innovative technology that is non-invasive and easy to use. Our approach utilizes a device that involves a personalized electrode that supplies electrical signals to the cymba conchae region of the auricle, a region innervated exclusively by the auricular branch of the vagus nerve.[66] Transcutaneous stimulation of the auricular branch of the vagus nerve has successfully treated refractory epilepsy[68,69] and shown promising results in inflammatory conditions[70,71] as well as pre-diabetes, tinnitus, memory, stroke, oromotor dysfunction, and rheumatoid arthritis,[72–77] with new studies planned and underway for treatment of depression, stroke, atrial fibrillation, and heart failure. TaVNS also shows promise in treating PTSD; it is proposed that the mechanism includes down-regulation of the inflammatory reflex through adjustment of the microbiome-brain-gut axis (see Figure 1).[39,78] In addition to a depression-impacting pathway via the immune system, taVNS affects the nucleus of the solitary tract (NTS), which projects to the hypothalamus and amygdala, key nodes in mood regulation and the limbic system, and to the locus coeruleus which subsequently projects to additional limbic nodes including the insula and cingulate cortex.[39] Moreover, from preclinical studies, it has been shown that VNS enhances memory consolidation and consolidation of extinction memory, and prevents reinstatement of conditioned fear in a single prolonged stress (SPS) rat model of PTSD.[56] VNS also promotes generalization of extinction of fear across conditioned auditory cues when the conditioning occurred within the same session. Further, a main limitation of the previous studies utilizing taVNS is that they did not have a sham control that was identical in nature to the intervention.[30,79] The proposed study is further innovative in that we are able to employ a double-blind placebo-controlled parallel design, as both the treatment and sham control will use the

same device, but the sham device will not be able to provide any stimulation. Due to the fact that there is no sensation perceived from the taVNS device, the two groups will appear identical. Additionally, given that many early studies were conducted utilizing invasive and implantable devices requiring surgery, there was considerable financial implications as well as the challenge of recruiting patients for this possibly anxiety-producing procedure.[30] One of the benefits found in an early randomized trial of taVNS for depression, was that patients could apply the unit themselves and did not need a physician to administer it for them, making it much more feasible to use with results comparable to results deriving from the implantable device.[79] Lastly, subjects reported that they felt a better placebo/sham needed to be found to limit the bias with potentially feeling the stimulation.[79]

These findings suggest that VNS possesses a rare combination of effects that include suppression of inflammation, modulation of the activity of mood-related brain centers, impacts on sympathetic tone and hyperarousal, as well as the enhancement of consolidation of extinction memories, along with rapid reduction of anxiety and PTSD-associated symptoms. However, no previous efforts have been made to specifically assess the feasibility or efficacy of taVNS on PTSD-affected human subjects. **The innovation of this work involves applying the latest advances in non-invasive bioelectronic medicine technology to a population with PTSD. This novel therapeutic approach is not only a radical departure from the current pharmacological-based treatments, but even from the cutting-edge invasive bioelectronic medicine devices used in the market for other indications.**

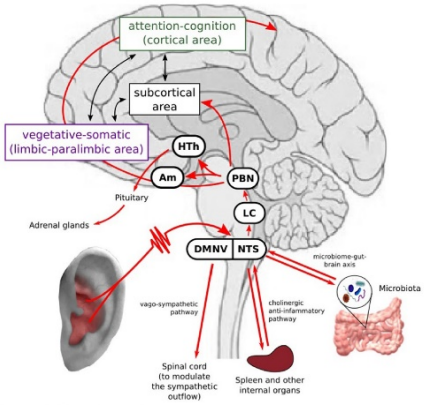


Figure 1. (Kong et. al., 2018)[39]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Aim1: Potential loss of privacy and/or confidentiality is the main potential risk to subjects associated with this portion of the study. This risk will be minimized by following Northwell's Protected Health Information (PHI) protocol that includes storing data in Research Electronic Data Capture (REDCap), or within a locked electronic folder on a secure, HIPPA-compliant, institutional server. Data received from the WTC Data Center will be uploaded into the password-protected REDCap database. Only designated research study staff will have access to the study database, to further minimize risk. At the start of the focus group, participants will be reminded about confidentiality and how it is important not to discuss the focus group content outside of the focus group. Only first names (or pseudonyms if preferable) will be used during the focus group. To minimize the potential impacts of discussing sensitive topics, a psychologist with qualitative research and a mental health care background will oversee qualitative data collection. The focus group will also occur at the site of the Queens WTCHP so that direct referrals to on-site WTC mental health staff can be made if necessary. The audio recordings will be stored in a password-protected file on the FIMR at Northwell Health's (NWH)s secure network, and deleted from the audio recorder. Recording transcripts will be stored in a locked

electronic folder on a secure, HIPAA-compliant, institutional server. If done remotely due to COVID-19 restrictions, only a Northwell approved platform will be used.

Aim 2: *Study Assessments*
There are no major risks around assessments. Potential loss of privacy and/or confidentiality is one potential risk to subjects associated with this portion of the study. As stated above this risk will be minimized by following Northwell's PHI protocol that includes storing data in REDCap, or a locked electronic folder on a secure HIPAA-compliant institutional server. Only designated study staff will have access to the study database and locked electronic folder, to further minimize risk. A unique identifying number will be assigned to each subject at the time of randomization in order to safeguard the subjects' PHI. Only the project coordinator will have access to the password-protected REDCap file that links the random identification number to the subject information.

There is a risk that some of the questions involved in the assessments could cause potential stress or discomfort. The investigative team will vigilantly observe each participant's emotional reactions during all study procedures, and offer referrals when appropriate. If the mental health symptoms of any participant were to worsen, Dr. Bellehsen would be responsible for assessing and referring for treatment within the WTC Health Program. Given the exclusion criteria (no signs of psychosis, mania, bipolar disorder, active substance dependence, or suicidal/homicidal intent) we hope to limit the likelihood of adverse events regarding mental health symptoms.

Aim 2: taVNS

The taVNS device is Nesos MAUI PROTECT System– a wearable, external stimulator that generates electrical pulses transcutaneously delivered to the auricular branch of the vagus nerve through the ear canal. The type of stimulation (including shape, frequency, pulse width, amplitude, total charge, and energy delivered to the subject) is comparable to the levels applied by commercially available transcutaneous electrical nerve stimulation (TENS) stimulators. The Nesos MAUI PROTECT System is a type of TENS, classified as non-significant risk by the FDA and does not require an IDE.

Although highly unlikely, for participants with any severe or persistently worsening symptoms or adverse reactions, the taVNS therapy will be immediately discontinued, they will be removed from the study, considered treatment failures, and receive medical treatment as necessary. Participants will be taught safe practice with the use of a taVNS unit, such as checking and cleaning skin before starting a session, monitoring skin for signs of irritation, securing electrodes with even pressure distribution and full contact, and watching for signs of unit malfunction requiring maintenance.

The patient manual also provides details for participants regarding the following risks and they are asked to contact their provider and site coordinator if any occur:

The Nesos System exhibits a safety profile similar to that of commercially available TENS units. Possible, but rare, side effects may include: ● Bradycardia ● Skin erosion at electrode site ● Pressure sores ● Unbearable pain at the electrode site ● Undesirable sensation at electrode site ● Uncomfortable stimulation of tissue around the electrodes ● Uncomfortable heating effects, discomfort or burn ● Intermittent stimulation ● Tingling, prickling or numbness ● Tissue reaction to stimulation ● Tissue reaction or allergy to materials ● External sources of electromagnetic interference that cause the device to malfunction ● Failure of device components including breakage, hardware malfunctions, loose connections, electrical shorts or open circuits and insulation breaches ● Failure or malfunction requiring discontinuation of use

Although the Nesos device delivers transcutaneous electrical stimulation, to date, there are no FDA cleared devices that use the auricular nerve of the vagus on the external ear to deliver stimulation therapy in the manner that we do. Based on safety data collected from all of the studies using the same device representing more than 200 patients and over 2500 hours of stimulation, including data from 15 patients who used the device for 12 months (daily). Nesos states they have also not had any reports of SAE or UADEs in any of our studies in rheumatoid arthritis, postpartum depression and migraine. This clinical data supports the risk analysis in accordance with the standard for risk management, ISO 14971:2019, that concludes that the risks related to the use of the Nesos System are low.

Aim 2: *Biological Assessments*

There are no physical risks associated with the non-invasive physiological recording procedures. These tests are commonly used in clinical and research settings.

For electroencephalogram (EEG), there may be some discomfort wearing the electrode cap; fortunately, only dry electrodes are used that require no gels to record a signal. Additionally, the size and tightness can be adjusted for each participant. The electrodes only record activity and do not produce any sensation.

For electrocardiogram (ECG), only four electrodes will be connected to the participant's body. There may be some discomfort or skin irritation at the sites of the electrode connections. However, this usually dissipates shortly after the electrodes are removed.

The non-invasive blood pressure (NIBP) system involves the use of a finger cuff to obtain a measurement. There may be some discomfort along the finger and wrist. However, this is remedied by properly adjusting the system to the comfort of the user.

The galvanic skin response (GSR) sensors involve placing 2 electrodes on the fingertips of the participant, assessing skin conductance by measuring the voltage difference between the two electrodes. As a result, there may be some discomfort to participants.

There are no known risks for either the eye tracking device or respiratory belt. However, they may cause discomfort in some participants. The wearable eye tracker is a pair of clear, plastic glasses with unobtrusive design (no side or bottom frame) to provide a normal and maximal field of view. The respiratory belt is placed around the torso and can be adjusted to a comfortable setting for the participant.

Aim 2: *Blood Draw*
There are no major risks associated with the drawing of blood. However, blood draws may cause discomfort or bruising. In rare cases, it can also cause fainting or an infection at the site. Treatment of this complication, if necessary, usually involves a warm compress to the area for one to several days. Only trained staff will draw blood. This study consists of 2 blood draws, and it is considered minimal risk since the study will only involve the collection of approximately 12mL of blood at baseline and follow-up. This is below the maximum blood collection volume generally deemed minimal risk for this study population (i.e., no more than 50 mL in an 8-week period, with no more than two draws occurring in any 7-day period).

2.3.2 KNOWN POTENTIAL BENEFITS

There is no direct benefit to the focus group participants. There is an indirect benefit to other Veterans whose access to these treatments in the future may be increased by this focus group participation.

The pilot clinical trial participants could potentially experience benefit in terms of a reduction in PTSD symptoms.

The results of the proposed project will have important implications for the next step in determining the effectiveness of taVNS as a potential treatment for individuals with PTSD. The pilot feasibility study is a first step toward bringing the latest advances in non-invasive, easy to use bio-electronic medicine technology to a population with high rates of PTSD who experience barriers to treatment engagement and adherence. Ultimately, the findings of the study can serve as a blueprint for the next stage of a large, randomized controlled trial research protocol, to assess the benefits of this novel and non-invasive approach to reduction of PTSD symptoms for WTC responders across sites. This could eventually be a successful approach to other responder populations in the United States and internationally.

3 OBJECTIVES AND ENDPOINTS

Aim 1:

The primary objective:

To conduct a formative phase evaluation in order to ensure that the taVNS intervention and the pilot study methodology are **feasible** for use with 9/11 WTC responders with PTSD using a focus group of 10 WTC responders with elevated PTSD symptoms.

A secondary objective:

To conduct a formative phase evaluation in order to ensure that the taVNS intervention and the pilot study methodology are **relevant and acceptable** for use with 9/11 WTC responders with PTSD using a focus group of 10 WTC responders with elevated PTSD symptoms.

Primary Study Endpoint:

Feasibility

Secondary Study Endpoint:

Relevance and acceptability

Aim 2:

The primary objective:

To conduct a randomized, double blind placebo controlled parallel-design pilot study with 30 WTC responders affiliated with the WTC Health Program (WTCHP) who have PTSD to determine whether the taVNS intervention and efficacy study methodology are feasible for use with this population.

A secondary objective:

To conduct a randomized, double blind placebo controlled parallel-design pilot study with 30 WTC responders affiliated with the WTC Health Program (WTCHP) who have PTSD to determine whether the taVNS intervention and efficacy study methodology are acceptable for use with this population.

Primary Study Endpoint:

The primary endpoint of this study will be the feasibility of the taVNS intervention. This will be measured at the 8-week follow-up. Feasibility will be evaluated as: (1) rates of recruitment (per month), (2) adherence to the taVNS intervention, (3) 8-week retention, and (4) duration and completion rate of study assessments. Feasibility is defined as the ability to recruit 75% of eligible participants who were approached, as well as to show adherence to the intervention and retention rates of 70% each.

Secondary Study Endpoint:

The secondary endpoint of this study will be acceptability of the taVNS intervention. This will be measured at the 8-week follow-up. Acceptability will be evaluated by assessing: (1) the time to completion of questionnaires, (2) percentage of missing data from questionnaires, (3) the time to completion of the biological data and blood draw, (4) the rate of refusal of biologic measurements and blood draw, and (5) the score on the taVNS Satisfaction and Usefulness Questionnaire.

Tertiary endpoints of this study include multiple mental health and biologic potential endpoints to be measured at the baseline of the pilot feasibility trial as well as at the 8-week follow-up time point. Tertiary outcome measures include potential taVNS endpoint measures. At the baseline and 8-week follow-up visits, validated self-report mental health measures, biological measures, and the CAPS PTSD interview (at screener and follow-up) will be administered. To examine potential mechanisms of action and any acute and longer-term change in these mechanisms, all biological measures will be administered at the baseline visit 10 minutes before using the device, and then again one time at the 8 week follow-up visit. These tertiary outcome measures and potential mechanisms of action will be used to inform the design of a future RCT to evaluate taVNS efficacy. We will assess measurement quality, amount of missingness/non-response, length of measurement collection, and costs. These measures will also be used to provide parameter estimates for power calculations for a future RCT.

We will also use the initial study results to understand signals that point to potential variables to include that best indicate taVNS efficacy, and potential mediators of the impact of taVNS on PTSD when implemented in a future RCT involving multiple WTCHP sites. As such, preliminary efficacy of taVNS on PTSD symptoms will be assessed.

Differences between baseline and post-treatment mental health measures will be used to generate hypotheses for a future larger RCT targeting PTSD symptoms as a primary outcome, and anxiety, depression, and sleep quality as secondary outcomes, in order to more robustly evaluate taVNS efficacy among a larger sample of WTC responders with PTSD thereby conferring greater statistical power. We will also use results from this pilot to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural and cardiovascular changes that correlate with treatment outcomes.

Blood will be drawn to assess markers of inflammation before using the device, and again at the 8-week follow-up visit. This allows us to collect data to understand potential acute and long term effects based on these preliminary efficacy results. These tertiary outcome measures and potential mechanisms of action will be used to inform the design of a future, RCT to evaluate taVNS efficacy. Measurement quality, amount of missingness or non-response, length of measurement collection, and costs will be also assessed. These measures will also be used to provide parameter estimates for power calculations for a future RCT.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Aim 1 is a formative phase evaluation to ensure that the taVNS intervention and the pilot study methodology are relevant and acceptable for use with WTC responders with PTSD. As such, it is appropriate to use qualitative methods. This will entail the implementation of a focus group that is guided by a discussion guide. The discussion guide will be finalized by the research team prior to recruitment. It will include questions to understand the relevance, feasibility and acceptability of: (1) using a taVNS device generally, (2) using it as treatment for PTSD, (3) the implementation protocol of the device, (4) the pilot study protocol (including the methodology details, timing, and both self-report, clinical, and biological assessments), and (5) the appropriateness of outcome measures.

Aim 2 seeks to conduct a randomized, double-blind placebo-controlled parallel-design pilot study, to determine whether the taVNS intervention and study methodology are feasible and acceptable for use with WTC responders with PTSD. It is important that the design is double-blind and placebo-controlled in order to have the most appropriate control and to limit bias on the part of the participant and investigators. In addition, as this is a feasibility study, it is important to replicate the methodology that will eventually be used with a larger trial in order to truly assess whether the intervention and methodology are acceptable, feasible and efficacious.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Posttraumatic Stress Disorder (PTSD) remains the most prevalent mental health (MH) diagnosis for first responders involved with responding to the 9/11 World Trade Center (WTC) terrorist attacks, with rates of PTSD much higher than that of the general population. There are a number of evidence-based treatments (EBT) for PTSD, with the strongest evidence base for trauma focused therapies, which typically require that patients engage with the index trauma and the associated fears and cognitions. This can be particularly difficult for PTSD patients for whom avoidance is a key symptom. Although these treatments are well supported, they are less effective in military and veteran populations in particular. Additionally, high dropout rates are observed across treatments for PTSD, with some studies yielding dropout rates of over 30%. Given the high rates of PTSD and the lower uptake of effective PTSD treatment among responders, there is a clear need to provide brief, easily accessible treatments to WTC responders to alleviate PTSD symptoms. There is a growing body of literature to support the use of vagus nerve stimulation (VNS) to treat a number of different disorders with promising animal model research regarding the use of VNS to address some of the features of PTSD, specifically, due to the impact that VNS has on key areas of the brain that are associated with fear extinction and hyperarousal in particular. The current study aims to determine whether the use of a novel, safe, non-invasive form of VNS, transcutaneous auricular VNS (taVNS), would be acceptable and feasible for use with WTC responders who have PTSD, and whether the methodology involved

with a larger randomized controlled trial (RCT) to test taVNS efficacy would be acceptable and feasible. As such, the current study involves conducting a formative phase evaluation in the context of a focus group with WTC responders with elevated PTSD symptoms, in order to tailor the taVNS intervention and the pilot study methodology so that it's relevant and acceptable for use. The taVNS intervention will then be piloted in a randomized, double-blind placebo controlled parallel-design study with 30 WTC responders affiliated with the WTC Health Program who have PTSD. Outcomes include taVNS intervention and study methodology feasibility and acceptability. In addition, differences between baseline and post-treatment MH measures will be used to generate hypotheses for a future larger RCT aimed at evaluating taVNS efficacy in PTSD symptom reduction among a larger sample of WTC responders with PTSD. We will also use results to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural and cardiovascular changes that correlate with treatment outcomes. This pilot feasibility study is a first step toward bringing the latest advances in non-invasive, easy to use bioelectronic medicine technology to a population with high rates of PTSD who experience barriers to treatment engagement and adherence.

4.3 JUSTIFICATION FOR STIMULATION METHOD

The stimulation method here is taVNS, an emerging noninvasive form of VNS. It delivers electrical stimulation to an easily accessible target that innervates the human ear and has allowed researchers to expand on the promising applications of VNS without surgical intervention.

Stimulation parameters to achieve the intended effect may vary between each tested individual. The impedance of the electrode-skin interface, placement of the electrode on the ear, and unique anatomy between individuals makes it arbitrary to set a choice of specific stimulation amplitude parameters. For example, a specific current may not be perceptive in one person but may be painful for another. By adjusting the level of stimulation amplitude per individual instead of a one-size-fits-all parameter, we can establish similar levels of activation of the auricular branch of the vagus nerve. The min/max current range that the patient may receive during this study is 1 mAmp - 2.6 mAmp. The sham arm participants will not receive any current.

The intensity will be established as a function of individual perceptual threshold. The stimulation current for taVNS sessions will be just below the minimum amount of current that elicits a perceived sensation of at the target site. To preserve bias between taVNS and sham data, all participants will be told that they may or may not feel any sensation at every test session.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all study tests and visits. If a study participant fails to complete all study tests and does not return for all visits, he or she will be considered lost to follow up. If a participant has an adverse event they will discontinued from the study. Anyone can choose to end their participation at any time.

The study is considered complete once the last participant completes their final study visit, and all identifiable data has been collected and analyzed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible for the focus group (Aim1):

- being a Queens WTCHP responder who agreed to be contacted to participate in research,
- having PTSD as per DSM criteria as indicated by the WTC General Responder Data Center (GRDC),
- having elevated PTSD symptoms, as per a PCL-S[85] score $\geq$ 44 during an annual monitoring visit between 2018-2020.

To be eligible for randomized pilot (Aim 2):

- being a WTCHP responder who agreed to be contacted to participate in research
- having PTSD as per DSM criteria indicated by the GRDC
- having elevated PTSD symptoms, indicated by a PCL-S[93] score $\geq$ 44 during an annual monitoring visit between 2018-2020
- having a score of 33 or greater on the PCL-5[94] delivered during the initial phone screen to determine current symptomatology
- meeting diagnostic indication of PTSD using a Clinician-Administered PTSD Scale (CAPS), which is a clinical interview assessment.[95]

5.2 EXCLUSION CRITERIA

Exclusion criteria for the focus group (Aim1):

- being physically or mentally unable to consent/participate,
- inability to speak, read, or write in English

Exclusion criteria for randomized trial (Aim 2):

- being physically/mentally unable to consent and participate
- inability to speak, read, or write in English,

- exhibiting any current psychotic or manic symptoms or active substance dependence, as per the standard MINI neuropsychological assessment.[96], or current suicidal or homicidal intent/plan, as per the Columbia-Suicide Severity Rating Scale (C-SSRS) [104]
- active disease involving the auricle or ear canal (e.g., otitis media, tinnitus, infection, perforated tympanic membrane, vestibular and/or balance, excessive cerumen production, skin irritation), unwilling to remove a piercing (e.g., daith or tragus), or use a device (e.g., hearing aid, cochlear implant) that would preclude daily use of the earpiece.
- history of unilateral or bilateral vagotomy.
- Current pregnancy (self-report)
- previously implanted electrically active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators, VNS).
- other major conditions, that in the judgment of the investigators/WTCHP medical staff, would make the participant unsuitable for inclusion or would interfere with the participant participating in or completing the study. these include:
    - current treatment with psychotropic medication, including tricyclics, antipsychotics, mood stabilizers, bupropion, barbiturates, stimulants, antiepileptics, opioid medications.
    - current diagnosis or history of any clinically significant cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, neurologic, gastrointestinal, or immunologic.
    - history of any of the following cardiovascular conditions: Moderate to severe congestive heart failure (New York Heart Association class III or IV); Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting; Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
    - history of or active seizure disorder.
    - history of recurrent vasovagal syncope episodes.
    - diagnosis of cancer (other than non-invasive skin cancer or carcinoma in-situ of the cervix) within the 5 years prior to study entry.
    - history of concurrent illness that requires hospitalization within 30 days prior to study entry
    - have hypertension/hypotension uncontrolled by medication
    - participation in another investigational trial during the 30 days prior to study entry or during this project

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Abstain from eating or drinking (besides water) for at least 3 hours prior to each visit
- Abstain from alcohol for at least 8 hours prior to each visit
- Abstain from tobacco and nicotine products for at least 1 week prior to each visit
- Abstain from recreational drugs for at least 1 week prior to each visit
- Abstain from exercise for at least 8 hours prior to each visit

- Women of childbearing potential should use birth control for the entire duration of the study. Double-barrier methods (condoms with spermicide, sponge with spermicide, or diaphragm with spermicide) or not having sex may be used.

5.4 SCREEN FAILURES

Screen failures are defined as participants who screened as potential participants in the clinical trial, but do not complete the first study visit or consent because they did not qualify based on their CAPS scored and become deemed ineligible.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment (Aim1):

The GRDC will provide a list of all Queens WTCHP responders who meet eligibility criteria, and their corresponding contact information, to the study team. A Collaboration Request Letter was granted by the GRDC to provide this information, and will be executed upon Notice of Award. From this list, a random sample of 10 responders will be contacted by phone, email, and/or mail for focus group recruitment. After 10 responders have consented, the focus group will be scheduled and conducted at the Queens WTCHP. Due to potential COVID-19 restrictions the focus group can be done remotely if necessary.

In order to maximize recruitment, mailings will be sent to all eligible Queens WTCHP responders (N=477) and the focus group will be advertised within the Queens WTCHP.

Recruitment (Aim 2):

As per the GRDC, there are currently 477 Queens WTCHP responders who consented to be contacted to participate in research with a PCL-S score ≥ 44 since 2018, and who met DSM criteria for PTSD. From that list of 477, 30 responders will be recruited over the course of 10 months as follows: First, the list of responders that meet initial eligibility requirements will be randomly ordered. Next, the coordinator will contact responders from this list in sequential order by phone, in which the PCL-5 will be administered to confirm current probable PTSD (score $\geq$ 33), so that the likelihood of bringing someone in for a diagnostic interview who does not currently meet criteria for PTSD is minimized. Then the coordinator will discuss participation in the CAPS interview, to determine further eligibility for the study. If the responder agrees to come in for a CAPS assessment, Dr. McCann or Ms. Shaam, Dr. Lieberman or Ms Ryniker will conduct a CAPS assessment and the standard MINI to assess for psychiatric exclusion. For the suicidality portion specifically, we will utilize the Columbia-Suicide Severity Rating Scale (C-SSRS). Dr McCann, Ms Shaam and Ms Ryniker will be trained and supervised on CAPS by Lynne Lieberman. If the CAPS is indicative of a current diagnosis of PTSD and exclusion criteria are not met, Ms. Shaam or Ms Ryniker will then come to the fitting appointment to consent and enroll the responder into the study if they continue to express interest. The consent form will be mailed or given ahead of time to review.

The responder will receive $20 and transportation costs, $25, for completion of the CAPS regardless of whether or not he or she is eligible for the pilot study. Based on our previous research,[97] we expect that of the 477 potential participants, approximately 182 will need to be called in order to reach a 33% screening participation rate, to yield 60 responders who meet the phone screen criteria and agree to come in for the CAPS interview. Of those 60 responders, we expect that 66% (n=40) will meet criteria for PTSD as per the CAPS, and will therefore be eligible for the study based on Dr. Bellehsen' s previous study involving recruitment and enrollment of military Veterans with PTSD.[98] Based on our prior experience of clinical taVNS studies on both healthy and disease cohorts,[37] of those 40, we expect that at least 75% (n=30) will agree to continue with study participation.

In order to increase recruitment, we are working with Mount Sinai WTCHP Data Center to identify additional eligible patients. These participants previously consented to be contacted for research.

This information includes: names, contact information (mailing address, phone numbers and email addresses) for members who scored ≥ 44 on their most recently completed PCL/PTSD checklist since 1/1/2019 who live within a 10 mile radius from the Feinstein Institutes for Medical Research (350 Community Drive, Manhasset, NY 11030).

This will be provided to us from Mount Sinai WTCHP Data Center, we will not be giving any information to them.

Even though we have a data use agreement in place, we are requesting a HIPAA waiver of authorization to receive and possess the WTCHP PHI. Providers previously gave permission to be contacted, but in order for us to only reach out to those potentially eligible, we need to know additional information and it isn't feasible to reach out to each participant for this information. All participants are consented prior to any research activity.

5.6 COSTS

There are no foreseeable costs that participants may incur through participation in this research study, other than costs of travel which will be reimbursed with a flat fee per study visit. No research procedures will be billed to insurance and all clinical laboratory tests conducted for this study will be paid for by the study.

5.7 COMPENSATION

Compensation (Aim1):

Participants will be compensated $25 for their participation in the focus group as well as a flat reimbursement for travel/mileage of $25 per participant.

Compensation (Aim 2):

CAPS Interviews: Incentives of $20 per participant as well as a flat reimbursement for travel/mileage of $25 per participant

taVNS Fitting: Incentives of $25 per participant as well as a flat reimbursement for travel/mileage of $25 per participant

Baseline Measurement: Incentives of $30 per participant, as well as a flat reimbursement for travel/mileage of $25 per participant

Follow-Up Measurement: Incentives of $35 per participant as well as a flat reimbursement for travel/mileage of $25 per participant

Greenphire ClinCards: **Greenphire ClinCards** will be used for reimbursement per institutional policy. Each participant will receive a new ClinCard at each study visit.

Amazon electronic gift cards will also be utilized for reimbursement for ease with participants

Study Incentives

Time point	***Incentive***	***Travel***	***Total***
Focus Group	$25	$25	$50
*CAPS Interview	$20	$25	$45
taVNS Fitting	$25	$25	$50
Baseline	$30	$25	$55
Follow-up	$35	$25	$60

* The responder will receive $20 and transportation costs, $25, for completion of the CAPS regardless of whether or not he or she is eligible for the pilot study. If not eligible the responder would not take part in any additional portion of the study.

** If focus group or CAPS interview are done remote, reimbursement for the transportation will not be given.

5.8 RESEARCH INJURY COMPENSATION

If participants are injured from study participation, s/he will be provided treatment by Northwell Health. However, s/he or their insurance company will be responsible for the associated costs. No money will be given to participants.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Aim 1: A Focus Group Discussion Guide will be finalized by the research team prior to recruitment (see Appendix 1 for example blank focus group data collection instrument). It will include questions to understand the relevance, feasibility and acceptability of: (1) using a taVNS device generally, (2) using it as treatment for PTSD, (3) the implementation protocol of the device, (4) the pilot study protocol (including the methodology details, timing, and both self-report, clinical, and biological assessments), and (5) the appropriateness of outcome measures. The estimated duration for the focus group is ≈ 90 minutes. Drs. Schwartz and Williams will co-lead the focus group and the coordinator will take notes, write the minutes, and audio-record the session. Dr. Zanos and/or Dr. Debnath will demonstrate the device. Individuals will have the opportunity to handle the devices and there will be sanitizing wipes to be used in between. The focus group will be transcribed for qualitative analyses.

Aim 2:

Table 1. Aim 2 Outcome Measures
Primary Outcome Measures (measured at 8 weeks)
FEASIBILITY
Recruitment -% responders who meet criteria 1-3 who accepted to come in for the CAPS interview (goal=33%) -% eligible responders who meet criteria 1-4 of those who came in for the CAPS interview (goal=66%) -% eligible responders who meet all criteria and were recruited and consented (goal = 75%) **Retention** -% participants who complete baseline and 8-wk measures (both survey and biological measures) (goal = 90%) **Adherence** -% participants who used taVNS 15 min/day once a day for 8 weeks (21 hours total) (goal=80%)
Secondary Outcome Measures (measured at 8 weeks)
ACCEPTABILITY
Collection of Measures -Time (minutes) to fill out questionnaires (goal =<30 min) -Missing data from questionnaires: % items complete on the baseline and 8-wk self-report surveys (goal=90%) -Time (minutes) to collect biological data and blood draw (goal=10 min at baseline and 10 minutes at follow-up) -Rate of refusal of biologic measurements/blood draw (goal=5% refusal) **Satisfaction** -taVNS Intervention Study satisfaction survey (Adapted from Bakken et al.) (range=12-60; goal=100%-with score >47 among intervention group)[100]
Tertiary Outcome Measures (measured at baseline and 8 week follow-up)
Mental health symptoms (assessed to indicate signals for hypothesis generation)
-PTSD diagnosis and severity: CAPS interview[95] (measured at screening and 8 week follow-up); PTSD Diagnosis: Yes/No; PTSD Severity score range=0-80) -PTSD symptom score (PCL-5[94], range=0-80) -Anxiety symptom score (GAD-7[101], range=0-21) -Depression symptom score (PHQ-9[102], range=0-27) -Sleep score (Pittsburg Sleep Quality Index[103], range=0-21)
Biologic Measures (assessed to indicate signals for hypothesis generation regarding potential mechanisms of action) At baseline, these will be measured 10 min before, during and 10 min after the initial taVNS administration
-Heart rate/HRV (6-lead ECG, DI Powerlab) (beats/min, range=40-150) -EEG(DSI-24) (band-power dB changes, range=0-10) -Pupil Dilation (Tobii Pro Glasses 2) (pupil diameter in mm, range=2-8mm) -Galvanic Skin Response (GSR electrodes, ADI Powerlab) (skin conductance in microSiemens, range=0-50mS) -Skin Temperature (Thermistor Pod, ADI Powerlab) (Celcius, range=30-35C) -Respiratory Rate (Respiratory Belt, ADI Powerlab) (breaths per minute, range=3-20BPM) -Beat-to-Beat Blood Pressure (Human Non-Invasive Blood Pressure Nano Interface, ADI Powerlab) (mmHg, range=50-150mmHg) -Inflammatory Markers (blood draws at baseline before and after initial taVNS and at 6 week follow-up: TNFα, IL-1β, IL-6, IL-10, IL-12, IL-17, CRP, Cortisol, Alpha Amylase -Facial & Neck Electromyography (EMG electrodes, ADI Powerlab) (millivolts, range=0-15mV)

Procedure: *After each of the 30 responders are enrolled (3 per month),* they will be scheduled within that same month for an appointment at FIMR to be fitted with a custom-made taVNS device, a wearable TENS unit called the Nesos System. They will be compensated for their time/transportation. We expect to have approximately 1 visit per month for fittings, *so that all 30 participants will be enrolled and fitted over 10 months*. Participant visits will be staggered in order to protect privacy. After the devices are customized and delivered to FIMR (within approximately 1 month), responders will be called to FIMR for a baseline visit. One of the researchers from the Feinstein Institutes will assess the fit of the device and calibrate the level needed for each responder. At the baseline visit, responders will be given the device that matches their randomization sequence ID number. Each responder will also be given, along with the taVNS device, a locked-down Android Nexus 5X or Pixel phone to interface with the device and record the usage data. Responders will then be given a self-report survey to complete that asks demographic information, MH treatment-related information, and validated measures of MH and sleep (Table 1). Appendix 1 contains blank, sample self-report/interview measures. A research nurse will also collect 12 mL of blood to assess baseline and follow-up levels of inflammatory markers including Tumour Necrosis Factor alpha (TNF α), Interleukin (IL)-1β, IL-6, IL-10, IL-12, IL-17, C Reactive Protein (CRP), cortisol, and alpha amylase. During the baseline visit, responders will also be shown how to use the device by Drs. Zanos or Debnath. The responders will use the device for one 15-minute session under the supervision of Drs. Zanos or Debnath. Biological non-invasive measures (not blood draw) of autonomic nervous system function and balance, as detailed in prior studies from the our group[80] and others, will be assessed 10 minutes before using the taVNS device. (see Table 1).

These non-invasive biological measures include: Respiratory belt, ECG, GSR, NIBP, EEG, Eye tracking.

The first sensor to be attached to the participant is a respiratory belt that goes around the torso. It is tightened without discomfort such that breathing causes the belt to stretch, which provides inspiration (inhalation) and expiration (exhalation) times to infer respiration rate. Next, the 6-lead electrocardiography (ECG) will be recorded from wires connected from a bio-amplifier, which gathers and increases physiologic signals, to four foam electrodes that are adhesively attached to the left shoulder, the right shoulder, the left ankle, and the right ankle. The right ankle provides a ground, while the remaining three leads provide recordings of the electrical potentials between different sites that represent the electrical activity of the heart in real-time.

Additional sensors are placed on the wrist and hands of the participant. The first set records galvanic skin response (GSR) by attaching two dry, metal electrodes with Velcro attachments on two fingers, preferably the pointer and ring fingers on the dominant hand. These electrodes measure the changes in skin conductance that can reflect changes in sweat gland activity. A wrist device will be placed to record non-invasive blood pressure (NIBP) from the middle finger on the participant's non-dominant hand. The wrist device is placed with a Velcro strap on the wrist, while a small cuff is placed on the middle finger. The wrist device provides air and power for the cuff to inflate and deflate to measure changes in blood pressure. A dry electrode electroencephalography (EEG) cap will be placed on the head of the participant. This cap offers low noise and high signal quality of non-invasive brain recordings without an uncomfortable cap that may require conductive gels. This cap can be placed on the head of the participant and record comfortably through hair without any gel. The final device to be placed on the participant is the eye tracking glasses. These are easily wearable and mobile glasses with multiple small cameras to track gaze and pupil size. If the participant wears prescription glasses, these will be removed and replaced with the eye tracking glasses (with the appropriate prescription lenses) for this study."

Responders will then be instructed to use the device once a day, every day at home, for 15 minutes intervals over 8 weeks. The devices have a safety feature where they cannot be used for more than the intended timepoints daily and the stimulation parameter will be set by the investigator and cannot be altered by the participant. The date and time stamp of each use will be recorded on the application. The application only assesses usage/compliance and has no ability to capture any personal or other information. All phones containing the Nesos application is collected at the end of the study. Responders are requested to come in 8 weeks post-baseline and the same measures will be recorded again (self-report, biological and blood draw; see Table 1).

6.1.2 ELECTRICAL STIMULATION AND ADMINISTRATION

The perceptual threshold will be determined at the initial session for every participant. This is 25% below the minimum amount of current required to perceive electrical stimulation on the skin at the target. Because of differences in the electrode-skin interface and anatomy of each individual, stimulation parameters will be adjusted for each participant to establish similar levels of activation over all participants.

A step-up and step-down binary parametric search will be used to establish the threshold and stimulation parameters. While delivering one second trains of stimulation, we will ask the participant whether s/he felt the stimulation. If yes, we reduce the stimulation intensity by 50%, while if no, we increase the stimulation intensity by 50%. This enables us to establish the minimum threshold for perception. Sensation is generally reported as a "tickle" or "pricking" sensation. Since taVNS is targeting a sensory nerve, perception and sensation remains the main indication that we are stimulating the auricular branch of the vagus nerve from locations on both the left and right ear.

6.2 HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

We will receive all taVNS devices at the Neural and Data Science Lab from Nesos Corp., where they will be kept in locked drawers, until they are handed out to the participants. Drs. Zanos and Debnath will be responsible for the timely acquisition and proper storage of the devices.

6.2.2 MANUFACTURING, PACKAGING, AND LABELING

The devices and all necessary components (stimulators, phones, ear mold and electrode materials) will be shipped to the Neural and Data Science lab as an investigational supply provided by the company. The company is listed as a consultant on our grant and we will be setting up a purchase order to provide them with a flat fee of funds in both year 1 and year 2.

The devices will bear the following labeling during the course of the study: "*CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use*" per 21 CFR 812.5.

6.2.3 PRODUCT STORAGE

Information on each use of the device will be documented, and a Device Accountability Log will be maintained.

Ear mold materials will be stored in a locked cabinet, inside a badge-access room of the Neural and Data Science lab. The ear molds will be fitted to the participants and each electrode will be connected to the external stimulator, and mobile app. The whole Nesos System will be put together by Shubham Debnath from the Neural and Data Science lab or Nesos personnel and will be brought to the Device Training Visit (Visit 2)

6.2.4 DEVICE RISK DETERMINATION

Description of Transcutaneous Auricular VNS (taVNS) Intervention: The taVNS device that will be used in this study is a wearable Transcutaneous Electrical Nerve Stimulation (TENS) unit called the Nesos System. The Nesos System, which is manufactured by Nesos Corp in Redwood City, California, consists of a wearable, external stimulator, and a neural interface earpiece (Figure 2 below). The device is considered a non-significant risk device not requiring an Investigational Device Exemption (IDE). The wearable, external stimulator generates electrical pulses that are transcutaneously delivered to the auricular branch of the vagus nerve through the ear canal. The external stimulator is made out of Acrylonitrile Butadiene Styrene (ABS) plastic, which has a proven history of safe use in similar applications. The earpiece contains 4 electrodes that carry current from the external stimulator to the auricular branch of vagus nerve. The earpiece is made out of a silicone material that has evidence of safety in wearable devices. The electrode surface is made out of a medical grade, biocompatible conductive hydrogel or conductive silicone material

The system is comprised of the following major components:

- Stimulator – The stimulator is housed in an enclosure which is placed on the user's neck. It delivers charge-balanced, current-controlled, biphasic, square waves to electrodes (in the earbuds) in contact with the skin of the user's ear. The type of stimulation (total charge and energy delivered to the user) is comparable to the levels applied by commercially available transcutaneous electrical nerve stimulators (TENS) or non-invasive vagus nerve stimulators (nVNS).

- Earbuds – The earbuds are designed to transcutaneously-deliver electrical stimulation to the external ear. Each earbud is manufactured using ear molds unique to each user's ears to facilitate proper contact of the electrodes (in the earbuds) with the skin. Commercially available electrolyte solution (e.g., Signa spray or its equivalent) is recommended to be applied on the electrodes before they are placed in the ear. This conductive electrolyte solution reduces the electrode to skin interface resistance.

- Nesos proprietary APP – The system comes with a proprietary APP that is downloaded onto a smartphone. The key function of the APP is to allow the user to turn stimulation ON/OFF, monitor (using periodic impedance measurements) and notify the user of poor electrode/skin contact. In addition, the APP shows the amount of time left in a stimulation session and will notify the user when it is time for a session. The system also comes with a custom charging cable for recharging the stimulator.

The Nesos MAUI PROTECT System was developed using a 13485:2016 ISO quality system and tested to ensure compliance with applicable clauses of standards.[83,84] The Nesos MAUI PROTECT System delivers charge-balanced, current-controlled, biphasic, square waves to the auricular branch of the vagal nerve on the subject's skin. The type of stimulation (including shape, frequency, pulse width, amplitude, total charge and energy) delivered to the subject is comparable to the levels applied by commercially available TENS stimulators.

Although its use in this study is considered investigational, its use is considered to constitute minimal risk. It is also believed that its usage in this feasibility study meets the FDA definition of a non-significant risk device. The device is intended to be used to administer a low amount of current to stimulate the vagus nerve. The non-significant risk determination was made because the device does not constitute a significant risk device since it is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject; is not purported to be for use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject; is not for use of substantial importance in diagnosing, curing, mitigating, or treating disease and does not present a potential for serious risk to the health, safety, or welfare of a subject; and does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Figure 2. PROTECT System: A) Representative picture of a user with the wearable PROTECT System B) Components of the system include the stimulator housed within the over-the-neck enclosure, earbuds with integrated electrodes and a mobile APP

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: A randomization schema will be pre-generated by the Biostatistics Unit at FIMR, using the Biostatistics Randomization Management System (BRMS) software, by a statistician not affiliated with the study. Responders will be randomly assigned in a 2:1 ratio to either taVNS or sham and given a unique randomization ID number. The randomization schema will be read into the randomization module in REDCap, a data management system that only the coordinator can access. The software will monitor the allocation progress and responder assignment.

Concealed Allocation: The coordinator will create and keep a crosswalk between participant ID, unique randomization ID number, and assignment in REDCap. Nesos Corp will use the unique randomization ID number to label the molds for fitting the device. After the fitted devices are received, the coordinator will give Nesos Corp a table with unique randomization ID number labels and assignment for Nesos Corp to designate the appropriate program to the device based on the responder's allocation. For the taVNS program, when the responder uses the app to activate the device, the taVNS will provide stimulation at a value that was calibrated to that responder. For the sham program, the device will not provide any electrical stimulation.

Blinding: Responders in the taVNS and the sham group will be blinded to their assignment. *Both groups will not be able to detect the stimulation provided* and thus, will not know which group they are in. The directions provided and the use of the application will be the same for both groups. All investigators will be blinded to participation assignment as well. Biologic outcome measures will be conducted by Dr. Debnath. The CAPS will be conducted by senior study staff and oversight of self-report survey completion will be provided by the research coordinator. Only the research coordinators will not be blinded to the assignment. They will receive the allocation assignment after enrollment and will coordinate with Nesos Corp to program the devices corresponding to assignment.

6.4 STUDY INTERVENTION COMPLIANCE

In order to verify compliance with the study procedures, the completion of case report forms is required for each study visit for participants. These records will be periodically reviewed investigator(s) to ensure all study procedures were adequately performed. In addition, investigator(s) will cross reference the documented information against the randomization schema to ensure participants were appropriately randomized and administered the procedures as specified.

7 STUDY DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of taVNS does not necessarily mean discontinuation from the study, as remaining study procedures may be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment, a qualified investigator will determine if any change in participant management is needed. Also, the participant may be notified of the finding and recommended to seek further clinical evaluation and care.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Given that participation in this study is voluntary, participants may elect to withdraw at any time by notifying a researcher. It is also possible that participation in this study may end without the participant's consent. This decision may be made by a researcher, the Northwell Health Human Research Protection Program, or a federal or state regulatory agency.

Reasons for withdrawal may include: failure to comply with study requirements; failure to keep study appointments; a change in their medical history, medications, or lifestyle (including alcohol, tobacco, or substance usage) that results in them no longer meeting study eligibility; inability to tolerate study procedures; it is not in the participant's best interest to continue on this study; or the study is stopped.

Participants that prematurely withdraw from the study due to an adverse event will be followed (e.g. telephone contact, follow-up visits, etc.) until resolution of the event or they indicate they no longer want to be contacted. In addition, a designated investigator will have access to treatment status at all times and provide that information to appropriate medical personnel in the event of medical emergencies. If the participant withdraws from this study or if s/he is withdrawn from the study, any data already collected will continue to be used, but no new data will be collected. The reason for participant discontinuation or withdrawal from the study will be recorded.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete all study visits and cannot be contacted for the visits. In this event, their participation will be considered complete, and the collected information will be used.

The following actions must be taken if a participant fails to return for a study visit:

- The site will attempt to contact the participant and reschedule the missed visit.
- The site will counsel the participant on the importance of following the study visit schedule and ascertain if the participant wishes to continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. This includes up to 3 telephone calls.
- All reasonable efforts will be made to recover equipment, including sending a prepaid label for return.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Aim 2: Primary Outcome Measure: Feasibility will be evaluated using criteria suggested by Leon[99]: 1) rates of recruitment (per month), 2) adherence to the taVNS intervention, 3) 8-week retention, and 4) duration and completion rate of study assessments. Feasibility is defined as the ability to recruit 75% of eligible, approached, participants and to demonstrate intervention adherence and retention rates of 70% each (Table 1). **Secondary Outcome Measure:**

Acceptability will be evaluated by assessing: 1) time to completion of questionnaires, 2) percentage of missing data from questionnaires, 3) time to completion of the biological data and blood draw, 4) rate of refusal of biologic measurements and blood draw, and 5) score on the taVNS Satisfaction and Usefulness Questionnaire[100] (Table 1). **Tertiary Outcome Measures** include potential taVNS endpoint measures. At the baseline and 8 week follow-up visits, validated self-report MH measures, including assessments of PTSD,[94] anxiety,[101] depression,[102] sleep,[103] and the CAPS interview[95] (at screener and follow-up) will be administered. To examine **potential mechanisms of action** and any acute and longer-term change in these mechanisms, the biological measures will be administered at baseline 10 minutes before using the device, again one time at the 8-week follow-up visit. Blood will be drawn to assess markers of inflammation before using the device, after using the device, and again at the 8 week follow-up visit. This allows us to collect data to understand potential acute and long-term effects. These tertiary outcome measures and potential mechanisms of action will be used to inform the design of a future, RCT to evaluate taVNS efficacy. Measurement quality, amount of missingness or non-response, length of measurement collection, and costs will be assessed. These measures will also be used to provide parameter estimates for power calculations for a future RCT (Table 1). We will also use the preliminary efficacy results from this pilot to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural and cardiovascular changes that correlate with treatment outcomes

Table 2.

Precision of estimated proportions given a sample size of 30			
Estimated Proportion	Lower CL	Upper CL	Width
0.70	0.51	0.85	0.35
0.75	0.56	0.89	0.33
0.80	0.61	0.92	0.31
0.85	0.67	0.95	0.28
0.90	0.74	0.98	0.24
0.95	0.80	1.00	0.19

CL=confidence level

Demographics and MH Treatment Variables: Demographics including age, gender, race, ethnicity, and education will be collected using self-report questionnaires, which will be designed in REDCap and recorded using i-Pads. *Past and current MH treatment data will be collected, including psychotherapy sessions, duration of treatment, and medications used, to be explored as potential covariates in a larger RCT.* Information on perceived barriers to engagement in MH care will also be gathered. Differences between baseline and post-treatment mental health measures will be used to generate hypotheses for a future larger RCT targeting PTSD symptoms as a primary outcome, and anxiety, depression, and sleep quality as secondary outcomes, in order to evaluate taVNS efficacy among a larger sample of WTC responders with PTSD.

Planned Data Analysis: The purpose of the pilot study is to determine whether an RCT evaluating the efficacy of taVNS on MH outcomes is feasible, acceptable, and satisfactory for WTC responders with PTSD. Primary outcomes are based on feasibility. Specifically, recruitment, retention, and adherence will be measured as described above. Secondary outcomes are indicators of acceptability including rates of non-response, time to completion of measures, and intervention satisfaction. Tertiary outcomes include MH and biologic measures. All measures will be described using frequency and percent or mean (SD) as appropriate, overall and by taVNS and sham group, with corresponding 95% confidence intervals to interpret the precision of the estimates. Median and interquartile range may also be used if discrete data are skewed. For the tertiary outcomes measuring MH and biologic data, descriptive statistics for each time point, as well as differences over time, will be calculated. Differences in outcomes will be assessed from the first time point at baseline and the last time point at 8 weeks, for long-term effects. Within-subject correlation of acute and long-term measures will be reported. **Precision of Estimates:** Primary outcome

Table 2.

Precision of estimated proportions given a sample size of 30			
Estimated Proportion	Lower CL	Upper CL	Width
0.70	0.51	0.85	0.35
0.75	0.56	0.89	0.33
0.80	0.61	0.92	0.31
0.85	0.67	0.95	0.28
0.90	0.74	0.98	0.24
0.95	0.80	1.00	0.19

CL=confidence level

measures are expected to be 75% for recruitment, 90% for retention, and 80% for adherence. Two-sided 95% confidence intervals for one proportion were calculated using the Clopper-Pearson method, with scenarios varying the expected percent (0.70-0.95), in order to estimate precision given a sample size of 30. The lower confidence level will be used to inform recruitment, retention, and adherence planning in the future RCT (Table 2). **Hypothesis Generation:** Differences between baseline and post-treatment secondary outcome measures will be used to generate hypotheses for a larger RCT targeting PTSD symptoms (with a particular focus on hyperarousal) as a primary outcome, and anxiety, depression, and sleep as secondary outcomes, in order to evaluate taVNS efficacy. Estimates and variances at each time point will be used to calculate effect sizes to plan the larger RCT. We will be cautious about using our findings from this pilot study to inform underlying assumptions regarding the true magnitude of the effect of taVNS. This is because effect sizes observed in pilot studies are crude, due to the small sample size, and may not be indicative of the true difference in the larger population. We will also use results to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural, and cardiovascular changes that correlate with treatment outcomes. We will explore whether the impact of taVNS on PTSD symptoms is mediated by biologic measures of physiological reactivity and inflammatory markers (Table 1).

D. Potential Limitations: Ideally, the activity of deep brain structures related to relevant neural circuits would also be measured using fMRI, given their role in mediating stress and the impact that innervation of the vagus nerve has on specific brain areas, such as the Nucleus Tractus Solitarius. Given the scope of this pilot feasibility study, however, it is not possible to conduct fMRIs on 30 participants. This is something that will warrant further exploration in the next phase of study- an RCT with a large sample size powered to detect differences in outcomes and mediational relationships. In addition, the inclusion of participants staying in their current MH treatment may dilute the ability to test the effects of taVNS. However, given that this is a pilot feasibility study and effect sizes will only be used for hypothesis generation, treatment dilution is less of a concern. We are now, however, examining the role of current treatment in an exploratory manner as its potential role as a likely covariate in future RCT analyses (or as a variable on which to block randomize). Finally, should distancing requirements of COVID-19 continue to be a concern in the beginning of the study period, the study team can easily pivot to implementing the focus group and screening procedures over secure video conference, and the survey measures can be completed electronically via a secure email link. Fitting for the taVNS devices as well as biologic measurements can be conducted quickly and safely with all appropriate precautions taken regarding PPE provision and use for both the study staff and the participant.

E. Dissemination: The results of this pilot feasibility study will provide the necessary foundation to inform a larger trial that tests the efficacy of taVNS at multiple WTCHP sites. As such, it is important that the WTCHP providers and the responder community at large are engaged as stakeholders and collaborators to facilitate community dissemination activities. Dr. Moline will be integral in these efforts given her strong ties to the WTC provider and responder communities. Updates on study progress and findings will be presented to stakeholders in the WTCHP including at the Biannual WTC Research Grantees meetings and at WTCHP committee meetings (e.g., WTCHP Mental Health Forum, WTC Steering Committee), as well as to patient stakeholder organizations (e.g., 9/11 Health Watch, FealGood Foundation). Additionally, results will be reported to the MH working group for the WTCHP, in which Dr. Bellehsen already participates, and at monthly meetings of the Queens WTCHP. Results will also be disseminated in peer-review publications, and will be presented at national and local conferences. This pilot feasibility study is a first, integral step toward bringing the latest advances in non-invasive, easy

to use bioelectronic medicine technology to a population with high rates of PTSD who experience barriers to PTSD treatment engagement and adherence.

8.2 SAFETY ASSESSMENTS

Co-primary Safety Endpoints: The primary safety endpoint is the occurrence of any discomfort or harm in healthy, able-bodied participants during taVNS protocol.

Secondary Study Endpoint: The efficacy and specificity of taVNS will be determined by the effect of noninvasive stimulation on the calculated index. This study will explore the changes in the ANS and its branches from taVNS, as well as the stimulation parameters to achieve significant results.

There are no anticipated problems that are associated with this non-invasive study. In the unlikely event that a participant is harmed from being in the study, medical care and treatment will be provided by Northwell Health. However, the participant will be responsible for the costs of any medical treatment, directly or through medical insurance and/or other forms of medical coverage.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any untoward medical occurrence regardless of causality assessment. An adverse event can be an unfavorable and unintended sign, symptom, syndrome, or disease associated with or occurring during an investigation, whether or not considered related to the investigation.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event is any undesirable experience or untoward medical occurrence associated with an investigation that:

- Led to death
- Led the health of a subject to diminish such that it resulted in:
    - Life threatening illness or injury
    - Required inpatient hospitalization or prolongation of existing hospitalization
    - Resulted in a permanent impairment of a body structure or a body function
    - Resulted in a congenital anomaly or birth defect
    - Resulted in medical or surgical procedure to prevent permanent impairment or damage to a body structure or function

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For consistency of labeling and categorizing adverse events, the Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be used on this study. The grading will be performed as follows:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

The identification of an adverse event may be from observation, participant notification, clinical assessment, or results from tests.

- **Mild** – Events that require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events that result in a low level of inconvenience or concern. Moderate events may cause some interference with functioning.
- **Severe** – Events that interrupt a participant's usual daily activity and may require treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Life-threatening** – Events that require urgent intervention to sustain life or prevent severely debilitating condition.
- **Death** – Events that are related to death.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study intervention assessed based on temporal relationship. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event 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 clinical event occurs within a reasonable time after administration of 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 event occurred within a reasonable time after administration of intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Not Related** – The adverse event is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

8.3.3.3 EXPECTEDNESS

The principal investigator, Rebecca Schwartz, PhD 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.

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

The occurrence of an adverse event or serious adverse event may come to the attention of study personnel during study visits, interviews of a study participant presenting for medical care, or upon review by a study monitor.

All adverse events not meeting the criteria for a serious adverse event will be captured on the case report form. Information to be collected includes event description, time of onset, assessment of severity, relationship to study intervention, and time of resolution/stabilization of the event. All adverse events occurring while on study will be documented appropriately regardless of relationship, and followed to resolution or until the participant no longer wants to be contacted.

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

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

The principal investigator, Rebecca Schwartz, PhD, will be responsible for the recording of all reportable events with start dates occurring any time after informed consent is obtained until resolution or until the participant no longer wants to be contacted. At each study visit, the investigator will inquire about the occurrence of adverse events.

8.3.5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

The study will record, assess, categorize, and report all adverse events and serious adverse events as per the reporting requirements of the Northwell Health Human Research Protection Program and the Food and Drug Administration, as applicable.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

If an adverse event or serious adverse event is observed, the participant will be notified immediately upon discovery in person or by phone call. In addition, participants will be told of any new findings that may change their decision to continue to participate.

If incidental findings that are deemed clinically-significantly are discovered, the participant will be notified and recommended to seek further clinical evaluation and care.

8.3.7 REPORTING OF PREGNANCY

- If an individual becomes pregnant during the course of the study, she will be withdrawn from the study, as early pregnancy may potentially impact measurements.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An unanticipated problem involving risks to participants or others includes any incident, experience, or outcome that is considered:

- Unexpected in terms of nature, severity, or frequency given the research procedures and participant population being studied;
- Related or possibly related to participation in the research; and
- Suggests that the research places participants or others at a greater risk of harm than previously known or recognized.

8.4.2 DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

An unanticipated adverse device effect is any serious adverse effect on the health and/or safety or any life threatening problem or death caused by, or associated with, the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in this study; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). An event will not be considered related to the device when it is the result of a pre-existing medical condition or medication.

A device malfunction is the failure of a device to meet its performance specifications or other performance as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the labeled use for which the device is labeled.

8.4.3 UNANTICIPATED PROBLEM REPORTING

The study will record, assess, and report all unanticipated problems involving risks to subjects or others and unanticipated adverse device effects as per the reporting requirements of the Northwell Health Human Research Protection Program and the Food and Drug Administration, as applicable. The report will include a detailed description of the event, incident, experience, or outcome; an explanation for its occurrence and assessment; and a corrective action plan.

8.4.4 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If an unanticipated problem involving risks to subjects or others or unanticipated adverse device effects occur, the participant will be notified immediately upon discovery in person or by phone call, if deemed necessary. Upon reporting to the appropriate regulatory agencies, the study team will implement the approved corrective action plan. This plan will outline the mechanism and time course for notifying study participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL ENDPOINTS AND HYPOTHESES

Our primary outcome measures are expected to be 75% for recruitment, 90% for retention, and 80% for adherence. We calculated two-sided 95% confidence intervals for one proportion using the Clopper-Pearson method with scenarios varying the expected percent (0.70 and 0.95) in order to estimate precision given a sample size of 30. The lower confidence level will be used to inform recruitment, retention, and adherence planning in the future RCT.

9.2 SAMPLE SIZE DETERMINATION

Table 2. Precision of estimated proportions given a sample size of 30

Estimated Proportion	Lower CL	Upper CL	Width
0.70	0.506	0.853	0.347
0.75	0.559	0.889	0.330
0.80	0.614	0.923	0.309
0.85	0.673	0.953	0.281
0.90	0.735	0.979	0.244
0.95	0.803	0.996	0.193

CL=confidence level

9.3 STATISTICAL ANALYSES

9.3.1 ANALYSIS OF THE EFFICACY ENDPOINTS

Planned Data Analysis. The purpose of the pilot study is to determine whether an RCT evaluating the efficacy of taVNS on mental health outcomes is feasible, acceptable, and satisfactory for WTC responders with PTSD. The total sample size for the Aim 2 pilot trial is 30 World Trade Center Health Program responders with PTSD. Primary endpoints are based on feasibility. Specifically, recruitment, retention, and adherence, will be measured. Recruitment is defined as the percent of eligible responders who meet all study criteria and were recruited and consented to be in the study. Retention is defined as the percent of participants who completed both baseline and 6-week measures. Adherence is defined as the percent of participants who used taVNS 15 minutes a day once a day for 8 weeks. Secondary endpoints of acceptability include participant satisfaction and ability to complete the various mental health, blood draw and biologic measures with limited refusal, limited non-response, and within acceptable amounts of time. Tertiary endpoints include mental health and biologic measures. Please see the outcomes measures section for detailed definitions.

All measures will be described using frequency/percent or mean (SD) as appropriate, overall and by taVNS and sham group, with corresponding 95% confidence intervals to interpret the precision of the estimates. Median and interquartile range may also be used if discrete data are skewed. For the tertiary outcomes measuring mental health and biologic data, descriptive statistics for each time point, as well as differences over time (baseline to 8 week follow-up), will be calculated. Differences in biologic (non-inflammatory) outcomes only will be assessed from the first time point at baseline and the last time point at 8 weeks for long-term effects. Within-subject correlation of acute and long-term measures will be reported. Estimates and variances at each time point will be used to generate hypotheses and calculate effect sizes for a larger future RCT. Since effect sizes observed in pilot studies are crude, due to the small sample size, they may not be indicative of the true difference in the larger population and will be interpreted with caution.

We will also use results to generate hypotheses regarding potential mechanisms of action including the various inflammatory, neural, and cardiovascular changes that correlate with treatment outcomes. We will explore whether the impact of taVNS on PTSD symptoms is mediated by biologic measures of physiological reactivity and inflammatory markers.

9.3.2 SAFETY ANALYSES

Adverse events (AEs) will be tabulated using frequency tables and will include summary incidence rates for all causalities and for those possibly-related, probably-related, and definitely-related to the study.

9.3.3 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics for demographic and clinical factors for each of the groups will be provided using frequency and percentages for categorical variables and mean, median, and standard deviation for continuous variables.

9.3.4 SUB-GROUP ANALYSES

There are no defined subgroups of participants based on shared characteristics. The same analysis and statistical considerations will be applied to all participants and all sessions.

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 DOCUMENT PROVIDED TO PARTICIPANTS

For pre-screening purposes, participants will be contacted by a member of the research team from the information provided to the World Trade Center Health Program (WTCHP). Participants will be asked a series of questions regarding experiences they had responding to the WTC terrorist attacks in order to determine initial eligibility for study participation. Participants then will be asked to participate in an additional in-person interview to determine further eligibility for the study. If eligible, participants will be asked to take part and then will be enrolled in the research study.

A consent form describing in detail the study purpose, study procedures, risks, and potential benefits is given to each participant. The study procedures will only commence after the individual has provided written informed consent for participation. There will be two separate consent forms, one for each aim.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

In order to participate in this study, each potential subject will be required to provide written informed consent themselves. After they sign and date the consent form, the witness and consenting investigator will also sign and date the consent form.

Consent for the RCT will be written. We will send the consent form ahead of time but this will be completed in person.

In all consent processes, the investigator authorized to obtain consent will have a discussion with

the potential participant and any other individuals the potential participant requests to be there. After being provided ample time and answering any questions, the potential participant will be asked to provide consent to participation. If so desired, those interested will be given a copy of the consent form so that they may have the opportunity to discuss participation further with family and/or advisors. If an individual joins the study by providing informed consent, the subject will receive a signed copy of the consent form.

The consent process will be conducted in a quiet and private setting within the Feinstein Institute for Medical Research or at the WTCHP. The entire process will be documented in enrollment notes that will be maintained in the regulatory binder along with the original copy of the signed IRB-approved consent form.

25. WAIVER OF DOCUMENTATION HIPAA AUTHORIZATION (remote only)

Prior to consenting into the study, participants will partake in a screener called the CAPS interview. Given the nature of the pandemic we will also have an verbal authorization option that can be done remotely for the screener CAPS interview portion only. We are asking for a waiver of documentation of consent and HIPAA authorization for CAPS interviews done remotely only given the rising COVID cases and necessity to complete remotely. The coordinator will review with the participant and document this within the part 11 compliant Redcap database that this was obtained verbally. This is only for the remote option.

The CAPS interview is a diagnostic interview used daily outside of the research context. Consent is not normally required for this CAPS interview outside of research and is used in the clinical realm in order to diagnose PTSD.

For the purposes of this study we need to use this to determine eligibility. Participants will be provided with written authorization form that will be read to them if remote and mailed ahead of time. If someone becomes distressed during this portion of the screening we will provide resources for them to talk to further.
There are no risks for this portion of the study besides potential breach of confidentiality and all efforts will be made to ensure that this does not happen with HIPAA approved part complaint 11 REDCap databases and anything else stored on a PHI protected Northwell drive.

This will be recorded in order to assure accuracy of results and criteria for inclusion/exclusion. This is required in order to determine if a participant is eligible to be part of this clinical trial. These recordings will only be seen by approved members of this study for the specific purposes of training. No one from outside of this protocol or health system would ever have access to this.

If the consent form is done over the phone, for the screener portion, we will make sure that there are no distractions and the participant is able to have ample time to answer any questions and we

will assure that they receive a copy of the consent form as well.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. This decision may come from the research team, the Northwell Health Human Research Protection Program, or a federal or state regulatory agency. In such an event, the study participants will be contacted, as applicable, to inform them of the study's status and any changes.

Circumstances that may warrant termination or suspension include, but are not limited to, the identification of serious and unexpected risks, insufficient compliance to the protocol requirements, or determination of futility.

In such an event, the study will only resume once the concerns or events leading to suspension or termination have been addressed, and the research team, the Northwell Health Human Research Protection Program, and any involved regulatory agency approves its continuation.

10.1.3 CONFIDENTIALITY AND PRIVACY

In order to protect the privacy of participants, the consent process and all study procedures will be conducted in a private setting by individuals authorized to do so, such that no others can observe.
If the consent form is done over the phone we will make sure that there are no distractions and the participant is able to have ample time to answer any questions and we will assure that they receive a copy of the consent form as well

In order to protect the confidentiality of participants, each individual will be assigned a study number. The participant will then be referenced by that number only. This identifiable information will be stored in the Research Data Capture application REDCap, a secure HIPAA-compliant web-based tool. The research team, the Northwell Health Human Research Protection Program, or a federal or state regulatory agency will only access participant information that is needed to conduct this study. The study's de-identified data may be shared to facilitate study conduct such as study progress and analysis. In addition, all study data will be securely maintained with access limited to investigators and authorized individuals only.

10.1.4 FUTURE USE OF DATA

Findings from the proposed study will be published in peer-reviewed publications. Findings may also be presented as abstracts, posters or oral presentations at academic conferences, internal Northwell Health meetings and at the NIOSH WTC research meetings. All investigators will be

included on any published or presented materials. All published documents will be in aggregate form and have no identifying information.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Contact PI and Sponsor-Investigator:
Rebecca Schwartz, PhD
Department of Occupational Medicine, Epidemiology and Prevention
Northwell Health
Feinstein Institute for Medical Research
175 Community Drive
Manhasset, NY 11030

10.1.6 SAFETY OVERSIGHT AND MONITORING

The research team will be responsible for monitoring the scientific integrity and participant safety for the full duration of the study with primary oversight from the study PI. The team will have bi-monthly meetings in order to discuss the progress of the study

Confidentiality, Protection of Subject Privacy and Database Protection

Aim 1: During the focus group portion of the study all data collected including audio files, transcripts and qualitative data analysis files, will be stored in a locked electronic folder on a secure, HIPAA-compliant institutional server, accessible only to those approved, by the Institutional Review Board (IRB), to be part of the study. Confidentiality will be ensured by use of identification codes and de-identifying the data. Any data analysis done using this data will be de-identified as well and reported in a manner maintaining complete participant confidentiality.

Aim 2: During this randomized pilot clinical trial, baseline and follow-up biological and mental health measures, as well as bloodwork, will be collected and assessed. All of the materials are collected for research purposes only, and data will be kept in REDCap (see below) with access only to those approved to be part of the study by our IRB. Confidentiality will be ensured by use of identification codes and de-identification of the data. All data, whether generated in the laboratory or in the offices, will be associated with a randomly generated identification code

unique to the subject. All data analyses will be de-identified. Only the project coordinator will have the key that links the personal information with the random identification number, and that will be stored as a password-protected file on the Feinstein Institutes for Medical Research (FIMR) at Northwell Health's (NWH) REDCap system, only accessible by the project coordinator. Electronic communication with outside collaborators will involve only unidentifiable information for manuscripts, abstracts, presentations, etc.

The Research Data Capture application, REDCap, a secure, HIPAA-compliant, web-based tool, will be used to create instruments for eligibility and recruitment tracking, survey questionnaires, and biological assessments. This application is accessible via the web through a secure login. Survey questionnaire responses will be entered directly into REDCap by responders from laptops or tablets provided at each visit. Tracking and biological measures will be entered into REDCap by the project coordinator after each visit. Usage data from the taVNS wearable devices will be extracted from the cloud by Nesos Corp and transferred to the study team following institutional secure data protocols after 8 weeks. Usage data will be stored in a locked, electronic folder on a secure, HIPAA-compliant institutional server, accessible only to those approved to be part of the study by our IRB. Data quality will be monitored by built-in validation checks in REDCap, such as bounds on numeric data, inclusion criteria flags, and missing data flags.

Adverse Events (AE)

Aim 1 & 2: As per FIMR Office of Research Compliance (ORC) policies, the PIs are required to notify the ORC promptly of any unanticipated problems involving risks to subjects or others occur. The PIs will monitor the progress of the study and safety of participants on an ongoing basis. All serious AE (e.g., medical occurrences resulting in death) that occur during the study, defined by the given protocol, regardless of the relation to the research, must be reported to the ORC by telephone, e-mail, or fax within 24 hours of the investigator's awareness of the occurrence of the event. The PIs will report Serious Adverse Events (SAE) to the ORC, and will disseminate information to other agencies (e.g., NIOSH) as necessary. These initial reports are followed by a safety report, which is a written account of the serious AE determined by a sponsor/investigator to be both related to the treatment under investigation and to be unexpected in nature. Serious AEs will be summarized annually in the ORC application for continuation or termination of research.

All adverse events not meeting the criteria for a serious adverse event will be captured on the case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention, and time of resolution/stabilization of the event. All adverse events occurring during the study will be documented appropriately

regardless of relationship, and followed to resolution or until the participant no longer wants to be contacted.

The study will record, assess, categorize, and report all adverse events and serious adverse events as per the reporting requirements of the FIMR ORC.

Stopping Rules

Aim 1: Participants are aware that they can end their participation in the focus group at any time. The focus group would only be stopped by the facilitators if a participant experiences a serious adverse event during the focus group.

Aim 2: The randomized pilot feasibility study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial

Data Quality and Management

Aims 1 & 2: Data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Monitor.

Aim 1: Focus groups will be recorded on 2 audio recorders so that there is a back-up recorder should there be any difficulties. The focus group will follow a discussion guide that is developed and approved by the study team. Only a FIMR-approved transcription service that is HIPAA-compliant will be used for focus group audio file transcription.

Aim 2: The principal investigator, Dr. Schwartz is responsible for oversight and monitoring of the data, assuring protocol compliance, and conducting the safety reviews after 5 participants or at bi-monthly meetings, whichever comes first or more frequently, if needed. The project coordinator will also be responsible for day–to-day oversight of research, and ensuring the integrity and privacy of the data. Additionally, Dr. Anne Golden will act as an independent data monitor and will be included in all correspondence.

Study progress and safety will be reviewed bi-monthly (and more frequently if needed). Progress reports, including participant recruitment, retention/attrition, and AEs, will be provided to the Independent Monitor following each of the monthly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address: (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB and, if applicable, the study sponsor. The IRB and other applicable recipients will review progress of this study on an annual basis

Data type	Frequency of review	Reviewer
Participant accrual (including compliance with protocol enrollment criteria)	Every 5 participants or bi-monthly meetings whichever comes first	PIs, (bi-monthly) Independent Monitor (monthly)
Status of all enrolled participants, as of date of reporting	Every 5 participants or bi-monthly meetings whichever comes first	PIs, (bi-monthly) Independent Monitor (monthly)
Adherence data regarding study visits and intervention	Every 5 participants or bi-monthly meetings whichever comes first	PIs, (bi-monthly) Independent Monitor (monthly)
AEs and rates	Every 5 participants or bi-monthly meetings whichever comes first	PIs, (bi-monthly) Independent Monitor (monthly)
SAEs	Per occurrence	PIs, Independent Monitor, Funder

Measurement and Reporting of Participant Adherence to Treatment Protocol

Aim 2: Participants will be given the taVNS unit to use at home by themselves for 8 weeks, regardless of treatment arm. They will be given the phone number for the project coordinator to contact if they have any questions or issues arise at any time. Additionally, during this window of 8 weeks, at the 4-week time point, the project coordinator will reach out, by phone, to check and see how the participant is doing, and assess if there are any issues. Adherence to the intervention will also be assessed through the device company's Nesos app, however this data

will not be utilized while the study is in progress. The only data collected are session metrics for evaluating usage compliance (user is intended to perform 1-2 15-minute sessions/day for 8 weeks). The phone is equipped with a Data-only SIM (no phone or SMS capabilities). This provides an Internet connection for the phone. Upon completion of treatment session, session metrics are transmitted from the application to the Nesos Google Firestore database. This information is transmitted securely through an SSL connection. The application is has write-only access to record treatment session metrics. Stored data is backed-up and replicated in a Google BigQuery database. This is done via a Google cloud function triggered by new data arriving in Firestore. The BigQuery database is accessible as a data source for Nesos's customized Google DataStudio dashboard. Data stored at rest is encrypted (https://cloud.google.com/security/encryption-at-rest/), and protected by Google's infrastructure. Data stores are only available to Nesos's internal cloud administrator. The Nesos dashboard is the only other means of accessing data. The dashboard is customized to display usage compliance data for each of the site's subjects. The dashboard cannot be used to modify any data, nor does it have any data-write access. No subject information is available nor stored. The dashboard is restricted in access and view-only for the research team. Authentication is via a Google account that has been granted access to the dashboard. Both the Firestore and BigQuery databases are secured to prevent unauthenticated access. The Nesos application on the phone is not generally available (i.e. not in app store), and all phones containing the Nesos application are collected at the end of the study. Participants will be asked to return all items at their last visit. In the event they left something at home they will be provided with a prepaid label for return.

Data Management Plan

REDCap will be used to create instruments for eligibility and recruitment tracking, CAPS interview and survey data, and biological assessments. The randomization schema will also be uploaded to the randomization module in REDCap. This application is accessible via the web through a secure login. Survey questionnaire responses will be entered directly into REDCap by responders from laptops/tablets provided at each visit. Participant tracking information and biological measures will be entered into REDCap by the project coordinator after each visit. Data quality will be monitored by built-in validation checks in REDCap, such as bounds on numeric data, inclusion criteria flags, and missing data flags. Data from the taVNS wearable devices will be extracted from the cloud by Nesos Corp, and transferred to the study team following institutional secure data protocols after 8 weeks. This data will be stored in a locked, electronic folder, stored on a secure HIPAA-compliant institutional server, accessible only to those approved to be part of the study by the IRB. Nesos's application runs on the locked-down Android Nexus 5X or Pixel phone, provided to participants for the duration of the study. The Nesos application is the only usable application on the phone. The phone is provided with the latest security patches and locked with a PIN. The application does not have any capability to capture any personally identifiable information. The application controls the Nesos stimulator during treatment sessions. The only data collected are session metrics for evaluating usage adherence/compliance (user is intended to perform 2, 15-minute sessions per day for eight weeks). The phone is equipped with a data-only SIM (no phone or SMS capabilities). This provides an internet connection for the phone. Upon completion of treatment session, metrics are transmitted from the application to the Nesos Google Firestore database. This information is transmitted securely through an SSL connection. The application has write-only access to record treatment session compliance metrics. Stored data is backed-up and replicated in a Google

BigQuery database. This is done via a Google cloud function triggered by new data arriving in Firestore. The BigQuery database is accessible as a data source for Nesos's customized Google DataStudio dashboard. Data stored at rest is encrypted (https://cloud.google.com/security/encryption-at-rest/) and protected by Google's infrastructure. Data stores are only available to Nesos's internal cloud administrator. The Nesos dashboard is the only other means of accessing data. The dashboard is customized to display usage compliance data for each of the site's subjects labeled with their device number only. The dashboard cannot be used to modify any data, nor does it have any data-write access. No subject information is available or stored. The dashboard is restricted in access and view-only for the research team. Authentication is via a Google account that has been granted access to the dashboard. Both the Firestore and BigQuery databases are secured to prevent unauthenticated access. The Nesos application on the phone is not generally available (i.e., not in the app store), and all phones containing the Nesos application are collected at the end of the study.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The principal investigator and team will perform internal quality management audits of study conduct, data and biological sample collection, and documentation completion will be performed by the principal investigator. In addition, she will cross reference the documented information with information stored in the randomization portal to ensure participants were appropriately randomized and administered the procedures as specified.

In the event of an audit, the study team will provide direct access to all trial related documents and reports for the purpose of monitoring and auditing by the Northwell Health Human Research Protection Program and/or federal and state regulatory agencies.

Aims 1 & 2: Data verification will be performed by someone other than the individual originally collecting the data, or by double entry. A statement reflecting the results of the ongoing data review will be incorporated into the annal report for the independent monitor.

Aim 1: Focus groups will be recorded on 2 audio recorders so that there is a back-up recorder should there be any difficulties. The focus group will follow a discussion guide that is developed and approved by the study team. Only a FIMR-approved transcription service that is HIPAA-compliant will be used for focus group audio file transcription.

Aim 2: The contact PI, Dr. Schwartz is responsible for oversight and monitoring of the data, assuring protocol compliance, and conducting the safety reviews after 5 participants or at bi-monthly meetings, whichever comes first or more frequently, if needed. The project coordinator will also be responsible for day–to-day oversight of research, and ensuring the integrity and

privacy of the data. Additionally, Dr. Anne Golden will act as an independent data monitor and will be included in all correspondence.

Study progress and safety will be reviewed bi-monthly (and more frequently if needed). Progress reports, including participant recruitment, retention/attrition, and AEs, will be provided to the Independent Monitor following each of the monthly reviews. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address: (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB and, if applicable, the study sponsor. The IRB and other applicable recipients will review progress of this study on an annual basis

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

For both **Aim 1** where data is collected through a focus group and **Aim 2** where data is collected via CAPS interview, self-report surveys and biological measurements, we will completely de-identify transcripts and datasets in compliance with HIPAA guidelines. This includes creating randomly generated encrypted identifiers and collapsing dates or ages. The data will either be uploaded into a database within Research Electronic Data Capture (REDCap), a HIPAA-compliant data management software or stored in a locked electronic folder stored on a secure HIPPA-compliant institutional server. Only necessary research staff will have access to both repositories of the data.

Recordings of the CAPS interview will be kept in a locked electronic folder stored on a secure HIPPA-compliant institutional server that only necessary research staff will have access to.

The Research Data Capture application REDCap, a secure HIPAA-compliant web-based tool, will be used to create instruments for eligibility and recruitment tracking, CAPS interview and survey data, and biological assessments. The randomization schema will also be uploaded to the randomization module in REDCap. This application is accessible via the web through a secure login. Survey questionnaire responses will be entered directly into REDCap by responders from laptops provided at each visit. Participant tracking information and biological measures will be entered into REDCap by the project coordinator after each visit. Data quality will be monitored by built-in validation checks in REDCap, such as bounds on numeric data, inclusion criteria flags, and missing data flags. Data from the taVNS wearable devices will be extracted from the cloud by Nesos Corp and transferred to the study team following institutional secure data protocols after 8 weeks and stored by in a locked electronic folder stored on a secure HIPAA-compliant institutional server which will only be accessible to those approved to be part of the

study by our institutional IRB. Nesos's application runs on the locked down Android Nexus 5X or Pixel phone provided to participants for the duration of the study. The Nesos application is the only usable application. The phone is provided with the latest security patches and locked with a PIN. The application does not have any capability to capture any personally identifiable information. The application controls the Nesos stimulator during treatment sessions. The only data collected are session metrics for evaluating usage adherence/compliance (user is intended to perform two 15 minute sessions per day for eight weeks). The phone is equipped with a Data-only SIM (no phone or SMS capabilities). This provides an Internet connection for the phone. Upon completion of treatment session, session metrics are transmitted from the application to the Nesos Google Firestore database. This information is transmitted securely through an SSL connection. The application is only permitted write-only access to record treatment session compliance metrics. Stored data is backed-up and replicated in a Google BigQuery database, this is done via a Google cloud function triggered by new data arriving in Firestore. The BigQuery database is accessible as a data source for Nesos's customized Google DataStudio dashboard. Data stored at rest is encrypted (https://cloud.google.com/security/encryption-at-rest/) and protected by Google's infrastructure. Data stores are only available to Nesos's internal cloud administrator. The Nesos dashboard is the only other means of accessing data. The dashboard is customized to display usage compliance data for each of the site's subjects labeled with their device number only. The dashboard cannot be used to modify any data nor does it have any data write access. No subject information is available nor stored. The dashboard is restricted in access and view only for the research team. Authentication is via a Google account that has been granted access to the dashboard. Both the Firestore and BigQuery databases are secured to prevent unauthenticated access. The Nesos application on the phone is not generally available (i.e., not in the app store) and all phones containing the Nesos application are collected at the end of the study.

10.1.8.2 STUDY RECORDS RETENTION

The study records will be retained for at least 7 years following completion and closure of the study.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any departure from the study protocol. The departure may be either on the part of the participant or the study team. As a result of deviations, corrective actions are to be developed and implemented promptly.

The study team will record, assess, categorize, and report all protocol deviations to the principal investigator, the Northwell Health Human Research Protection Program, and federal and state regulatory agencies as per their reporting requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

The study will abide by Northwell Health policies regarding data sharing and publication of study results.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. As a result, all investigators participating on this study have been assessed by the Northwell Health Office of Research Compliance, and determined to not have a conflict with this study.

10.2 ABBREVIATIONS

taVNS	Transcutaneous Auricular Vagus Nerve Stimulation
PTSD	Post-Traumatic Stress Disorder
WTC	World Trade Center
MH	Mental Health
REDCap	Research Electronic Data Capture
EBT	Evidence-Based Treatment
VNS	Vagus Nerve Stimulation
RCT	Randomized Clinical Trial
WTCHP	World Trade Center Health Program
DSM	Diagnostic and Statistical Manual of Mental Disorders
CAPS	Clinician-Administered PTSD Scale
SAE	Serious adverse event
PCL-3	PTSD Checklist -3 item
PCL-5	PTSD Checklist – 5 item
MINI	Mini International Neuropsychiatric Interview
CPT	Cognitive Processing Therapy
EMDR	Eye Movement Desensitization Reprocessing
PE	Prolonged Exposure
GRC	General Responder Cohort
FDNY	Fire Department New York
HPA	Hypothalamic Pituitary Adrenocortical
CRP	C Reactive Protein
EMG	Electromyography
HR	Heart Rate
GRS	Galvanic Skin Response
RR	Respiratory Rate
PD	Pupil Diameter
BP	Blood Pressure
EEG	Electroencephalography
ECT	Electroconvulsive Therapy
rTMS	Repetitive Transcranial Magnetic Simulation

HIPPAA	Health Insurance Portability and Accountability Act
BRMS	Biostatistics Randomization Management System
FIMR	Feinstein Institute for Medical Research
TNF α	Tumour Necrosis Factor alpha
(IL)-1β	Interleukin
TENS	Transcutaneous Electrical Nerve Stimulation

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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