	Protocol Name:	Vagus Nerve Stimulation: A Non-Invasive Treatment to Improve the health of Gulf Veterans with Gulf War Illness
	Principal Investigator:	Benjamin H. Natelson, MD
	Primary Contact Name/Contact Info:	Benjamin Natelson: 212-844-6665
	Date Revised:	07/15/2019
	Study Number:	HSM# 16-00097

## **HRP-503 PROTOCOL TEMPLATE**


- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section “N/A”. Do not delete any sections.*
- **For any items below that are already described in the sponsor’s protocol, the investigator’s protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document. Do not refer to the Sample Consent document, or information on the application form in this document..**
- *Keep an electronic copy of this version of the document. You will need to modify this copy when making changes.*

### **Brief Summary of Research (250-400 words):**

Gulf War Illness has been a recognized consequence of our fighting the first Gulf War since spring of 1991 and still no treatments specifically for it exist. Since then, pharmaceutical treatments have become available for one complaint of Gulf veterans with GWI – namely widespread pain and achiness. However, these treatments have three major drawbacks – they don’t work on all patients; their effect often does not last more than a few months; and the side effects they produce are often so bad as to preclude their use. We present here a plan to test a new treatment to improve the widespread pain reported by many Gulf veterans – a hand-held device that stimulates the vagus nerve in the neck.

Vagus nerve stimulation (VNS) is FDA approved for treatment-resistant epilepsy and depression. We became interested in using VNS as a modality to treat widespread pain for two reasons: first, patients receiving VNS reported having less pain and second, drugs to treat epilepsy and depression are in the same class as newly approved drugs to treat the widespread pain characteristic of fibromyalgia, a diagnosis which many Gulf vets also have. We did a safety and tolerability study in 14 women with fibromyalgia who tolerated surgical implantation and activation of the device as well as patients with the other FDA-approved indications for its use. Strikingly, many of the women got so much better that they no longer fulfilled criteria for the diagnosis of fibromyalgia. To determine that this effect was specific to VNS and was not a non-specific “placebo” type of response, a follow-up study comparing the actual device to one designed not to stimulate the vagus nerve is necessary.

We propose doing such a study on Gulf veterans with GWI, characterized by a problem with widespread pain. Besides their pain, we will also assess the effect of VNS in alleviating migraine headache, another complaint of Gulf veterans, common in the presence of widespread pain. Importantly, we are partnering with a company that has made a hand-held device that allows for stimulation of the vagus nerve without the need for surgery; it works by the patient putting it on the skin overlying the vagus nerve in their neck and then turning it on for 120 second periods three times a day. The device is programmed to deliver only 6 bouts of stimulation per day – one to each side of the neck three times a day; it is then inactive until the next day. The fact that this device can be used without surgery and is non-invasive makes it extremely practical for use.

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After collecting pre-treatment measurement of pain severity and headache severity, veterans will receive either the actual active VNS device or an inactive device, which does not stimulate the nerve. Veterans will use their device for ten weeks – providing similar information periodically over this period by responding to questions about the severity of their pain and headaches, They will then return to the Center for the final phase of the study where all veterans will receive active devices. Ten weeks later, they will return to the Center to provide information to allow the investigators to gain further knowledge as to the effectiveness of actual VNS in relieving pain – both throughout the body and in the head.

### 1) Objectives

**Research Question:** The major research question is to determine if VNS reduces the widespread pain of GWI while sham VNS does not. Next, for those veterans with comorbid migraine, the question is to determine if number and severity of migraine headaches are lessened by VNS in contrast to sham VNS.


**Specific Aims:** (1) To conduct a small randomized clinical trial ( $n \leq 44$ ) to evaluate the efficacy of self-administered, non-invasive, active nVNS in veterans with GWI as compared to sham treatment. (2) To provide clinical proof-of-principle data and support future development of broader efficacy studies for GWI

### 2) Background

Approximately 25% of veterans who were deployed to the Persian Gulf for the 1990-1991 conflict returned home with the new onset of medical complaints without any obvious medical cause. The major symptoms comprising this multi-symptom illness were widespread pain, fatigue and difficulty with attention and concentration. This syndrome is now known as Gulf War Illness (GWI). Widespread pain, one of the major symptoms comprising GWI, has been recently reported to occur in approximately 56% of Gulf veterans with GWI<sup>17</sup>; as we will indicate later, we have found an even higher rate in our own sample. In this proposal, we will present a plan for a double-blind, sham-controlled trial of transcutaneous vagus nerve stimulation (nVNS) to treat this symptom and, by doing so, to improve the general health of Gulf veterans with GWI.

More than 20 years have passed since this conflict and there is still no treatment for GWI besides symptomatic treatment. Fortunately, drugs do exist to treat the complaint of widespread pain. These drugs come from two classes – anti-epileptic drugs or serotonin-norepinephrine reuptake inhibitors. However there are two major problems with the use of these drugs. First, their side effect profile, including more fatigue, more cognitive problems plus weight gain, makes veterans loathe to use them and, second, their efficacy is often limited both in the percentage of patients helped and in the duration of effect<sup>19</sup>. Clearly other modalities of treatment are necessary.

One such modality is vagus nerve stimulation (VNS). VNS is a treatment that is FDA approved for two treatment resistant disease processes – epilepsy and major depressive disorder. Because pharmaceutical

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treatments for these two disorders also treat widespread pain (WSP), we hypothesized that VNS might also impact the same pathophysiological processes and relieve WSP. That hypothesis was initially supported by several papers showing a reduction in pain in patients receiving VNS for treatment of their seizures<sup>11, 15</sup> or for their depression<sup>3</sup>. These data led us to propose a study to determine if VNS would reduce pain and improve the health of patients with treatment-resistant fibromyalgia (FM), a syndrome of WSP with tenderness on palpation<sup>25</sup>. That study, allowing us to assess the safety and tolerability of VNS in FM, was funded by an NIH grant, and is now completed with results published in the medical literature<sup>13</sup>.

In our study of VNS treatment of FM, we used three outcome measures: (1) a 30% improvement from baseline ‘usual pain ratings in the last week’ (at least 5 on a 0 to 10 pain intensity scale was required on intake to participate); (2) Patient Global Impression of Change score rated as markedly or moderately improved (highest two self ratings on a 7 point scale); and (3) an improvement of at least 6 points (0.6 SD) on the Physical Function subscale of the SF-36<sup>24</sup>. Most drug trials in FM use only pain reduction as the major outcome variable. For this study, we required patients to fulfill all three criteria – a very conservative outcome measure.

*Adverse events.* Fourteen FM patients, all non-veteran women, signed their informed consent to participate in the trial. Following recovery from the surgery necessary to implant the device, patients received stimulation for 30 sec every 5 min around the clock at the highest tolerable current. There were two unanticipated adverse reactions. The first was the complaint of stimulus-bound electric-like sensations across one patient’s chest and into her left arm that was reduced by lowering VNS intensity; this side effect of stimulation was tolerable but continued throughout the entire 12 months of the trial. The second was the complaint of such severe dyspepsia as to require device deactivation; the dyspepsia continued despite the device’s being off and so it was not thought to be device-related. After 3 months of stimulation, one patient requested explanation because she thought the VNS had exacerbated her existing headache condition (this patient actually reported improvement in her FM). Another patient was dropped due to noncompliance with scheduled visits. Analysis was therefore limited to 12 evaluable patients.

Consistent with the already FDA approved indications of implanted VNS, the most common device and stimulation related adverse events included voice alteration ranging from mild (n=5) to moderate (n=4), neck pain ranging in severity from mild (n=1) to moderate (n=3) to severe (n=3), dyspnea ranging from mild (n=3) to moderate (n=4), nausea ranging from mild (n=2) to moderate (n=3), facial pain ranging in severity from mild (n=1) to moderate (n=3) to severe (n=1), and sleep difficulties/insomnia of moderate severity (n=4). All of these adverse events were either self limited or decreased in severity over time.

While rates of occurrence for voice alteration for FM patients (64%) were similar to those of patients with treatment resistant MDD (58%) and epilepsy (54%), rates of neck/facial pain (50%), headaches (21%), and dyspnea (50%) were greater in the FM sample than those with treatment resistant MDD (13-16%, less than 5%, and 14-16%, respectively), but again these adverse events were either self limited or decreased in severity over time. These observations in this small sample do suggest, however, that individuals with treatment resistant FM, a chronic pain disorder, may be more sensitive to pain related to VNS. However, this increased sensitivity never resulted in termination of stimulation.


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*Therapeutic outcome:* After three months of active stimulation, five (36%) of the 12 participants fulfilled all three outcome measure criteria for improvement simultaneously – i.e., the criterion we had chosen for effective treatment. Baseline pain, self rated on a 0 to 10 visual analog scale, averaged 8.5 ( $\pm$  1.0 SD). After 3 months of stimulation, average pain ratings had decreased significantly to 4.2 ( $\pm$  2.1;  $z = 2.94$ ;  $p < 0.01$ ); the decrease in pain was  $\geq 30\%$  for 9 patients. Patient Global Impression of Change for 12 of the 14 patients was given as either “markedly” or “moderately improved.” And finally, the physical function component of the SF-36 at baseline averaged 27.0 ( $\pm$  5.1) and increased significantly to 36.4 ( $\pm$  9.6) after 3 months of stimulation ( $z = 2.04$ ,  $p < 0.04$ ); an improvement  $\geq 0.6$  SD improvement in physical function occurred in 7 of the 12 patients.

An unexpected consequence learned during the study was that efficacy was so marked that some patients no longer fulfilled both the WSP criterion and the tenderness criterion necessary for the diagnosis of FM. Specifically by the end of 3 months of stimulation, 2 of the 14 patients no longer fulfilled both of the two diagnostic criteria for FM; these numbers increased to 5 patients by study end – 12 months after the start of stimulation. When viewed in the context of the actual outcome data, these results suggest that improvement in self-reported symptoms reaches asymptote after 3 months of stimulation, but functional improvement continues beyond this point. Results like these have never been reported in drug trials<sup>1,2,4</sup> or with brain-activating devices<sup>5,9,18,22,23</sup>.

*Advantage and limitations of design:* The major advantage of the design in the FM study was that patients could enter the trial without having to stop their usual medical regimen. Since the widespread pain in these non-veterans is the same as that in veterans, moving the device to the treatment of veterans with WSP is a natural step. The design in the original study had two major limitations that we plan to rectify here: first, practicality of use – the stimulation electrodes and battery had to be surgically implanted by either a vascular surgeon or neurosurgeon, and the implantable system was expensive – costing more than \$30,000, including the costs of surgery; cost and need for surgical implantation greatly limited the practicality of using this treatment. Second, the design – the study had no sham-control limb, and so the dramatic therapeutic effects observed could have been non-specific responses to being in a therapeutic trial – i.e., placebo responding. Since Dr Natelson has never seen such a level of improvement either in his practice or in a recently completed double-blind placebo controlled trial of milnacipran in FM, he doubts the latter possibility. Nevertheless, the design we will present in this protocol will have a sham stimulation limb, and the trial itself will also be a double-blind study design. We expect that an important outcome of the study will be data to indicate that the positive results of the preliminary trial<sup>13</sup> were directly due to vagus nerve stimulation and not due to a placebo effect.

To get around the cost issue, we have partnered in preparing this proposal with electroCore LLC (Basking Ridge, NJ), a biomedical device company that has developed a much less expensive hand-held, transcutaneous, non-invasive (nVNS) stimulator that eliminates the risks associated with surgery and can immediately be put to use as patients self-administer therapy. The device has recently received FDA approval for the acute treatment of pain associated with both cluster and migraine headaches. Importantly a recent study identified migraine in 64% of Gulf veterans with GWI<sup>17</sup>. A secondary goal of this study will be to determine if Gulf veterans with WSP who also report having migraine will show improvement in their headache condition with nVNS when compared with sham nVNS treatment.


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*Pathobiological mechanisms being targeted by nVNS*

In the widespread pain condition of FM, an up-regulated nociceptive system known as central sensitization as well as dysregulation of descending pain-ameliorating systems have been identified<sup>21</sup>. Thus FM patients report sensitization of pain producing stimuli rather than habituation<sup>20</sup>, have lower pain thresholds than controls<sup>8</sup>, and do not show the normal inhibition to a painful probe produced by applying a prior painful stimulus (abnormal descending nociceptive inhibitory control)<sup>12</sup>. VNS appears to reverse these abnormalities – at least in part. VNS activates afferent vagal fibers, which synapse onto the nucleus tractus solitarius (NTS) in the brain stem. Projections from the NTS connect to noradrenergic and serotonergic neural structures implicated in pain modulation<sup>16</sup>, including the locus coeruleus and the nucleus raphe magnus. These pontine and medullary structures have well established roles in descending inhibition of pain and have efferent fibers that travel along ventrolateral and dorsolateral funiculi to dorsal horn nociceptive neurons<sup>16</sup>. Vagus nerve innervation is also found in the periaqueductal gray, hypothalamus, and thalamus, from where it progresses to the insula, as well as the cingulate, orbitofrontal and prefrontal cortices – i.e., brain regions known to be involved in pain modulation. Importantly, these same structures are activated by VNS, suggesting that VNS may have a therapeutic role in pain relief via descending inhibition of spinal nociceptive signals<sup>14</sup>.


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### 3) Setting of the Human Research

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Recruitment of veterans with GWI will be done at the East Orange VA Medical Center’s (EOVAMC’s) War Related Illness & Injury Study Center (WRIISC), which Dr. Natelson established in 2000. One of the physicians there, Dr Anays Sotolongo, will supervise recruitment efforts and will supervise a full time research assistant at the EOVAMC WRIISC. Potential research subjects, i.e., Gulf veterans with GWI and widespread pain, will sign their VA-based informed consent to allow WRIISC personnel to share PHI with Icahn School of Medicine at Mount Sinai(ISMMS) research personnel. Thus, the East Orange VA’s IRB will review this study and approve the local IRB before this study moves forward.


Suitable veterans will then come to the Annenberg Building at ISMMS where they will sign their informed consent to participate in the actual sham-controlled, blinded treatment trial.

**4) Resources Available to Conduct the Human Research**

The call for proposals leading to the current study required individual investigators to partner with industry. The preliminary data on which the current proposal builds had been collected via an NIH grant using a surgically implanted VNS device. The company making this implanted device had no interest in using it in pain syndromes, and the cost of the device as well as the costs for implanting it made it impractical for large scale use. In the meantime, it came to the attention of Dr Natelson, the PI, that electroCore (eC) Ltd. was manufacturing and testing a rechargeable, externally delivered, transcutaneous device for VNS. As published preliminary clinical efficacy data using this device were encouraging and the use of the device less cumbersome and more economical, he approached eC to partner with him in this study to fulfill the requirements of the Department of Defense (DoD) contract for partnership with industry. That partnership led first to a LOI which was approved and then the full proposal which was funded at the end of the last government fiscal year. Thus the work will be done at ISMMS in collaboration with eC.

Recruitment goals and determination of sample size: Sample size was determined based on Lange et al.’s published paper on implanted VNS in non-veterans [i.e., 12 evaluable patients] on which Dr. Natelson was the senior author. In these participants mean pain severity decreased by 4.2 units on a scale from 0 to 10 over a 3-month period of active stimulation, a large effect (Cohen’s d = 1.92). Based on this result, we tested the power to determine a large effect of VNS condition (Cohen’s  $f^2 = .35$ ) on post-intervention pain-severity, controlling for pre-intervention pain severity. The power analysis was conducted with G\*Power 3<sup>9</sup>, specifying a standard Type I error ( $\alpha = .05$ ) and desired power of .80. Results indicate that a total sample of 26 would be sufficient. Given a sample of 40, the proposed research should be amply powered to detect a condition difference in pain severity, even allowing for attrition. Therefore, we will target enrollment to obtain data from 40 evaluable subjects. We are requesting IRB permission to screen as many as 100 patients to get to the desired sample size. Since our associates at the EOVAMC’s WRIISC are already involved in other GWI studies, we expect no problem in attaining this target.

Personnel resources and qualifications: As the maximal amount of funding appropriated for this study by DoD would have been insufficient to do the proposed trial, the CEO of eC has agreed to support the study by providing personnel for instruction of veterans on use of the device, data management, and for regulatory matters. Therefore, Arde Montasser, the eC person in charge of data management will

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assist in setting up appropriate data capture methods. Gudrun Lange, a Pain and Fatigue Study team members, will act as the person training veterans on the use of the VNS device; she will be blinded as to whether the device is actual or sham. The company will provide the devices at no charge.

Besides Dr Natelson and the study coordinator, funds were requested for part of the time of Michelle Blate, APN, the Pain and Fatigue Study Center’s research nurse-practitioner. She has previously worked with Dr Natelson on his milnacipran trial and on his several NIH grants. The final member of the team will be Dr Aaron Stegner, a researcher at University of Wisconsin who has his own independent practice for statistical analysis and who has worked with Dr Natelson in the past on statistical analysis of data collected at MSBI. In addition, the study coordinator and Dr Gudrun Lange, an unpaid collaborator will work on regulatory issues, consult with Drs Natelson and VA research personnel on the progress of the study and meet with study staff on a quarterly basis to get feedback from the Data Monitor, Mr Mulligan. Dr Cynthia Harden will serve as Independent Safety Monitor and Jonathan Mulligan will serve as Independent Study/Regulatory Monitor.

Potential research subjects will be identified at the East Orange VA Medical Center’s War Related Illness & Injury Study Center. This Center is one of three national VA Centers devoted to the health concerns of the Gulf War veteran. Dr Natelson competed for this Center when he was in the VA system and, after it was approved and funded, served as its director from 2000 to 2004. While the Center has expanded its focus to include the medically unexplained symptoms of veterans of current conflicts, it continues its focus on Gulf War Illness and has several ongoing studies on this topic.

Process to ensure all study personnel are adequately informed and trained: All study staff will have read the Investigational Plan and the consent which are FDA approved and will be IRB approved. Instruction to the patient on use of the VNS device will be done by an blinded trainer who will be trained on all aspects of device use by eC personnel.


**5) Study Design**

**a) Recruitment Methods**

The three nation-wide WRIISCs were established to study the medical complaints of veterans of the 1990-91 Gulf War. Since then, the NJ WRIISC has continued to accrue names of Gulf veterans with an interest in participating in research. To date, the NJ WRIISC has 583 Gulf veterans in its database with 90% having agreed to be contacted for future research. Of these, the WRIISC has health related information on 103 Gulf veterans. Of these veterans, 86 (83.5%) reported having chronic widespread pain.

Over half of these 103 veterans reported that they also have headaches consistent with the diagnosis of migraine. Only 7% of these veterans reported having migraine without having comorbid widespread pain (WSP). Because migraine without WSP is not common in our sample population, we will focus our recruitment on Gulf veterans with GWI in whom WSP is a major symptom and will identify the subgroup that also fulfills criteria for the diagnosis of migraine headache. Thus, the study will allow us to determine whether nVNS improves WSP and whether it also improves migraine.



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We will initiate recruitment by having the research study coordinator, who will be an MSBI employee working half time at MSBI and half time at the WRIISC, contact the 86 Gulf veterans who have reported having WSP and who have consented to be contacted for potential research studies. These 86 subjects should be a large enough recruitment group to achieve the required sample size of 40 participants (we are budgeting for 44 participants to allow for drop out). If additional subjects are needed for study, the research study coordinator will identify these from the remaining approximately 400 Gulf veterans whose contact information has been collected at the WRIISC and who have agreed to be contacted for research. The coordinator will call subjects, as needed, and collect symptom information to determine if they may have GWI with widespread pain. Subjects will then go to the WRIISC to learn about this study, go through the necessary screening and sign their informed consent to allow their PHI to be transmitted to ISMMS. Veterans will also be given a brochure summarizing what they will expect during the study and a schedule of all visits, both phone and face to face. We have developed flyers which will be distributed to places that Gulf veterans will see to inform them about the study, which includes health and veteran related online websites, in addition to being distributed over a course of time to veteran emails and to mobile devices.


General study info will also be posted on the Pain and Fatigue Study Center’s website [painandfatigue.com] for informational purposes, as well as for possible subject recruitment. The specific text that will be posted on the website is included with the study submission in a file titled “Website Info.”

**b) Inclusion and Exclusion Criteria**

**Inclusion Criteria**

To be eligible for enrollment in the Study, patients must meet all of the following criteria:

1. Patient is a veteran of the 1990-91 Gulf War, aged at least 42 years old.
2. Patient fulfills Kansas criteria for Gulf War Illness including endorsement of musculoskeletal pain at moderate or severe intensities. This means patient has to endorse symptoms in at least 2 more of the following problem areas: Fatigue/sleep; cognitive and mood; Gastrointestinal; respiratory; skin.
3. Patient has widespread chronic pain as evidenced by endorsement of pain in at least 3 bodily quadrants plus in the axial skeleton.
4. Patient has a median 24 hour widespread pain score of at least 5 on a 0 to 10 VAS.
5. To be considered having migraine, the patient must fulfill IHS criteria.
6. Patient agrees to use the study device as intended, follow all of the requirements of the study including completion of diary after each self-treatment, follow-up visit requirements, complete self

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assessment questionnaires as scheduled, and report any adverse device effects to the study center within 24 hours of such adverse device effect.

7. Patient is able to provide written Informed Consent.

## Exclusion Criteria

Patients with any of the following will not be eligible for enrollment:

1. Patient has a history of intracranial aneurysm, intracranial hemorrhage, brain tumor or significant head trauma.
2. Patient has in the opinion of the investigator a clinically relevant structural abnormality at the gammaCore-R treatment site (e.g., neoplasm, lymphadenopathy, previous surgery, abnormal anatomy).
3. Patient has pain at the gammaCore treatment site (eg, dysesthesia, neuralgia, cervicalgia).
4. Patient has other significant pain problem (e.g., cancer pain or other head or facial pain disorder) that in the opinion of the investigator may confound the study assessments.
5. Patient has known or suspected severe cardiac disease (e.g., symptomatic coronary artery disease, prior myocardial infarction, congestive heart failure (CHF), significant premature ventricular contraction) or a history of cardiac arrhythmia.
6. Patient has known or suspected cerebrovascular disease (e.g., prior stroke or transient ischemic attack, symptomatic carotid artery disease, prior carotid endarterectomy or other vascular neck surgery).
7. Patient's electrocardiogram shows evidence of heart disease or arrhythmia including an abnormal baseline ECG (e.g. second and third degree heart block, prolonged QT interval (corrected QT (QTcB) interval >470 msec for women and > 450 for men), atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, or clinically significant premature ventricular contraction) or a history of cardiac arrhythmia.
8. Patient has had a previous cervical vagotomy.
9. Patient has uncontrolled high blood pressure (systolic bp >160, or diastolic bp > 100) after 3 measurements within 24 hours.
10. Patient is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant, Sphenopalatine ganglion stimulator or Occipital nerve stimulator).
11. Patient has been implanted with metal cervical spine hardware or has a metallic implant near the gammaCore-R stimulation site.
12. Patient has a history of significant syncope within the last 5 years.


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13. Patient expresses widespread pain of < 5 on the numeric scale of 0-10 Pain VAS on the first encounter at the WRIISC in EO VANJ.
14. Patient has a history of non-epileptic or epileptic seizures within the last 5 years.
15. Patient, in the opinion of the investigator, has a known history or suspicion of substance abuse or addiction within the last 5 years.
16. Patient, in the opinion of the investigator/research staff, is incapable of operating the gammaCore-R device as intended and performing the data collection procedures.
17. Patient has a self-reported psychiatric or cognitive disorder and/or behavioral problem which in the opinion of the clinician may interfere with the study (e.g. Bipolar Disorder, depressive disorder with psychotic features, Specific Phobia, Acute Stress Disorder).
18. Patient is pregnant or thinking of becoming pregnant in the next 6 months, or is of childbearing years and unwilling to use an accepted form of birth control or is unwilling to undergo pregnancy testing.
19. Patient is nursing.
20. Patient has undergone botulinum toxin (BOTOX) injections of the head and/or neck in the last 3 months.
21. Patient is participating or has participated in any other therapeutic clinical investigation during the last 30 days.
22. Patient belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with follow-up requirements, or provide self-assessments is compromised (e.g., homeless, developmentally disabled, prisoner).
23. Patient has evidence of suicidality based on question #9 from the Patient Health Questionnaire [PHQ] - 9.
24. Patient has previously used a gammaCore device.
25. Patient is the spouse or housemate of someone else in the trial.

**c) Number of Subjects**

Up to 100 subjects will be enrolled initially. The research plan will be to have at least 40 evaluable subjects [half receiving true stimulation and half sham stimulation during the blinded phase of the study]. Thus we are allowing for up to 60 subjects who may be screen failures or drop outs for any reason.

**d) Study Timelines**

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The VA part of the study will take up to 2 weeks. The ISMMS part of the study will consist of two parts – the blinded phase of the study which will be 10 weeks in duration and which will be followed by the open label phase of the study for an additional 10 weeks.

Allowing for scheduling, an individual will be in the study for up to 24 weeks.

The study is funded for three years. We expect to complete enrollment and data collection by the third quarter of the third year. We expect to have results in the final quarter of that year and will use them to prepare a proposal for funding a multi-site follow up trial to provide data to obtain FDA approval for use the device in treating the widespread pain of GWI.

### e) Endpoints


**Primary:** To assess the effectiveness of the active treatment compared with the sham treatment groups in reducing widespread pain severity occurring in the past 24 hours as measured by five assessments using a VAS one week prior to study enrollment and one week prior to termination of the blinded phase of the trial. Assessment of this objective will be based on differences between active vs sham treatment data as well as between baseline and end of treatment data.

#### Secondary:

- Change in the Patient’s Global Impression of Change (PGIC) scale scores of overall symptom burden as completed by the subject from study onset to end of the blinded phase of the trial. Assessment of this endpoint will be based on a comparison between change occurring in active-treated versus sham-treated.
- Change in physical function subscale of the SF-36, a questionnaire assessing health related quality of life from study onset to end of the blinded phase of the trial. Assessment of this endpoint will be based on a comparison between change occurring in active-treated versus sham-treated.
- The difference between the active and sham treatment groups in change in number of migraine/headache days in the final week of the randomized/blinded period from the week prior to randomization.

#### Others:

- Improvement in the subject’s coexisting disorders as measured by the corresponding scales below, as compared with baseline measures to the blinded period:
  - Migraine: Migraine Disability Assessment Test (MIDAS)
  - Anxiety and Depression: Hospital Anxiety and Depression Scale (HADS)
- Comparison of active versus sham device data as to change in the use of pain or headache medications taken at the end of the randomized/blinded period compared to baseline.
- Adverse events

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- A subject's study participation would stop if a patient's symptoms became such that the patient requested stopping or the study doctor felt symptom severity required stopping.

## f) Procedures Involved in the Human Research

### Source data to be used in Study

*Numerical Rating Scale:* This is a zero to 10 visual analog scale asking veterans to rate the severity of their body-wide pain in the last 24 hrs where zero is no pain and 10 is worst pain possible.

*Kansas Criteria:* These criteria are followed in diagnosing Gulf War Illness. This is done via the history which collects medical information used to diagnose GWI through the endorsement of musculoskeletal pain at moderate or severe intensities. In addition to pain, veterans must endorse symptoms in at least 2 more of the following problem areas: Fatigue/sleep; cognitive and mood; Gastrointestinal; respiratory; skin.

*SF-36:* This is a 36 question vehicle used to assess a patient's health related quality of life. The version for veterans will be used. The physical function subscore will be one of the outcome measures

*Patient Global Assessment of Change:* This scale consists of 7 questions, each scored with a scale ranging from +3 [very much improved] through 0 [no change] to -3 [very much worse]

*Number of migraine days in the past week:* A migraine day is one where a patient has a headache lasting at least 4 hours

*Diary:* Patients will be required to complete a diary after they self administer each treatment to each side of his/her neck. The diary asks the time of the treatment and the stimulus intensity elected by the subject. After the final treatment for that day, the diary asks the patient if s/he has had a headache lasting at least 4 hours.


*Electronic Diary:* Patients will be required to complete a diary after they self administer each treatment to each side of his/her neck. The electronic diary asks the time of the treatment and the stimulus intensity elected by the subject. After the final treatment for the day, the diary asks the patient if s/he has had a headache lasting at least 4 hours. The electronic diary mirrors the paper diary, except that it is online with a secured web address. The subject can access with any electronic device with the capability of accessing the internet. A subject is given a unique 10 digit subject number to access the website. No other information is collected by the subject. Upon logging in for the first time, the subject creates a password and is the only person that can log into their eDiary. This is given as an option for subjects who prefer to use the electronic version over the paper version.

*Migraine Disability Assessment Test (MIDAS):* This is a 7 item questionnaire that assesses the effect that migraine has on a patient in the past 2.5 months.

*Hospital Anxiety and Depression Scale (HADS):* This is a 14 item questionnaire that quantifies the amount of anxiety and/or depressed mood a subject has had in the past week.

*Measure of Certainty Questionnaire:* This is a four choice vehicle that asks a subject how certain s/he was that s/he was getting the active treatment.



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**The Three Phases of the Study**

**Subject Identification Phase of Study**


Encounter 1: face to face visit at the WRIISC at EOAMC for subject identification, consent, enrollment and screening. At this visit Participants will sign a consent document, complete several surveys including the PCL5 and PHQ8, a history and physical, vital signs and a 12 lead electrocardiogram (ECG) performed by a trained clinician. Veterans who complete screening criteria will begin the blinded phase of the study if they wish to do so. They will receive additional information about the risk, benefits and function and operations of the neuro-stimulator at ISMMS through a separate informed consent process occurring with ISMMS Investigators at ISMMS. No other study procedures with the Veterans will be done at the EOAMC.

Encounters 2-5: 4 phone contacts done in the week after Visit 1 to assess pain in the past 24 hours.

**Blinded Phase of Study**

Encounter 6 – Office Visit [first time at ISMMS]: Confirmation of eligibility, randomization and device and diary training Visit. Subjects deemed eligible for study participation up to this point, will be invited to ISMMS in the Annenberg Building located at 1468 Madison Avenue, New York NY 10029, within one week after Visit 5. They will sign consent for study participation. They will provide a fifth rating of widespread pain severity over the past 24 hours at this encounter on a 10-point VAS. The fifth pain rating will be added to the 4 VAS pain ratings done in the week after intake at the VA. If the median of all 5 VAS widespread pain ratings remains at least a 5, subjects remain eligible to participate. Then medical and eligibility information obtained on Encounters #1 through 5 will be briefly reviewed, a pregnancy test will be administered, and a medication history will be taken. If still deemed eligible to continue on in the study, they then complete questionnaires [MIDAS, SF-36 and HADS] and undergo a brief baseline medical evaluation consisting a physical examination including vital signs and a tender point examination and of asking the veteran questions to determine if s/he fulfill criteria for chronic fatigue syndrome, fibromyalgia, and/or irritable bowel syndrome and for Gulf War Illness. Subjects are then randomized and trained by the blinded trainer to use the device to which they have been assigned [devices are received with serial numbers covered and numbered sequentially so the trainer is blinded to condition]. Subjects will receive identical instruction and guidelines regardless of which device they receive. To be sure the subject knows how to use the device; s/he will be given a quiz about using the device after training. They will also be trained on use of a daily diary (paper and electronic) to be completed after each of the three daily treatments. Subjects will be given an unique 10 digit identifier that they will used to log into the Merge IBM site, in which they will be prompted to create a username and password.

Veterans will be reminded [as specified in the study consent form] that in order to proceed to the open label phase of the study, they must administer at least 70% of all programmed stimuli as well as complete at least 70% of the diary entries; however, because the device needs to be sent back to the

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manufacturer in order to obtain the stimulation data, resulting in a 3-4 day delay in retrieving the data, we will not be able to use this criterion to advance subjects to get an actual unit in the open label phase of the study. Therefore, although we will tell subjects they have to deliver at least 70% of all programmed stimuli in order to get an active unit, the only criterion that will be enforced is that they will have had to complete 70% of diary entries, which will be verified by reviewing their diary logs at Encounter #14. This procedure is in place so that veterans who do not perceive benefit from the treatment [i.e. those receiving sham stimulation] will continue to treat themselves per protocol; this is critical for the overall purpose of the study in order to be able to infer that it was the active treatment that produced the therapeutic effect. If subjects did not continue stimulating themselves, we would be unable to determine whether a placebo effect existed or not.

Encounter 7 – Phone Call: Within 7 ( $\pm 4$ ) days after Encounter 6 (Day 0), subject will receive a phone call from study personnel to inquire about any negative effects of stimulation (Adverse Events, AEs) and to check if they are using the diary after each stimulation.

Encounter 8 – Phone Call: Within 23 ( $\pm 4$ ) days after Encounter 6 (Day 0), subject will receive phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.

Encounter 9 – Phone Call: Within 46 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.


Encounter 10 – Phone Call: Within 63 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.

Encounter 11 – Phone Call: Within 65 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS. .

Encounter 12 – Phone Call: Within 67 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS.

Encounter 13 – Phone Call: Within 69 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS.

Encounter 14 – Office Visit: Within 70 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will come to ISMMS. They will provide the 5<sup>th</sup> pain rating to arrive at the median pain rating. They will fill out same questionnaires they filled out on study Encounter 6 as well as the patient global measure of change and the measure of certainty, and will provide information about AEs and medication changes. They will again have the same brief medical evaluation as was done on Encounter #6 to provide data as to whether they fulfill criteria for GWI, CFS, IBS, MCS or FM. They will exit the blinded part of the study and return their original unit. Subjects who have completed at least 70% of diary entries will be given the active unit and will be trained on it again. They will be given new paper diaries and sent home. They will continue to use their electronic diary logon information to access their diary.

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**Open Label Phase of Study**

Encounter 15 – Phone Call: Within 77 ( $\pm 4$ ) days after Encounter 6 (Day 0), subject will receive phone call from study personnel to inquire about any negative effects of stimulation (Adverse Events, AEs) and to check about use of diary..

Encounter 16 – Phone Call: Within 93 ( $\pm 4$ ) days after Encounter 6 (Day 0), subject will receive a phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.

Encounter 17 – Phone Call: Within 116 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.

Encounter 18 – Phone Call: Within 133 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to inquire about AEs, check as to use of diary, rating of widespread pain over past 24 hours on a 10-point VAS, and potential desire to reduce medications.


Encounter 19 – Phone Call: Within 135 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS.

Encounter 20 – Phone Call: Within 137 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS.

Encounter 21 – Phone Call: Within 139 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will receive phone call from study personnel to rate their widespread pain over past 24 hours on a 10-point VAS.

Encounter 22 – Office Visit: Within 140 ( $\pm 4$ ) days after Encounter 6 (Day 0) subject will come to ISMMS. They will provide the 5<sup>th</sup> pain rating to arrive at the median pain rating; they will fill out the same questionnaires they filled out on Encounter 14 [except for Measure of Certainty], provide information about AEs, indicate any medication changes. They will again have the same brief medical evaluation as was done on Encounter #6.

During this visit, the subject will be informed that although the requirement to deliver at least 70% of the programmed stimulus was to be checked at Visit #14, along with completion of at least 70% of the diary entries, the device criterion was not actually enforced at that time because the data were not available until analyzed by the manufacturer. Subjects will be explained that this deception was in place in order to ensure that they continued to use the device as instructed, regardless of whether they thought they had a sham or active unit, allowing us to assess whether a positive effect of their using the actual device was related to its stimulating the vagus or was simply a placebo response. They will also be informed that even if the device data were to indicate that they did not meet the minimum 70% use requirement, it would not have affected their eligibility to participate in or complete the open label phase of the study.

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### g) Specimen Banking


NA

### h) Data Management and Confidentiality

- *What information will be included in that data or associated with the specimens?* Information collected on CRF's related to this study (i.e., ECG data, diary entries, outcome data based on questionnaires) will be included in the data. Each of the electronic CRF's used in this study is listed in the attached, approved FDA IDE application identified as G150261 under section "eClinicalOS Unique Pages."
- *Where and how data and specimens will be stored.* This information is provided in the attached DoD submission GW140-157, Attachment 8, pages 4 through 6.
- *How long the data will be stored.* Data will be stored for no longer than seven years from study onset.
- *Who will have access to the data?* Data will be available to study team members of the Pain and Fatigue Study Center as well as to the data management team of electroCore listed in the attached DoD submission GW140-157, Attachment 8, page 3. Dr Aaron Stegner will be doing the statistical analysis of the data set. He will be given a coded data set comprised of the study outcome variables for analysis.
- *Who is responsible for receipt or transmission of the data and specimens?* The study team of the Pain and Fatigue Study Center will be responsible for receipt and transmission of the data.
- *Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.* This information is provided in the attached DoD submission GW140-157, Attachment 8, pages 4 through 7.
- *Describe any procedures that will be used for quality control of collected data.* This information is provided in the attached DoD submission GW140-157, Attachment 8, pages 5 through 6.

*Describe the data analysis plan, including any statistical procedures. Provide a power analysis, if applicable (e.g. pilot study).*

*Power analysis:* A power analysis was conducted with G\*Power 3<sup>9</sup>, specifying a standard Type I error ( $\alpha = .05$ ) and desired power of .80. Results indicate that a total sample of 26 would be sufficient. Given a sample of 40, the proposed research should be amply powered to detect a condition difference in pain severity, even allowing for attrition. Therefore, we will target enrollment to obtain data from 40 evaluable subjects.

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*Statistical approach to data:* Safety data will be derived from every subject who used either sham or non-sham apparatus for any period of time. Therapeutic efficacy will be evaluated using both intent-to-treat (for all subjects who sign consent with those dropping out recorded as showing no change from baseline) and per protocol (for subjects who completed the 10 weeks of the blinded phase of the trial).

*Blinded study:* Our primary outcome variable will be post-intervention pain severity in the treatment versus sham condition, controlling for pain severity prior to randomization. We will define success for this variable if it decreases by 30% or more over the course of the trial. Five days of VAS data on pain severity will have been collected prior to randomization and during the last week of the 2.5-month stimulation period. For the primary analysis, these will be averaged to create a single pre-intervention and a single post-intervention pain severity score for each person. Post-intervention pain severity will be regressed on pre-intervention pain severity and intervention condition, using an analysis of covariance (ANCOVA) procedure.

A second analysis will use the pre and post measures of pain severity described above, along with pain severity assessments collected a third of the way and two thirds of the way through the 10 week blinded phase of the trial. These four equally spaced assessments over the 10 week study period will form the basis of a repeated measures analysis of variance in order to plot trajectories of pain as a function of treatment condition. We hypothesize a linear decrease in pain from baseline in the nVNS but not in the sham nVNS condition. Other variables (e.g., MIDAS, physical function part of the SF-36, CES-D) will be analyzed using the same general analytic approach; a simple *t*-test will be used to compare PGIC values between the groups at study end. We will define success criteria for PGIC and PF subscale of the SF-36 as scores of 5-7 and 0.5 SD improvement, respectively. Rate of drop out between the two groups while participating in the blinded phase of the trial will be tested for significance by Fisher’s test.


In order to test whether subjects may have become aware of their treatment condition, we will also test for differences by condition in Measure of Certainty data collected at the end of the 2.5 month blinded treatment phase of the study.

*Open label data analysis:*

In addition to the analyses reported above, the open label methodology permits a test across all participants of improvement following 2.5 months of treatment. Regardless of condition, patients’ 2.5-month pain scores, at the end of the open label phase, will be compared to their baseline scores using a dependent samples *t*-test. It is possible that the sham group will show even greater improvement than those in the actually stimulated group had shown at the end of the blinded trial period. Any such increase in improvement would probably reflect a factor related to their knowing they were receiving the effective treatment – i.e., not blinded. Among patients originally in the active treatment condition, we can test for additional improvements beyond 2.5 months using a repeated measures analysis of variance (ANOVA) approach.

**i) Provisions to Monitor the Data to Ensure the Safety of Subjects**



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**Part I: Elements of a Data and Safety Monitoring Plan**

1. List the name(s) of the individual(s) at MSSM who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information. The Principal Investigator may be the only monitor of a study.

If the qualifications of an individual to serve as a monitor are not contained in the PPHS application, they must be added to the DSMP either as a narrative description or as a CV.

***MSSM Principal Monitor:***

**Name: Natelson, Benjamin: PI**

**Academic Title: Professor**

**Department: Neurology**

**Mailing Address: Department of Neurology - Icahn School of Medicine at Mount Sinai Annenberg 20-81, Box 1137. One Gustave L. Levy Place, New York, NY 10029**

**Phone: 212-844-6665 or 212-844-6768**

**E-mail: [bnatelson@mountsinai.org](mailto:bnatelson@mountsinai.org)**

***Additional Monitor: Medical/Safety***

**Name: Harden, Cynthia: Independent Medical Monitor**

**Mailing Address: 138 W 8<sup>th</sup> St; New York, NY 10023**

**Phone: 212-844-6665**

**E-mail: [clouish17@gmail.com](mailto:clouish17@gmail.com)**

***Additional Monitor: Clinical Study Monitor***


**Name: Mulligan, Jonathan: Independent Clinical Data/Study Monitor**

**Mailing Address: M Squared Associates; 575 Eighth Ave #1212, New York, NY 10018**

**Phone: 703-562-9800**

**Email: [jmulligan@msquaredassociates.com](mailto:jmulligan@msquaredassociates.com)**

2. The hand held, patient controlled, transcutaneous nVNS device presents minimal risk to the user. That interpretation can be made from the fact that the device has been now used with hundreds of research subjects and by thousands of patients in Europe and Australia (where it has been approved for sale) with minimal side effects. There has never been a serious adverse effect attributed to its use.
3. The specific items that will be monitored for safety include adverse events, subject's compliance with the protocol, and drop outs.
4. Since no clinical trial using nVNS has ever had to be halted, we doubt this will happen herein but should it happen that information will be passed onto appropriate DOD personnel monitoring the Human Studies regulatory issues related to this trial.
5. Data accuracy and completeness: The data collection tool for this trial will be a validated electronic data capture (EDC) system using eCRFs. Subject data necessary for analysis and reporting will be entered into a validated database or data system using source documentation

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available at the site. The PI is to maintain all source documents as required by the protocol, including laboratory results, Subject Case Report Forms, supporting medical records, documentation of all study visits and telephone calls and Informed Consents. The source documents will be used at monitoring visits to verify information submitted on the Subject Case Report Forms.

5. Duties of the Independent Medical Monitor: Both the study PI, Dr Natelson, and the Independent Medical Monitor, Dr Harden, will review any unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. Dr Natelson will transmit information concerning such an event to the IRB with his input as to whether the event was related to the study device; this material will also be given to Dr Harden to allow her to comment on whether she concurs with the details of Dr Natelson’s report. Reports for events determined by either Dr Natelson or Dr Harden to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the FDA, to the device manufacturer, electroCore, and to USAMRMC ORP HRPO. The independent Medical Monitor has the authority to stop the research protocol in progress, remove individual human subjects from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB assesses the Independent Medical Monitor's report. Dr Natelson and Dr Harden will meet biannually.


7. Duties of the Independent Clinical Study Monitor: The Clinical Study Monitor will assure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that the safety and rights of subjects is being protected. This will include on-site checking of the eCRF for completeness and clarity, crosschecking with source documents, and clarification of administrative matters as follows:

- Ongoing compliance with the study protocol.
- Ongoing compliance with any conditions of approval of the reviewing IRB and the IDE regulations.
- Maintenance of complete and accurate study records including quality control checks on CRFs
- Continued acceptability of the site’s facilities.

All monitoring tasks will be carried out in such a manner as to protect patient confidentiality and protected health information. Data problems will be addressed in contacts with the study staff. Dr Natelson will meet with Mr Mulligan on a quarterly basis.

8. If a temporary or permanent suspension of this study should occur, in addition to the PPHS, Dr Natelson will report this immediately to DoD and to electroCore LLC.

**j) Withdrawal of Subjects**

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- The subject is non-compliant with the study protocol or follow-up requirements;
- The subject withdraws consent;
- The Investigator decides that it is in the subject’s best interest.

Subjects who withdraw or are withdrawn will be asked, but not obligated, to provide a final set of data via questionnaires. These subjects will not be allowed to participate in phase 3 of the study, the open label part. Subjects who are randomized but withdraw consent or are withdrawn prior to first treatment with the study device will be replaced.

**6. Risks to Subjects**

The potential risks and complications are anticipated to be mild to moderate in nature, and are anticipated to resolve shortly after discontinuation of the stimulation procedure without medical intervention or clinical sequelae. The following risks and complications have been associated with other VNS devices and may potentially occur with gammaCore:

- Muscle twitching and/or contractions to the face/head/neck including facial droops and/or lip pull
- Light-headedness or dizziness
- Headaches
- Shortness of breath (dyspnea)/hoarseness or change in voice tone during treatment/cough
- Irregular heart beat (arrhythmia)
- Metallic taste
- Gastrointestinal discomfort or nausea


Risks that are also potential anticipated adverse events resulting from the use of the nVNS device include, but are not limited to:

- Application site discomfort and/or local pain in the face/head/neck area including toothaches
- Application site irritation/redness
- Muscle twitching and/or contractions, face/head/neck area including facial droops and/or lip pull
- Headache/Migraine
- Tingling, pricking or a feeling of “pins and needles” on the skin where the device is applied (paresthesia/dysesthesia)

Should a volunteer become pregnant, she will be exited from the study as pregnancy is an exclusion.

**6) Provisions for Research Related Harm/Injury**

Dr Natelson and Ms Blate will be available to deal with any adverse event that may come from this study. Research participants will have the phone numbers of both these investigators and can be called as needed.

	Protocol Name:	Vagus Nerve Stimulation: A Non-Invasive Treatment to Improve the health of Gulf Veterans with Gulf War Illness
	Principal Investigator:	Benjamin H. Natelson, MD
	Primary Contact Name/Contact Info:	Benjamin Natelson: 212-844-6665
	Date Revised:	07/15/2019
	Study Number:	HSM# 16-00097

If a problem arises for a veteran not living near ISMMS, the investigators will get in touch with the research participant’s doctor.

If a subject is injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to the subject or the subject’s insurance in the ordinary manner, and the subject will be responsible for all treatment costs not covered by his/her insurance, including deductibles, co-payments and coinsurance. This does not prevent the subject from seeking payment for injury related to malpractice or negligence.

**7) Potential Benefits to Subjects**

VNS has been shown to be useful in fibromyalgia, a syndrome of widespread pain and tenderness and in several headache conditions. Therefore we expect that use of the active unit will produce diminution of pain and reduction in frequency and severity of migraine headaches, if these also are present. Because 50% of the veterans will not receive the active unit during the blinded phase of the trial but instead will receive a placebo unit which does not stimulate the vagus, we have included an open label trial during which every research participant will receive and will use the active unit. This procedure extends the potential benefit of participating in this study to all veteran participants.

**8) Provisions to Protect the Privacy Interests of Subjects**


Subjects will only be contacted after expressing interest to participate in research and will only be contacted at the phone number they specify to be contacted at. All study steps will be outlined in the informed consent and subjects will have the chance to clarify or ask any questions before moving forward. Subjects are reminded that all parts of their study participation are voluntary and they may opt out or withdraw from the study at any time.

We will be sensitive to the wishes of research participants as to their desire to control how, and with whom, they will interact and communicate. To maintain privacy, we will encourage research subjects to communicate via telephone rather than email. We will follow their direction as to how to leave phone messages on voicemail if the veteran does not answer the phone.

**9) Economic Impact on Subjects**

Veteran participants will incur no costs for participating in this study. They will have received the diagnosis of Gulf War Illness at the NJ VA Medical Center and that diagnosis will be corroborated on intake at ISMMS.

**10) Payments to Subjects**

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The total payment for participating will be based on the number of visits they complete. The subject will receive \$100 per visit for a possible total of \$300. Subjects who had previously consented and participated will be contacted and offered additional compensation as well. In addition, based on receipts for local travel incurred coming to ISMMS, the subject can be reimbursed up to \$85 per visit for a possible total of \$255.

### 11) Consent Process

Informed consent will be obtained on the subject’s arrival in the Annenberg Building of the ISMMS located at 1468 Madison Avenue New York, NY 10029. At that time, research staff will give the potential research participant the informed consent, allow him/her to read the consent and then answer any questions they may have. This process will be done by either Dr Natelson, Ms Blate or the research coordinator. These researchers will allot sufficient time for the veteran to be comfortable signing his/her informed consent. The veteran will be given a copy of the signed consent.

The consent form will indicate that the device and the diary will be checked to ensure that the subject completed the minimum 70% of the use and completion requirement, however the device criterion will not actually be used as a check for them to move onto the open label phase of the study due to the delay in obtaining the data from the manufacturer. This involves some deception; however it is important to leave this criterion in place so that the subject uses the device per protocol, regardless of whether it is a sham or an actual device. This is critical to assure the integrity of the experimental design which is to use the sham stimulation to assess whether any therapeutic effect is specific to the active device or simply a placebo. Subjects will be debriefed on this discrepancy at the end of the study and given an explanation as to why the procedure was in place.


### 12) Process to Document Consent in Writing

Subject will sign the consent on the usual PPHS template.

### 13) Vulnerable Populations

<i>Include</i>	<i>Exclude</i>	<i>Vulnerable Population Type</i>
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	x	<i>Adults unable to consent</i>
	x	<i>Individuals who are not yet adults (e.g. infants, children, teenagers)</i>
	x	<i>Wards of the State (e.g. foster children)</i>
	x	<i>Pregnant women</i>
	x	<i>Prisoners</i>

**14) Multi-Site Human Research (Coordinating Center)**

NA

**15) Community-Based Participatory Research**

NA

**16) Sharing of Results with Subjects**

Once data have been published in the medical literature, a copy of the paper will be forwarded to every subject who provided his/her informed consent.

**17) External IRB Review History**

NA

**18) Control of Drugs, Biologics, or Devices**

The Principal Investigator at ISMMS is responsible for device accountability. The Study Coordinator, or designee, is responsible for maintaining the device accountability log, which will include tracking the receipt and return/disposition of the devices; that information will be made available to the coordinator or designee by the blinded trainer, who will be giving the device to the patient. The serial numbers and disposition of the devices will be maintained off campus at electroCore. At monitoring visits, the study monitors will review and reconcile the device shipment records, the site's device log, the site's device inventory, and allocation/return of devices to subjects.