VA Project#: 0006- -*Neuromodulation as a New Treatment for Post-Traumatic Stress Disorder in Veterans: Evaluating the Effectiveness of Trigeminal Nerve Stimulation*

Principal Investigator: Andrew F. Leuchter, M.D.

Study Sites: UCLA, VA Greater Los Angeles

Contents

RESEARCH PROTOCOL

04 December 2018

1. Protocol Title: **Neuromodulation as a New Treatment for Post-Traumatic Stress Disorder in Veterans: Evaluating the Effectiveness of Trigeminal Nerve Stimulation**

PERSONNEL

2. Principal Investigator: Andrew F. Leuchter, M.D.
3. Co-investigator(s): Mark Barad, M.D., Aimee M. Hunter, Ph.D., and Bruce Kagan, M.D.
4. Study Staff: Michelle Abrams (Research Nurse/Study coordinator)
   Sarah Chang (Study staff)
   Nikita Vince-Cruz (Study Contact)
   Thomas Belin (Data Analyst)
   Robert Pynoos (Consultant)
   David Krantz (Medical Monitor)

5. Investigator Qualifications: Each study team member has prior experience and is fully qualified to fulfill their assigned roles. Drs. Leuchter, Kagan and Barad are licensed physicians and qualified to counsel distressed subjects enrolled in research on PTSD. Study coordinators have several years of experience in researching mood disorders and administering questionnaires/assessments. All persons in contact with the subjects are trained in dealing with adverse events and the suicide protocol.

FUNDING

6. Sources of Support for this project pending,

   - Indicate internal and/or external funding source: Department of Defense/ **USAMRAA**
   - Grant/contract number: N/A
   - HRPO Log Number: A-18040
   - Proposal Log Number: 12041006
   - Name of PI on Grant: Andrew F. Leuchter, M.D.
   - Grant title: Neuromodulation as a New Treatment for Post-Traumatic Stress Disorder in Veterans: Evaluating the Effectiveness of Trigeminal Nerve Stimulation

DESCRIPTION OF RESEARCH

7. **Description of Research:**

   In this project, we propose to use this clinical trial to test Trigeminal Nerve Stimulation (TNS) as a new treatment for Post Traumatic Stress Disorder (PTSD) in veterans. This study is a collaboration between VA GLA and UCLA. The project's scientific aims will be accomplished by testing hypotheses using data collected from a clinical trial, so that all tasks and milestones are tied to the two hypotheses. The achievement of these aims breaks into three phases of work: (1) activities prior to the clinical trial, (2) the trial itself, and (3) data analysis and reporting. The tasks and subtasks will be accomplished within the framework of these three phases, which occupy a 1) 6 month period, 2) 36 month period, and 3) 6 month period, respectively. This project is a collaboration between the VA and UCLA. Subjects will be identified in the PTSD

Clinic or the Domiciliary Care Program at the VA, where they will be consented for participation. Funding for the project is provided by the Department of Defense to UCLA, and this funding will be used to cover study costs. The VA will not be covering any of the costs for personnel, study visits, devices, or procedures associated with this study.

An emerging method for treatment of mood and anxiety disorders is neuromodulation, or stimulation of the brain to adjust nervous system function. Newer forms of neuromodulation can be performed at little or no risk to the subject and can relieve mood or anxiety symptoms without the side effects of medication. TNS is a novel method for neuromodulation that holds promise for the treatment of mood and anxiety disorders (DiGeorgio et al., 2011). The trigeminal nerve is the largest of the cranial nerves and carries nerve impulses from the forehead and face to locations throughout the brainstem, the limbic system, and the cortex. Through placing two electrodes on the forehead just above the eyes, it is possible to pass low-voltage, high frequency electrical impulses through the trigeminal nerve to the brain. This method of brain stimulation has shown promise for the treatment of Major Depressive Disorder (MDD) (Schrader et al., 2011). The treatment is very easy to use; subjects simply apply the two electrodes to their forehead, and the stimulation is provided through wires attached to a stimulator about the size of a deck of cards. Subjects sleep with the stimulator on for approximately eight consecutive hours per night. The stimulator should be used while asleep but may also be used while awake. In early trials, subjects reported no significant adverse events and that the treatment is convenient and acceptable to them (Schrader et al., 2011). We have conducted preliminary, open-label studies of TNS in subjects with PTSD and have shown that the treatment is well-tolerated and is associated with a significant improvement in PTSD symptoms.

Eventually, TNS has the potential to be of significant benefit to most Veteran and non-Veteran patients suffering with PTSD. It is non-invasive, very easy treatment to administer, appears to be well-tolerated with minimal side-effects, and therefore would be a very useful adjunctive treatment for PTSD. Our preliminary data indicates that patients see significant improvement in general PTSD symptoms, as well as depressed mood, within eight weeks. TNS has the potential to complement existing therapies for PTSD: it is a non-pharmacologic treatment that can be delivered in the home, and it is administered at night with a low-cost device while the patient sleeps. TNS could constitute a unique and useful addition to the treatment armamentarium for PTSD.

8. Background Justification:

PTSD is a major public health problem for our nations veterans. It has been estimated that up to 31% of personnel deployed to Iraq and Afghanistan, respectively, manifest symptoms of PTSD upon returning home (Sundin et al., 2010). Recent PTSD rates among active troops have been estimated at 16.7%, and even higher among reservists at 24.5% (Milliken et al., 2007). The impact of PTSD upon warriors, veterans, and their families is overwhelming. Those suffering from PTSD are at six-fold greater risk of committing suicide, and greatly increased risk of dropping out of school and having marital difficulties (Kessler, 2000). The costs to society are enormous.

Most veterans with PTSD receive a variety of treatments. There is evidence that psychotherapy, sometimes with adjunctive medication, reduces symptoms in most patients. Although the majority of patients improve, most continue to have significant residual symptoms for many years following the diagnosis (Bradley et al., 2005). There is no one treatment that is likely to totally

alleviate all symptoms of PTSD, and patients are likely to need multimodal therapy involving psychotherapy possibly augmented by pharmacotherapy in order to achieve maximal benefit (Pratchett et al., 2011). These findings highlight the need to develop additional treatment approaches that, alone or combination, may improve outcome above and beyond existing treatment methods.

9. Multi-center Study: 2 Study Sites-UCLA and VA GLA

a) Name and FWA number of each participating institution:

1) Laboratory of Brain, Behavior and Pharmacology
Semel Institute
University of California, Los Angeles
FWA:00004642

2) VA Greater Los Angeles
11301 Wilshire Blvd.
Los Angeles, CA 90073
FWA:00000734
a) PTSD Clinic
Building 256, 2nd Floor
b) Domiciliary Care Program
Building 217, 2nd Floor

b) Contact name and information for the Investigator(s) at each participating institution:

Contact for both sites:
Andrew Leuchter, M.D.
Semel Institute at UCLA
760 Westwood Plaza, Suite 57-456
P (310) 825-0207
F (310) 825-7642
E: afl@brain.ucla.edu

c) Role of each participating institution (e.g., recruitment, sample/data collection, sample/data analysis, etc.):
VA GLA -- Identification, recruitment, and consenting of the total 74 participants at the VA GLA PTSD Clinic or Domiciliary Care Program. Week 0 (baseline), week 4 and week 8(final) visits will be performed at the VA. Additional study visits may take place at the VA GLA.
UCLA – All other study visits including Weeks 1-3, weeks 5-7 and the follow up visit may be conducted at UCLA depending on subjects' preference.

d) Contact name and information for IRB of record at each participating institution:

Contact for both sites (UCLA and VA GLA):

UCLA IRB of Record:
UCLA Office of the Human Research Protection Program
The Medical Institutional Review Boards 1, 2, & 3 (MIRB)
11000 Kinross Ave, Suite 211
Box 951694
Los Angeles, CA 90095

Telephone: (310) 825-5344
Email: mirb@research.ucla.edu

Nikita Vince-Cruz
Research Administration
UCLA Semel Institute
760 Westwood Plaza
Suite 57-430
P (310) 825-4781
F (310) 825-7642
E: nikita@brain.ucla.edu

e) Method for assuring all participating facilities have the most current version of the protocol:

Study staff at UCLA and VA GLA will be notified via lab or office email of any protocol changes, and provided with the updated versions of study materials as soon as they are IRB approved. Personal emails will not be used to communicate any information regarding study activities, protocol or participants.

f) Method for confirming that all amendments and modifications in the protocol have been communicated to participating sites:

Study staff (investigators and research coordinators who have contact with subjects) will be notified via lab or office email and specifically asked to acknowledge receipt and use of amended or modified study materials. Personal emails will not be used to communicate any information regarding study activities, protocol or participants.

g) Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others:

David Krantz, Ph.D., M.D. is appointed as the research monitor and will also act as chair of the Safety Monitoring committee (SMC) for this study. He will use his expertise to assess all reported adverse events and report all serious adverse events (SAEs) regardless of the effect on study procedures or protocol. All SAEs will be reported to the IRBs as required by procedure as well as to all investigators by lab or office e-mail.

h) Method of communicating regularly with participating sites about study events:
Lab and office e-mail will be used to communicate regularly with all investigators and research assistants about study events that occur both at VA GLA and UCLA. This will ensure that all staff who are involved in execution of the protocol are updated in a timely manner about protocol changes.

i) Approval letters from all the IRB of record for all participating sites (or indicate that they are pending and provide upon receipt): UCLA IRB approved this study on 13 JAN 2014. UCLA IRB# 13-001670

j) Confirm that the PI at GLA will maintain documentation of all correspondence between participating sites and their IRBs of record:

The Principal Investigator for both UCLA and VA GLA, Dr. Andrew Leuchter, will maintain documentation of all correspondence between participating sites and their IRBs of record for UCLA, VA GLA and the Department of Defense/USAMRAA.

10. Subject Population

We plan to enroll a total of 74 subjects for this study. We will identify the 74 subjects from the VA GLA Healthcare System who are currently in treatment and have received treatment-as-usual (TAU) for the last 3 months in the PTSD Clinic or the Domiciliary Care Program. TAU may consist of medication and/or group psychotherapy. In addition to TAU, Veterans who have begun a structured, evidence-based therapy such as cognitive behavior therapy (CBT), cognitive processing therapy (CPT), or Prolonged Exposure (PE) therapy at least 6 weeks prior to beginning the study, and who continue to receive therapy, may also be eligible. Subjects will be enrolled into an eight-week treatment protocol in which they will be assigned to one of two treatment groups: 1) active TNS plus TAU; or 2) sham TNS plus TAU. Study activities will be performed at the VA GLA and the Semel Institute at the University of California, Los Angeles.

Participants will be recruited as described below from the PTSD Clinic (Leslie Martin, LCSW, Director) and the Domiciliary Care Program (Beverly Haas, Ph.D., Director) of the VA GLA Healthcare System.

PTSD Clinic:

The PTSD Clinic caseload includes over 1,800 veterans with PTSD, including approximately 400 veterans from Iraq or Afghanistan (OIF/OEF/OND). The clinic receives an average of 25 referrals a week.

Subjects will be recruited from those who are enrolled in TAU in the PTSD Clinic. This program is staffed by four UCLA psychiatry residents, each of whom treats veterans under the direct weekly supervision of Drs. Kagan and Barad, who are co-investigators in this study. The average score on the Clinician-Administered PTSD Scale (CAPS-5) of subjects entering the program is approximately 108, and patients experience on average a 34-point improvement in symptoms, such that at the end of treatment they are significantly improved but still quite symptomatic (median CAPS-5 score of 78). Because many of these patients remain significantly symptomatic, are motivated to receive new treatment, and are relatively stable as evidenced by stable medications and the absence of a substance abuse diagnosis for a month prior to treatment, they constitute an excellent population from which to recruit for this study.

Drs. Kagan and Barad, co-investigators on this study, are the primary attending physicians in the Clinic, and will coordinate efforts with the appropriate mental health staff to refer patients to the study. All subjects will be informed that Drs. Kagan and Barad are investigators in the study as well as treating physicians in the PTSD Clinic. If patients have any questions and would like to speak with someone who is not part of the study, they also will be afforded the opportunity to

speak with Ms. Martin or other study staff who are not part of the study. The study will be explained to all PTSD Clinic staff who will be asked to mention the study and provide veterans with a study brochure. Patients will be asked by clinic staff for permission to be contacted by the study coordinator. Any patient who gives permission will then be contacted by the coordinator and a screening will be scheduled.

Domiciliary Care Program (DOM):

Director Beverly Haas, Ph.D. and staff at the Domiciliary provide a supportive residential rehabilitation and treatment service center for Veterans. The program combines a wide range of programs for Veterans to solve the immediate issues of mental health and substance abuse while continuing long-term support in their transition to stability and housing independence. Dr. Haas and staff (including Gilad Dakik, LCSW, and Binyamin Amrami, M.D.) will support this study by facilitating the identification and recruitment of potential subjects.

The DOM caseload from which we will be recruiting currently includes an estimated 40 Veterans with PTSD who would meet study criteria. The typical length of stay within the DOM program is 5-6 months. Subjects undergoing TAU will be identified by their treating physician as eligible for the study and then will be invited to participate voluntarily in the study. Patients in the DOM are required to be sober and undergo weekly drug testing and are breathalyzed when they return from pass. Many patients from the identified DOM caseload of PTSD patients are combat veterans who have already been screened and accepted into the program based on the same entry criteria as for the PTSD Clinic, namely: 1) meet DSM-IV criteria for PTSD; 2) not meet DSM-IV criteria for a substance abuse disorder for at least one month; 3) not have been diagnosed with significant traumatic brain injury (TBI); 4) be able to commit to, attend, and tolerate weekly psychotherapy sessions in the clinic; and, 5) if receiving psychotropic medications, have been on stable doses for at least one month. These patients therefore constitute an appropriate population from which to recruit for this protocol.

11. Consent Process

Potential subjects who are referred by clinic staff will speak with the study coordinator who will provide information (goal of the study, treatment conditions, risks and benefits of participating, use of double-blind random assignment, time commitment, compensation for participation, and schedule of payments) allowing them to decide whether they want to participate. Staff will make clear to the subjects that their participation in the study is strictly voluntary and that their refusal to participate in the study will in no way prejudice their ongoing care in the PTSD Clinic or Domiciliary Care Program. Those who are interested will have an appointment scheduled. All participants will receive a copy of the Subject's Bill of Rights prior to discussions of consent to participate. Discussions will take place in a private office to ensure the confidentiality of the discussions and safeguard the privacy of the participants. The consent form outlines procedures, potential risks and anticipated benefits, right to withdraw, and confidentiality; it will be read with each participant, allowing time for questions. The research coordinator will review the consent form to ensure that all subjects comprehend the requirements and procedures of the study, and will ask the potential subjects questions about the protocol after they have explained it to ensure that they truly comprehend the nature and procedures of the study. All potential participants will be offered time to decide if they want to participate and the opportunity to take a copy of the consent form home to read and discuss with family or friends before giving their consent. When subjects are prepared to consent, they will review the procedures of the study with one of the co-investigators who will obtain the subjects' consent. Participants who qualify after passing screening will be randomized as a subject to a treatment condition. Those who do not pass

screening will be referred for continued treatment as usual in the PTSD Clinic or Domiciliary Care Program. Only subjects who are capable of giving consent themselves will be eligible to participate in this study. Participants may withdraw from the study at anytime without any consequences or impact on other services or medical care they may be receiving. No procedure beyond notification to the study staff is necessary on the part of the subjects to withdraw from the project. We will inform study staff of any subjects who withdraw from the study so that they can assess them as indicated to determine if there has been any significant change in the subjects' clinical status, and take appropriate action.

All study personnel are well trained in subject protection and consent procedures. All study personnel have completed the Collaborative Institutional Training Initiative (CITI) Biomedical Course in the Responsible Conduct of Research Protection of Human Research Subjects (http://www.citiprogram.org). CITI training is considered a national best practice for those involved with research and review. The CITI course is composed of online tutorials and quizzes. The average time needed to complete the Basic Course is between 2-4 hours, and Certificates of Completion are granted after satisfactory completion each of the quizzes. This course provides excellent training regarding the history and application of The Belmont Report and the current Code of Federal Regulations (CFRs) that govern human subjects research. Training in the protection of confidentiality and the details of the Health Insurance Portability and Accountability Act (HIPAA) has been completed similarly through online programs, the "HIPAA Clinical Research Training Course" (http://www.training.arc.ucla.edu/) at UCLA and the "VA Privacy Awareness Training" through the Veterans Administration Learning Management System (LMS) at VA GLA (https://www.lms.va.gov).

12. Eligibility Screening:

Potential participants will be recruited from the VA GLA PTSD Clinic and the Domiciliary Care Program. Drs. Kagan and Barad, co-investigators on this study, are the primary attending physicians in the PTSD clinic, and will coordinate efforts with the clinic staff to refer patients to the study. Directors of the recruiting VA GLA programs will coordinate efforts with the staff to refer potential subjects to the study. The study will be explained to all PTSD Clinic and Domiciliary Care Program staff who will be asked to mention the study and provide potentially eligible veterans with a study brochure. The brochure will explain in lay language the goals of the study, the procedures and time commitment, and that compensation will be provided. Simple one-page flyers also will be prepared that can be left in the clinic waiting room. These will contain a brief lay language summary of the study and the telephone number for research staff to call for further information. The brochure and flyer will not be coercive or offer any undue inducements for participation, and will be approved by the IRB prior to distribution.

Inclusion criteria: In order to be included in the study, subjects must:

1) 21-65 years old and be a patient in the PTSD Clinic or the Domiciliary Care Program at the VA GLA;
2) have experienced trauma while serving in a war zone in the following U.S.Military conflicts;
   Multinational Force in Lebanon (1982-1984)
   Invasion of Grenada (1983)
   Invasion of Panama (1989-1990)
   Gulf War (1990-1991)
   Iraqi No-Fly Zone (1991-2003)

Somali Civil War (1992-1995)
Intervention in Haiti (1994-1995)
Bosnian War (1994-1995)
Kosovo War (1998-1999)
War in Afghanistan (2001-present)
Iraq War (2003-2011)

3) meet DSM-V criteria for current warzone-related PTSD with a duration of at least 3 months;
4) currently receiving treament as usual (TAU) and have received TAU treatment for the last 3 months, and *may* be receiving structured, evidence-based therapy such as Prolonged Exposure therapy (PE), Cognitive Processing Therapy (CPT), or Cognitive Behavior Therapy (CBT), so long as the therapy was not initiated within 6 weeks of beginning the TNS protocol;
5) significant residual PTSD symptoms as evidenced by a CAPS-5 (Clinician-administered PTSD scale) score $\geq$ 50;
5) consent to be randomized to active or sham TNS treatment;
6) if receiving medication for depression, anxiety, sleep, or mood stabilization, must have been on stable dose for at least six weeks prior to randomization.

We have minimized exclusion criteria in order to support inferences applicable to as broad a mix of patients presenting with PTSD as practicable. In order to avoid confounds that might make it impossible to interpret findings from the study due to a lack of exchangeability of experimental subjects, we will not include patients who exhibit:

Exclusion Criteria:

1) current substance abuse disorder not in remission for at least 3 months;
2) a history of bipolar, schizophrenia, other psychotic disorder, or dementia;
3) current suicidal or homicidal ideation requiring hospitalization, or suicide attempt within six months;
4) report of severe TBI with coma duration (30 minutes or more) at time of screening interview and/or duration of post-traumatic amnesia (1hour or greater) on the Post-traumatic Amnesia Questionnaire (PTAQ);
5) reported use (by patient or clinic staff) of antidepressant, antianxiety, antipsychotic, or mood-stabilizer medication where the dose has not been stable for a minimum of six weeks prior to entering the randomization;
6) reported participation (by patient or clinic staff) in psychosocial or medication treatment through a clinic or facility other than the VA GLA PTSD Clinic or the Domiciliary Care Program;
7) infection or loss of integrity of skin over the forehead, where the electrode pads will be placed.

We will exclude participants who are receiving treatment for PTSD *outside* of the VA GLA PTSD Clinic or Domiciliary Care Program because such treatment may deviate from accepted treatment as usual (TAU), and the details of such treatment may not be available to the investigators. We will not exclude participants who are currently in TAU for PTSD at the VA GLA with the exception of the initiation of or change in medication status (i.e., starting or changing dose) occurring within the prior six weeks. Subjects, as well as staff providing treatment, will be informed that TAU may not change during the eight week blinded study period if the subject wishes to remain enrolled in the study. If a change in TAU is indicated based upon the subject's clinical situation, the subject will be withdrawn from the study and the clinic staff so

informed. This exclusion is designed to reduce the confounding effects of changes in concomitant treatment with those of TNS. Because of the relative stability of this patient population after 3 months of TAU, we anticipate that this exclusion will affect only a small number of patients. Although a blanket exclusion of subjects receiving medication would avoid certain complexities in the assessment of TNS efficacy, given the frequency with which these medications are prescribed, excluding such individuals could be expected to negatively affect not only recruitment success but also generalizability.

We have chosen not to exclude subjects who may be initiating naturalistic psychosocial treatment through the PTSD Clinic or the Domiciliary Care Program. There are a number of outpatient group treatments available including:

OEF/OIF group - Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) combat Veterans, discussions of issues pertaining to readjustment hack to civilian life;

Combat Trauma group - 12-week class discussion of issues related to combat trauma;

PTSD/Substance Abuse group - helps veterans remain safe in their behavior and manage emotions;

Grief Group - helps veteran who have experienced losses;

Anger Management - a 12-week program that teaches understanding of anger and coping skills;

Emotional Management - 12-week program teaches how to negotiate emotionally charged situations;

Strategies for Living – 12-week program that teaches how to more effectively use cogntive resources.

We are allowing these treatments for two reasons. First, the subjects in this study will be significantly symptomatic, and it could be impractical or unsafe, and correspondingly unethical, to deny them access to some type of psychosocial intervention for their ongoing symptoms. Second, all subjects will be receiving TAU which may include a combination of treatments including medications, breathing exercises, and talk therapy. While a course of another psychosocial treatment through the PTSD Clinic or the Domiciliary Care Program may provide valuable support and some symptomatic relief, we believe that it is unlikely that one of these treatments would result in a significant magnitude of symptom reduction that would confound the study results. We will require that all non-study treatments be provided through the VA GLA PTSD Clinic or Domiciliary Care Program which will make it possible for us to carefully record any non-study medication or psychosocial treatments that the subjects are receiving for their PTSD. We will use uncontrolled treatment as a covariate in analyses if indicated due to unbalanced frequency or intensity of treatments received between the active and sham TNS groups.

Individuals with Major Depressive Disorder (MDD) will not be excluded if they meet the inclusion and exclusion criteria. MDD often is comorbid with PTSD, so that excluding these

subjects would limit generalizability of results. Individuals with active substance dependence, bipolar or other psychotic disorders, or severe TBI will be excluded because TNS may not work in the same manner or achieve the same degree of effectiveness in such individuals compared with patients who do not have these conditions. In this initial blinded efficacy study, we believe that it is important to eliminate these potential confounds. We do not anticipate that many subjects will be excluded because of bipolar or psychotic disorders because such patients generally have been identified prior to their registration in the PTSD Clinic or Domiciliary Care Program and are being treated elsewhere in the VA GLA. Some patients will have suffered or will suffer from an active substance use disorder, and these subjects will be excluded from the study.

Similarly, we do not anticipate exclusion of many subjects because of TBI because patients with significant TBI would have been identified and referred to another clinic in the VA GLA system. Nevertheless, we recognize that we need to make provision for identification of such subjects who may not have been identified by usual clinical screening and may have entered treatment in the PTSD Clinic or Domiciliary Care Program: PTSD and TBI are highly comorbid in recently returning veterans (Hoge et al., 2008) and both conditions share cognitive (e.g., inattention, memory impairment), physical (e.g., sleep disturbance, reactivity/sensitivity to sensory stimuli), and emotional (e.g., increased irritability, depressive symptoms) sequelae (Belanger et al., 2009; Luethcke et al., 2011; Qureshi et al., 2011). It would not be ideal to utilize neuropsychological testing of symptom screening measures in an attempt to identify severe TBI because of the overlapping symptoms. Therefore, to help ensure that our sample is primarily suffering from the effects of PTSD and not TBI, we will utilize the Post-traumatic Amnesia Questionnaire (McMillan et al., 1996). Any individuals who report a history of coma duration 30 minutes or more and/or duration of post-traumatic amnesia of 1 hour or greater resulting from any one episode of TBI will be judged to have suffered severe TBI and will be excluded from the study. We will rely on subjects' reports of TBI for this screening. We considered excluding subjects with lesser degrees of TBI from the study, but decided not to do so for two reasons. First, traumatic injuries are extremely common in this population, and it could be difficult to reliably identify lesser degrees of TBI because of the overlap in symptoms between PTSD and TBI. Second, a history of mild TBI is common in patients with PTSD, and eliminating such subjects could make it difficult to recruit sufficient numbers of subjects to conduct the study. Third, because of the possibility that significant numbers of veterans will have mild degrees of TBI, it is important to include such subjects in this study in order to have a representative sample of PTSD patients. If this initial efficacy study is positive, it will be important in future studies to more systematically evaluate the effectiveness of TNS in patients suffering from different degrees of TBI.

13. Methods and Procedures

Overview:

This is a 74-subject study designed to examine the use of TNS as an adjunctive treatment for adults with PTSD. Subjects undergoing Treatment as Usual (TAU) in the PTSD Clinic or the Domiciliary Care Program at the VA GLA will be identified and referred by their treating physician as eligible for the study, and only then will be invited to participate voluntarily in the study. The study population will consist of 74 male and female Veterans who meet diagnostic criteria for PTSD on the basis military service in a war-zone. Veterans are the most appropriate population for this preliminary study because research has shown suboptimal outcomes for combat veterans using existing treatments (Bradley et al., 2005), indicating a need for improving

treatment options for this population.

This is a collaboration between the VA GLA and UCLA. All study activites will will be performed at the VA Greater Los Angeles or UCLA as determined by the Principal Investigator, in consultation with the PTSD Clinic and Domiciliary Care Program directors, as well as the subject's preference. Identification, recruitment and consenting of subjects for participation will be performed at the VA GLA PTSD Clinic or the Domiciliary Care Program. The baseline visit, Week 4 visit, and Week 8 visit will be conducted at the VA GLA PTSD Clinic or Domicialiary Care program without exception. All other study activities and visits will be performed at UCLA, or at the VA GLA PTSD Clinic or Domiciliary Care Program. If subjects prefer that visits be performed at the VA, the clinic director approves such visits, and space is available in the clinic, these visits will be performed at the VA GLA PTSD Clinic or the Domiciliary Care Program. Subjects will be randomized to treatment with either active or sham TNS for a period of eight weeks. Subjects will be randomly assigned in a double-blind manner (n=37 in each group); all subjects and the research staff who interact with them will be blinded to assignment, and a separate UCLA staff member of the research team who has no contact with subjects will program the TNS device settings. Subjects assigned to the sham treatment condition will receive a TNS stimulator that will look identical to the active treatment stimulator, and will follow identical procedures for the use of this stimulator. The sham unit, however, will deliver no actual nerve stimulation (i.e., it will pulse at 0 Hz). It will be explained to all subjects that they may or may not feel any sensation while using the device and any sensations or lack there of is not indicative of which treatment they are receiving. There is no noise associated with the device. The TNS device is equipped with a lighted display which will turn on to indicate to the patient when stimulation is being administered. The display on the sham device will turn on when stimulation is given at 0 Hz to avoid the appearance of a difference between the sham and active treatment.

Subjects will be followed weekly with ratings of PTSD symptoms, mood and anxiety, as well as examinations for risk of suicidality. Week 8 endpoint measures will include severity and frequency of PTSD symptoms, quality of sleep, and quality of life measures. The primary endpoint measure is the change in symptom severity at the week 8 visit. The week 8 time point will be used to compare changes in symptoms between subjects who were randomly assigned to the active vs. sham TNS treatment condition. Subjects also will be interviewed an additional 4 weeks after the conclusion of the sham controlled treatment, and their mood and anxiety symptoms assessed, to examine the durability of any symptom change that subjects experienced during the initial 8 weeks. At the end of week 8, subject improvement will be assessed and those showing a $\geq$ 25% improvement from baseline at the end of 8 weeks of treatment will be eligible to participate in the 42-month extension phase to monitor and observe possible benefits of prolonged TNS in responders. Subjects who participate in the extension phase will remain blinded. Subjects complete the PCL-M and BDI monthly during their participation in the extension phase. The PCL-M monthly score determines on-going inclusion in this phase. Subjects will be withdrawn in the case of adverse events, or symptom worsening (quantified as > 25% worsening in symptoms after one month as compared to the beginning of the extension phase as assessed using the PCL-M total score). Subjects way also voluntarily withdraw from the extension phase at any time.

Subjects who do not participate in the extension phase will be unblinded and told whether they received the active or sham-controlled treatment after all study and follow-up visits have been completed. This includes completion of the eight-week double-blind treatment phase and four-week follow-up phase for a total of 12 weeks in this study. Data will be examined for differences

between active and sham treatment, as well as safety and acceptability of the treatment. If positive, this preliminary study will serve as the basis for a larger pivotal trial of effectiveness.

Screening Procedures and Instruments: After signing the consent form, the research coordinator will interview subjects to ask about demographic data and assess for possible exclusion criteria. The instruments listed below will be used to determine eligibility for the study and assess symptom severity. Instruments will be administered on the schedule shown in Table 1 below. *Clinician-Administered PTSD Scale for DSM-V (CAPS-5-5)* (Blake et al., 1995; Weathers et al., 2001): The CAPS-5 will be used both to establish eligibility for inclusion in the protocol and as an outcome measure. This 30-item structured interview assesses the presence, frequency, and severity of symptoms of PTSD. It provides a continuous score of frequency and severity for each symptom, with overall severity characterized by summing the total score for the individual items. The CAPS-5 has good psychometric properties across a wide variety of clinical populations and research settings (Weathers et al., 2001). We first will determine using the CAPS-5-5 whether the subject has at least one Criterion A stressor related to warzone exposure. If the subject meets this criterion, the remainder of the CAPS-5-5 will be administered to confirm the presence of PTSD and assess severity. Frequency and severity of symptoms are rated separately on a 0-4 scale.

Mini International Neuropsychiatric Interview for DSM-IV, Version 5.0 (MINI) (Sheehan et al.,1998): The MINI is a short yet accurate structured diagnostic interview used to diagnose current and lifetime Axis I disorders according to DSM-IV criteria. The assessment takes approximately 15 minutes to administer (Sheehan et al., 1998) We will specifically assess current substance dependence, current and/or history of psychosis, bipolar disorder, and to assess possible presence of exclusion criteria through use of relevant modules from the MINI. We also will utilize this instrument to determine the presence of Major Depressive Disorder (MDD); subjects will not be ruled-out because of the presence of MDD, but the presence of the illness will be used as a covariate. If presence of MDD appears to affect outcome, we may perform a subgroup analysis in subjects with comorbid MDD.

Post-traumatic Amnesia Questionnaire (PTAQ) (McMillan et al., 1996) will be used as a screen to identify subjects who may have suffered significant TBI. This questionnaire will be administered only to those potential subjects who report a history of TBI. It is unlikely that many such individuals will be in the population of subjects eligible for screening for this study because such individuals will generally have been identified clinically and referred elsewhere in the VA GLA system. This simple questionnaire will be used, however, to help ensure that no subjects with significant TBI are enrolled in this study. The PTAQ estimates the severity of TBI based upon the length of time that individuals report coma or amnesia following injury. Subjects with coma duration 30 minutes or more and/or duration of post-traumatic amnesia 1 hour or greater will be excluded from the study. The PTAQ shows good psychometric properties. It has a strong association (0.87) with prospective assessment post-traumatic amnesia (McMillan et al., 1996).

PTSD Checklist (PCL-5) (Wilkins et al., 2011): The PCL is a 20-item self-report measure of the 20 DSM-V symptoms of PTSD. We will use this instrument to track changes in PTSD symptoms on a weekly basis throughout the study. It is a self-report measure that can be completed by patients in the waiting room in approximately 5-10 minutes. There are no corresponding PCL-5 or PCL-C versions of PCL-5. The PCL has demonstrated strong psychometric properties. Estimates of internal consistency (Cronbach's alpha) range between .94 (Blanchard et al, 1996) to .97 (Weathers et al. 1993).

Beck Depression Inventory-II (BDI-II) (Beck et al. 1988): This 21-item self-rated questionnaire will be used to assess characteristics and severity of depression. We will use this instrument on a weekly basis to track changes in depressive symptoms throughout the study. Each item is rated on a 4-point scale (0 = not present; 3 = present in the extreme). This questionnaire will be used to rate the severity of depressive symptoms and any improvement during the course of the trial. The total score ranges from 0 to 63. Psychometric properties of the instrument are good. Beck and Steer (1984) demonstrated internal consistency of .86, while Gallagher, Nies, and Thompson (1982) reported high internal consistency of .91.

Addiction Severity Index (ASI) (McLellan et al., 1992): This standardized clinical interview will be used to assess severity and functional impact of substance use for each subject. We will exclude subjects who meet criteria for a current substance dependence disorder, but because of the high prevalence of substance use in this population, we will assess the severity of current use. In addition to providing data on substance use in the previous thirty days, the ASI assesses functional impact and use severity in seven specific areas, including drug use, alcohol use, family-social, medical, and psychological functioning, employment, and legal involvement. The instrument has good psychometric properties. Concurrent and interrater reliabilities are strong (.74-.93) and validity is acceptable (Kosten et al., 1983; McLellan et al., 1983).

36-item Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992): This scale is widely used to assess the effects of health on quality of life (QoL). It recently has been used in OEF/OIF veterans to assess the impact of PTSD on QoL (Pittman et al., 2011). It consists of 36 questions covering eight health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. Two summary scores are constructed based on the eight domains. The SF-36 was constructed to satisfy minimum psychometric standards necessary for group comparisons. It has been extensively evaluated and has robust psychometric properties (http://www.sf-36.org/tools/sf36.shtml#MODEL).

Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989): The PSQI measures the quality and patterns of sleep. Because TNS is administered at night, this scale will be used specifically to assess the effects on sleep. It will provide a more comprehensive assessment of subjects' sleep patterns than the other scales. It can be used to differentiate "poor" from "good" sleep with seven measures: subjective quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The client self-rates each of these seven areas of sleep on a 0 to 3 Likert scale. Each area can be examined independently, and a summary score is calculated with 5 or greater indicating a "poor" sleeper. The scale has good psychometric properties. It has strong internal consistency, with Cronbach's alphas 0.80 across groups and moderate to high correlations between global and component scores (Carpenter and Andrykowski, 1998). *Assessment of safety, compliance, and tolerability* will be performed at the weekly subject visits. All subjects will be provided with a log booklet with space to record any treatment-emergent adverse events, how long they were able to wear the TNS system each night, and whether they encountered any problems. The research coordinator will examine this booklet each week and record any specific adverse events as well as the degree of compliance. In addition, subjects will be asked to rate tolerability of treatment-emergent adverse events by completing the *Systematic Assessment for Treatment Emergent Events-Specific*

Inquiry (SAFTEE-SI) (Levine and Schooler, 1986), an easy to use 55-item self-report (with an additional overall severity item) that rates most commonly reported side effects expected with the clinical study interventions. While developed for medication studies, it is applicable to device studies as well, and will be used to describe side effects associated with treatment. The SAFTEE-SI will be administered at enrollment and at each follow-up visit, to detect treatment-emergent events or events which worsen during treatment. The SAFTEE-SI will be supplemented by an open-ended question ("general inquiry") to capture any adverse reactions not enumerated in the SAFTEE-SI items. Events will be categorized using the Medical Dictionary for Regulatory Affairs (MedDRA), a clinically validated terminology that applies to all phases of drug and medical device development, and developed by the International Conference on Harmonisation (ICH) as a successor to the earlier COSTAR ("Coding Symbols for Thesaurus of Adverse Reaction") nomenclature.

Scales from the Deployment Risk and Resilience Inventory-2 (DRRI-2) (baseline)

This 'Trauma and Adversity Exposure' protocol includes the following four self-reported, deployment-related subscales from the Deployment Risk and Resilience Inventory-2 (DRRI-2) (Vogt et al., 2013): Difficult Living and Working Environment (14 items); Combat Experiences (17 items); Aftermath of Battle (13 items); and Perceived Threat (12 items). Items are rated on Likert-style scales and added together to give a score for each scale.
See: http://www.ptsd.va.gov/PTSD/professional/assessment/deployment/index.asp

Difficult Living and Working Environment Scale (14 items) DRRI-2 Section: C; Survey Label: "Deployment Environment." This scale assesses exposure to events or circumstances representing repeated or day-to-day irritations and pressures related to life during military deployment. These personal discomforts or deprivations may include the lack of desirable food, lack of privacy, poor living arrangements, uncomfortable climate, cultural difficulties, and constraints to performing one's duties.

Combat Experiences Scale (17 items) DRRI-2 Section: D; Survey Label: "Combat Experiences." This scale covers exposure to combat-related circumstances such as firing a weapon, being fired on, being attacked or witnessing an attack (e.g., encountering an explosive device), encountering friendly fire, and going on special missions and patrols that involve such experiences. This war-zone factor refers to objective events and circumstances and does not include personal interpretations or subjective judgments of the events or circumstances.

Aftermath of Battle Scale (13 items) DRRI-2 Section: E ; Survey Label: "Postbattle Experiences." Assesses exposure to the consequences of combat, including observing or handling human remains, interacting with detainees or POWs, and observing other consequences, such as devastated communities and homeless refugees. This factor is conceptualized as cataloging more objective war-zone events and circumstances.

Perceived Threat Scale (12 items) DRRI-2 Section: G; Survey Label: "Deployment Concerns." Assesses fear for one's safety and well-being during deployment, especially as a response to potential exposure to warfare (e.g., attacks by enemy combatants, encountering explosive devices), as well as nuclear, biological, and chemical agents (NBCs) in the war zone (e.g., depleted uranium in munitions, pesticides, or other routinely used chemicals). This factor

reflects emotional or cognitive appraisals of situations that may or may not accurately represent objective or factual reality.

The Life Events Checklist for DSM-5 (LEC-5) (baseline)
LEC-5 is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. We will use the LEC-5 as it is typically used, i.e., to facilitate identification of an index trauma for assessment of PTSD symptoms with the CAPS-5-5.

PTSD Treatment History and Effectiveness (baseline)
The Emory Treatment Resistance Interview for PTSD (E-TRIP) (Dunlop et al., 2014) is a combination self-administered questionnaire and interview that includes a PTSD Medication Treatment Record, a PTSD Psychotherapy Treatment Record, and a Treatment Resistance Interview for PTSD. The time required to administer the E-TRIP ranges from one minute for treatment-naïve patients to 20 minutes for more extensively treated patients. Mean time to administer the instrument was 6.41 ± 5.47 minutes (Dunlop et al., 2014).

Visit Type	**Week 0 (Baseline)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
Visit Length	***6 hrs**	**2 hrs**	**2 hrs**	**2 hrs**	**4 hrs**	**2 hrs**	**2 hrs**	**2 hrs**	**4 hrs**
Questionnaire /Survey:									
MINI	X								
CAPS-5	X				X				X
PTAQ	X								
PCL-M	X	X	X	X	X	X	X	X	X
BDI	X	X	X	X	X	X	X	X	X
ASI	X								X
SF-36	X				X				X
PSQI	X	X	X		X				X
SAFTEE-SI	X	X	X	X	X	X	X	X	X
DRRI-2 (4 scales)	X								
LEC-5	X								
E-TRIP	X								
Treatment Blinding Questionnaire									X
Safety and Compliance		X	X	X	X	X	X	X	X
Study Procedures:									
Urine Test	X								
Pregnancy Test (Females only)	X								
Simulation Log Check	X	X	X	X	X	X	X	X	X
Device Setting Adjustments	X				X				

Table 1 Schedule for administration of diagnostic and rating instruments in the main study

Visit Type	Monthly	Final visit
Visit Length	**30 mins**	**4 hrs**
Questionnaire/Survey:		
MINI		X
CAPS-5		X
PTAQ		X
PCL-M	X	X
BDI	X	X
ASI		X
SF-36		X
PSQI		X
SAFTEE-SI		X
DRRI-2 (4 scales)		X
LEC-5		X
E-TRIP		X
Treatment Blinding Questionnaire		
Safety and Compliance	X	X

Table 2: Schedule for administration of diagnostic and rating instruments in the extension phase

MINI Version 5.0: Mini International Neuropsychiatric Interview for DSM-IV
CAPS-5: Clinician-Administered PTSD Scale for DSM-V
PTAQ: Post-traumatic Amnesia Questionnaire
PCL-5: PTSD Checklist for DSM-V
BDI: Beck Depression Inventory
ASI: Addiction Severity Index
SF-36: 36-item Short Form Health Survey
PSQI: Pittsburgh Sleep Quality Index
SAFTEE-SI: Systematic Assessment for Treatment Emergent Events–Systematic Inquiry
LEC-5: Life Events Checklist for DSM-5, self-report
E-TRIP: Emory Treatment Resistance Interview for PTSD
Treatment Blinding Questionnaire: Survey to assess what treatment is thought to be received
DRRI-2 Section C, Deployment Environment: 14-item scale assesses exposure to events or circumstances representing repeated or day-to-day irritations and pressures related to life during military deployment.
DRRI-2 Section D, Combat Experiences: 17-item scale assesses exposure to combat-related circumstances.
DRRI-2 Section E, Postbattle Experiences: 13-item scale assesses exposure to the consequences of combat.

DRRI-2 Section G, Deployment Concerns: 12-item assesses fear for one's safety and well-being during deployment.
Safety and Compliance: Assessment will be performed by the research coordinator to assure the device is being used safely and as directed.

Assessment instruments will be administered by the study coordinator (Michelle Abrams, R.N., Dr. Aimee Hunter and Sarah Chang). Ms. Abrams has over 20 years experience in assessment of psychiatric patients in clinical trials. She will undergo standardized refresher training in conducting the MINI interview, and in administering or supervising completion of the instruments utilized in this study. She will undergo training in administering the CAPS-5 through the Trauma Psychiatry Program at UCLA (Robert Pynoos, M.D., Director). Training will include practice interviews and feedback from trainers designed to calibrate to a consistent acceptable standard of administration.

TNS stimulation procedure. TNS will be performed using a CE-mark approved neurostimulator, the Monarch eTNS System™ (NeuroSigma, Inc., Los Angeles CA); in August 2012, NeuroSigma received CE mark certification for use of the Monarch for adjunctive treatment in epilepsy and MDD in adults and children age 9 and older. The Monarch comprises two elements: the electrical pulse generator and the hypoallergenic, self-adhering custom electrodes for delivery of the signal to the supraorbital and supratrochlear branches of the V1 division of the trigeminal nerve. The system offers features not available in off-the-shelf transcutaneous nerve stimulators, such as limiting the applied current to known safe ranges and two levels of lock-out codes to prevent the device from being used by others or reprogrammed by the subject. As well, the composition and geometry of the electrodes has been engineered to provide the optimal amount of adhesion to be worn for 7-9 hours with a gel devoid of volatile compounds that are present in most surface electrodes used for nerve stimulation and that lead to skin irritation.

The stimulators are the same device for the active and sham treatment conditions; the only differences are the frequency at which the device is set to deliver stimulation, the pulse width, and the duty cycle. The programming will be set at the UCLA site prior to the baseline visit and the week 4 visit by a member of research staff who has no contact with subjects to deliver TNS in a double-blind manner at one of two frequencies of stimulation, active (120 Hz) or sham (0 Hz); these are the active and sham stimulation conditions previously described in epilepsy studies (DeGiorgio et al., 2003; 2006; 2009; in press) as well as in MDD (Schrader et al., 2011). Preliminary data indicate that subjects report comparable perceptions of being stimulated in the two stimulation conditions. Once the device is programmed, the user will not be able to change the stimulation parameters. Current can be adjusted within a narrow range for the comfort of the subject. Preliminary data (reviewed above) indicate that in the treatment of epilepsy, a 120 Hz stimulation frequency had a significantly greater effect than 2 Hz on mood under double-blind treatment conditions. In both conditions, the current will be adjusted to maintain comfortable but perceptible levels of stimulation. TNS will be performed for approximately 8 hours each night, a protocol that subjects found acceptable in the pilot work.

Conduct of the study. After subjects are consented and qualify to enter the study, the full assessment of symptoms will be performed. The estimated time for all these procedures at the baseline visit is approximately 3 hours.

Following the baseline assessment, subjects then will be randomized to one of the two treatment conditions. Treatment assignment will be randomized within cells defined by gender, symptom severity, and presence of current medication treatment to provide a degree of balance on key underlying characteristics that otherwise would have the potential to confound the interpretation of study findings. Specifically, there will be eight strata for randomization defined by the 2 x 2 x 2 combinations of gender (male or female), symptom severity (lower or higher defined by whether the CAPS-5 score on entry is less than 78, the median value for this sample, versus being 78 or greater), and presence of current medication treatment (yes or no). Within these strata, randomization will occur in blocks of two, so that after every two patients with a given combination of stratum-defining characteristics, there will be one patient assigned to the active intervention and one to the control arm. The randomization will be carried out by associating strata with rows of the random-number table in Cochran (1977, p. 19). For the first member of each successive pair of patients presenting with a given set of stratum-defining characteristics, if the next number in the row is in the range of 5 through 9, then the patient will be assigned the active intervention, else the patient will be assigned to the sham. If the first subject was assigned the active intervention, then the next subject would be assigned the sham, and vice versa; for the next subject after that, the random-number table will be used in the same way. The pairing in the design could be considered in the analysis, and we will plan to do so using a permutation-test approach for purposes of being complete. The core motivation for the pairing, however, is to ensure that treatment assignment remains balanced across arms rather than because we believe that there is anything scientifically important about whether the subject arrives at an odd or an even number in the sequence. For our primary analysis, we will use a randomized-block ANOVA that accounts for the 2 x 2 x 2 stratification in the design but does not reduce the error degrees of freedom on account of the pairing.

Following randomization, subjects will be scheduled to come back for a second visit when they will be given a pre-programmed stimulator, a supply of electrodes, and instructions on how to apply the electrodes and use the device. No more than one week will elapse between the first and second baseline visits. Baseline measures will not be repeated at the second baseline visit except for the CAPS-5, PCL-5, and BDI measures, which will be repeated in order to have PTSD, anxiety, and depression severity measures immediately prior to the start of treatment. Subjects will return to UCLA or the VA GLA for weekly visits and will undergo assessment of symptoms with instruments as specified in Table 1 above. The research coordinator will assess compliance, ensure that the device continues to be in good working order and that the subject has a sufficient supply of electrodes, and encourage continued compliance. In addition, the research coordinator will assess the subject for safety, inquiring specifically about any suicidal ideation and evaluate the results of scheduled assessments. If the research coordinator has any concerns about subject safety, she will immediately contact a study physician who will interview the subject and perform an independent assessment. Subjects will be removed from the study and hospitalized for any safety concerns per the procedure in the Human Subjects section.

At the conclusion of the main study (week 8 visit or sooner if the subject drops out or is removed from the study), subject improvement will be assessed and those showing a $\geq$ 25% improvement from baseline at the end of 8 weeks of treatment will be eligible to participate in the 42-month extension phase to monitor and observe possible benefits of prolonged TNS in responders. Subjects who participate in the extension phase will remain blinded and will be asked to complete the Beck Depression Inventory(BDI) and the PTSD checklist during a monthly phone visit. Subjects who do not participate in the extension phase will be unblinded and told whether they

received the active or sham-controlled treatment after all study and follow-up visits have been completed. The device will be collected from the subject and the subject will be continue treatment in the PTSD Clinic or the Domiciliary Care Program. A summary of the results for each subject in the study will be provided to the clinic staff with the subject's permission.

Four weeks after the week 8 endpoint, all subjects who did not participate in the extension phase will be contacted again and interviewed to examine the durability of any symptom changes that they experienced during the eight-week double-blind controlled trial period. All of the instruments from the week 8 time point will be administered again to determine if symptom improvement persists after discontinuation of the device, whether symptoms have returned, and whether any adverse events have resolved.

14. Compensation:

Compensation will be provided in the amount of $200.00 plus reasonable expenses for travel costs (bus fare, mileage, etc.) for all participants who complete the study. The amount of $200.00 reflects payments commensurate with the amount of time the subjects will be spending in the study ($40 for the screening visit, plus $20 for each subsequent study visit in the 8-week main study). This level of compensation is standard for studies at the VA GLA for this level of time commitment, and has been deemed to be fair and non-coercive in other outpatient research protocols at the VA GLA. Participants who voluntarily withdraw or are involuntarily removed from the study will be compensated by check for completed study visits and transportation at the conclusion of each research visit.

15. Cost: There will be no costs to the participants enrolled in this study.

16. Medical Devices

The medical device used in the study is the NeuroSigma Monarch eTNS System manufactured by NeuroSigma, Inc.

The UCLA MIRB-3 Committee has reviewed NeuroSigma's Monarch eTNS System for use in protocol 11-002580 "Trigeminal Nerve Stimulation for Epilepsy" and decided that it met criteria for non-significant risk. Please see also our attached document "Abbreviated IDE Materials - TNS as NSR Device" for discussion. TENS units are FDA cleared for use in the treatment of pain by stimulating peripheral nerves. As per our protocol, we will use TNS units for stimulating peripheral nerves cutaneously, but for effects on the symptoms of major depression rather than of pain. Please see our attached documents for information about the risks associated with this offlabel use in prior and on-going research studying trigeminal nerve stimulation. Regarding reporting of the data to FDA, if this study finds that there are therapeutic benefits in PTSD and/or depression symptoms from TNS, then it is likely that data from this study may be reported to the FDA.

TNS is a relatively new treatment, so there are limited published data from sham-controlled studies. All data available to date, however, show a pattern of consistent efficacy for TNS in alleviating mood and anxiety symptoms in patients with epilepsy, MDD, and PTSD (Cook et al., 2014). Significant improvements in mood have been described with TNS in an open-label study of subjects with MDD (Schrader et al., 2011; Cook et al., 2013) and a controlled trial of epilepsy (DeGiorgio et al., 2011).

We recently concluded an open-label trial of TNS in adults with PTSD and comorbid MDD. Twelve adults (mean age 52.8 (13.7 s.d.) years, 8F:4M) with median 37 yrs since traumatic exposure (range 3-61) and with PTSD and MDD, were studied in an 8-week open label outpatient trial. Three of these subjects had PTSD based upon military service. Current episodes were required to be of at least 4 months duration, with non-response to at least 1 antidepressant trial over at least 6 weeks during the current episode (ATHF $\geq$1), and concomitant use of at least 1 antidepressant. All had prominent symptoms at entry, with mean scores on the CAPS-5 of 80.2 (12.5), PTSD Patient Check List (PCL) of 63.3 (7.8), of 25.8 (4.6) on the 17-item Hamilton Depression Rating Scale (HDRS), and of 17.8 (4.0) on the Quick Inventory of Depressive Symptomatology (QIDS-C). Subjects placed stimulating electrodes over the supraorbital branches of the trigeminal nerve for at least 8 hours each night, primarily while asleep, with current adjusted to maximal comfortable levels. Co-primary outcomes were change in PCL and QIDS-C at 8 weeks. Results show that TNS was well tolerated, with no subjects discontinuing treatment because of difficulty or unacceptability of using the device. Decreases in PCL score were significant, from 63.3 (7.8) at entry to 43.0 (18.3) at week 8 (2-tail paired t-test p=0.003). QIDS-C score decreases were also significant, falling from 17.8 (4.0) to 8.8 (4.3) ($p<0.001$), as were scores on the HDRS, improving from 17.8 (4.0) to 11.9 (7.3) $p<0.001$). All reflect a large effect size comparing end-of-trial to start (Cohen's *d* 1.5 for PCL, 1.8 for QIDS-C, and 2.1 for HRSD). We do not have data on the durability of these effects.

In order to elucidate mechanisms through which TNS may produce therapeutic effects on mood, we undertook a functional neuroimaging study to evaluate patterns of regional activation that might be relevant to understanding the effect of TNS in mood and anxiety disorders. We examined four adults with nonpsychotic unipolar MDD (2M:2F; all right-handed; age 46.9 $\pm$ 5.8 yrs) who had enrolled in a trial of adjunctive TNS. All subjects had non-response to greater than six weeks antidepressant treatment in the current episode at enrollment. All subjects had moderately severe residual symptoms, with mean Hamilton Depression Rating Scale ($HDRS_{17}$) (Hamilton, 1960) scores at entry of 19.5 $\pm$ 4.4. A total of 24 [O-15] water PET scans were performed at pre-treatment baseline. TNS then was initiated via bilateral supraorbital electrodes for periods of 60 sec during the PET scan sequence. Half of the scans for each subject were acquired while receiving 60 sec TNS, and half with the device deactivated. In device-on scans, the TNS system was activated at the time that the [O-15] water bolus was administered intravenously. PET data were analyzed both by standardized volume of interest (sVOI) and statistical parametric mapping (SPM) methods. Both methods normalized local metabolism to whole brain activity. SPM measured activity values within 240 standardized regions of interest that were clustered into 47 volumes. PET data were contrasted for scans collected with and without TNS.

There were significant differences between scans collected with and without TNS. With only brief exposure to TNS, significant increases in regional cerebral blood flow were detected in anterior cingulate gyrus (bilateral BA 32,24) and medial and middle frontal gyri of the DLPFC (right BA 6,8, 45, 46), as well as the inferior frontal gyrus (left BA 44,6,22) and parietotemporal cortex (bilateral BA 39,40). All regions had peak voxels showing highly significant differences ($p<0.0005$) and significant cluster size ($p_{cluster\ corr}<0.05$). The largest activation cluster was in the left inferior frontal gyrus ($p_{cluster\ corr}=0.008$). SPM findings were corroborated with sVOI analyses. These findings indicate that several key areas implicated in regulating mood and anxiety are

affected by TNS. Future studies may clarify the role of these changes in regional activity in the mechanisms underlying symptom improvement with this novel approach to neuromodulation.

Taken as a whole, these data present a compelling picture of the promise of TNS as an innovative potential treatment for mood and anxiety disorders. Because of the limited pilot data available on TNS in PTSD, the fact that the sham condition has not been tested in subjects with PTSD, and the complex nature of TAU in PTSD, this pilot intervention study is a necessary step in development of the technology.

17. Biological Samples

We will request urine samples to test drug use for all participants and pregnancy in female participants. The sample will be discarded immediately after test results are confirmed (5-30 min. after sample is given).

18. Anonymity or Confidentiality

De-identified demographic, historical, and clinical data will be collected on each subject using the clinical and functional rating scales and entered into a secure SQL computer database. Subjects will be identified in the database by a code number that will be stored in a logbook in a locked cabinet that will be accessible only to the PI, and the PI will oversee all data access. No personal identifying information will be available to those analyzing data. The only people who will have access to the Informed Consent forms or the data are members of the study research team. Informed Consent forms will not be attached to assessment instruments and will be stored in a separate locked cabinet from interview data forms. Assessments will at no time contain names or identifiers of participants. The above data confidentiality plan will be followed exactly as described and strictly enforced at all times. The research team and research sponsor (Department of Defense/USAMRAA) may use the research report and share it with others to perform more research, place it into research database *(TNS-related research database, stored at UCLA),* use it to improve the design of future studies, use it to publish articles or for presentations to other researchers, share it with the sponsor, or file applications with U.S. or foreign government agencies to get approval for new drugs or health care products.

a) Records of participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. These records may be examined at by staff from the appropriate IRBs as well as the US Army Medical Research and Materiel Command (USAMRMC), and other government agencies as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. To further protect privacy, a Certificate of Confidentiality will be obtained for this study. As required by law the site PI will report any child abuse or neglect to the Family Advocacy Program or to local child protective services. Participant names will not appear in any published paper or presentation related to this study. Research study staff will also abide by the Health Insurance Portability and Accountability Act (HIPAA) Risks.

The physical research records will be stored in locked file cabinets within locked offices. Other data will be kept in locked offices on password-protected computers and in locked file cabinets, so that only members of the research team will have access to the information. The physically- and electronically-secure SQL database server will be employed as the main electronic data

repository; it will be located behind a dedicated firewall system. Data will be archived to an off-campus backup server via an encrypted data communications link (e.g., rsync protocol employing ssh "tunnel") to guard against data loss from on-campus catastrophe (e.g., fire, earthquake) and in compliance with HIPAA regulations. Research records will be retained for a period of five years after the latter of the following two dates: the date on which the investigation is terminated or completed and a study report accepted for publication, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

Foreseeable risks of participation. It is possible that some subjects may suffer a worsening of symptoms as a result of the assessments or discussing traumatic experiences during the intake process. The assessments are likely to be no more upsetting, however, than standard clinical assessments and treatment. Because subjects will recently have completed a course of PE treatment, they will be familiar with discussions of their symptoms and should not suffer any significant change in their condition.

The primary risk of this sham-controlled treatment protocol is the potential for lack of clinical improvement. Subjects may suffer some fluctuation or worsening of symptoms in either the active treatment arm (if the treatment is ineffective or they are a non-responder) or the sham arm (which, like a pill placebo, is designed not to be effective). Evidence would suggest that the TNS procedure itself carries minimal risk. The external nerve stimulator for TNS in this project is not implanted, and the stimulation provided through cutaneous electrodes on the forehead. The procedure is safe and well tolerated, having been performed in more than 100 subjects over eight years as an adjunctive treatment for medication-resistant epilepsy (DeGiorgio et al., 2003; 2006; 2009; Heck et al., 2011), as a treatment for MDD (Schrader et al., 2011; Cook et al., 2013), and most recently in our group, in subjects with PTSD or MDD (unpublished data). It has been examined in preliminary studies for its efficacy, tolerability, and safety profile. For subjects with epilepsy, TNS was very well tolerated. No serious adverse events due to the stimulator or stimulation occurred. Side effects included skin irritation in approximately one-third of subjects who were wearing the stimulator continuously in early epilepsy trials, and this adverse effect was ameliorated by reducing the duration of stimulation to 12-16 hours per day. In the current study, subjects will wear the stimulator for only 8 hours per day (while they sleep). The use of hydrocortisone 1% cream applied topically also can be helpful with skin irritation. Some subjects reported sensations of tingling, pressure, or headache, and lowering the current of stimulation was used to address any discomfort for these individuals. Vital signs were monitored and there were no significant effects on heart rate, systolic blood pressure, or diastolic blood pressure, either with acute exposure to stimulation (i.e., first hour of device use) or after six months of daily use. For the subjects who have completed our pilot studies of TNS in PTSD or MDD, none has experienced serious adverse events related to the use of the device. In these studies, none developed skin irritation requiring the use of hydrocortisone cream or reduction in the number of hours of use each day. Use of the system was not limited by any sensation experiences, and there were no significant effects on vital signs, similar to the findings in subjects using TNS for epilepsy as above. One subject who did not respond to treatment did commit suicide during the last week of participation in the current open label PTSD protocol. This subject had consistently denied any suicidal ideation on his bi-weekly symptom ratings. This adverse event was reviewed by the UCLA IRB and was determined not to be related to use of the device.

We have carefully reviewed FDA guidance, and believe this is a NSR device because (a) it does not meet the FDA's criteria for being a Significant Risk (SR) device (per 21 CFR 812.3(m)) and (b) the FDA has previously classified non-implanted TENS devices as NSR devices when used to stimulate cutaneous nerves for the treatment of pain in the same general way that this study will stimulate cutaneous nerves (branches of cranial nerve V) for a different indication (i.e., a psychiatric disorder). The UCLA IRB has determined that use of the Monarch system to provide TNS qualifies as a Non-Significant Risk (NSR) investigational device under FDA guidelines and as such is governed by the provisions of the Abbreviated IDE process.

Management of the Risks of Participation. For the project proposed here, we will submit requests to the VA GLA and UCLA IRBs to classify the TNS system as non-significant risk (NSR) for the purpose of this study. The NSR process will be administered by the VA GLA and UCLA IRBs as delegated by the FDA per 21 CFR 812.2(b), and will involve review and concurrence with the investigator-sponsors' determination that this is an NSR device, and that the investigators will adhere to the rules and regulations specified for NSR device studies. In accordance with FDA guidance, we will follow the abbreviated requirements at 21 CFR 812.2(b):

- Labeling: all devices will be labeled in accordance with §812.5 with the text "CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use." All subjects will also receive a statement concerning relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions (attached).
- IRB approval: this study will not commence until IRB approval is granted
- Informed consent: all research subjects will provide informed consent under 21 CFR 50, and this will be document with the study's Informed Consent Form, as approved by the VA GLA and UCLA IRBs.
  Monitoring: we will comply with the monitoring methods described in the project protocol, including monitoring for any unanticipated adverse device effects; adverse events will be reported to the VA GLA and UCLA IRBs in accordance with IRB policies.
- Records: records will be maintained regarding use of the devices and will be available for VA GLA and UCLA IRBs and FDA inspection [§812.140(b)(4)] as needed, including
  - the objectives of the investigation;
  - a brief explanation of why the device is not a significant risk device;
  - the name and address of each investigator;
  - the name and address of the VA GLA and UCLA IRBs;
  - a statement of the extent to which the good manufacturing practices (21 CFR 820) were followed in manufacturing the device by the outside manufacturer
  - records concerning complaints and adverse device effects whether anticipated or not [§812.140(b)(5)]
  - any other information required by FDA
- Reporting: the investigators will report to the full research team and the VA GLA and UCLA IRBs any unanticipated adverse device effects, changes in IRB approval status, protocol deviations, or other events, in accordance with IRB policies.

• Compliance with prohibitions: §812.7 prohibits promotion or misrepresentation of the device and other practices (e.g., any advertisements for recruitment of research subjects will be

approved by the VA GLA and UCLA IRBs before use; the device will be represented as investigational and not as FDA-cleared for this indication).

The overall risks of clinical worsening in this study are mitigated because all subjects will be able to receive some naturalistic non-study treatment in the clinic. Specifically, subjects will be permitted to continue to receive medications so long as they have been on a stable dose for at least six weeks. They also will be able to participate in a number of groups or psychotherapies while in the study. All subjects will continue to be followed as regular patients in the PTSD Clinic or the Domiciliary Care Program, so that if additional intervention is needed, subjects will be called to the attention of the staff who will be available to respond.

We anticipate that any symptom worsening that the subjects would experience due to evaluation or ongoing ratings would be short-lived and mild in intensity. Nevertheless, we will have procedures in place to ensure subject safety at all times during evaluation and treatment. Participants will be fully advised about all study procedures and risks through the informed consent process. They also will be advised that they can refuse to answer any questions that they find intrusive or upsetting or can stop the interview at any time. Any subject who shows significant distress will be observed carefully and will be asked to remain with study personnel until safety can be assured. All subjects also will be reminded at each visit about the availability of their study clinician should the subject develop any event of concern, including suicidality or adverse events. PTSD Clinic or Domiciliary Care Program staff will be contacted immediately during regular working hours if there are any concerns about the subjects' emotional state or safety. Because all subjects will be patients of the PTSD Clinic or Domiciliary Care Program, they are eligible for emergency services at the VA GLA Healthcare System, including inpatient hospitalization on the same station as the Clinic. If clinic staff are not immediately available to handle a subject in need of immediate care, he or she will be taken by research staff to the VA GLA Emergency Department (ED) or, as needed, to another emergency facility that may be closer to where the subject is located (e.g., if an individual's condition deteriorates while at home). Study physicians may petition the subject to be brought involuntarily to the nearest emergency room if necessary, as provided for under state mental health laws in California where the study is being conducted. Physicians will be available 24/7 on pager for emergencies, and will ensure that appropriate emergency facilities will be used after hours and on weekends for sudden worsening of clinical status.

Should an adverse event emerge, the subject will be instructed to contact his/her study physician who will assess the clinical significance of the event. This assessment will categorize the serious adverse event (SAE) as emergent or non-emergent. For non-emergent events, the physician will manage as they see fit. Rapid consultation with the Principal Investigator is available at the physician's request; the PI will be responsible for reporting the event as an SAE per study protocol. If a consultation with the PI is not pursued in real-time, the physician will inform the PI of the event within 24 hours of having identified the event. All reports of adverse events will be reported to the relevant Institutional Review Board in accordance with its policies, as well as to the Medical Monitor (Dr. Krantz). Reports for serious events that may be related to participations also will be reported to the Army Human Research Protection Office (HRPO).

The medical research monitor for this study will be David Krantz, Ph.D.,M.D. He is responsible for overseeing the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

All serious adverse events and unanticipated problems will be reported to the monitor within 24 hours of occurrence. He will issue a written opinion on the relationship of study procedures to the event and this report will be filed with the IRBs and kept in the subject's file. The medical monitor will indicate whether he concurs with the details of the event as reported by the investigator. Reports for serious events that may be related to participations also will be reported to the Safety Monitoring Committee (SMC) that will be created for this study and the HRPO. If in his professional opinion, the procedures of the study pose a risk to subjects, he will have the authority to halt the study at any time. The SMC will meet every six months or more often as deemed necessary by the chair of the Committee, Dr. Krantz, and will be composed of three physicians on the UCLA and/or VA medical staff who are unaffiliated with the study and without any conflicts of interest regarding this study. The SMC will review SAEs that occur in the study after the medical monitor has reviewed them and will have the authority to halt the study at any time for reasons of subject safety. If this should happen, the relevant IRBs and HRPO would be notified.

19. Benefits:

If TNS proves to be an efficacious treatment, subjects who receive the active treatment may have a significant reduction in their symptoms and would benefit from this innovative treatment. Subjects in this study will receive a level of interpersonal interaction and follow-up care from a research coordinator that is of greater intensity than they ordinarily would receive in the PTSD Clinic or Domiciliary Care Program, which may provide some symptom reduction whether or not the subject receives some benefit from TNS.

In addition to the possible direct benefits to subjects, this project offers significant benefits to patients suffering from PTSD. This novel treatment could be a safe, non-pharmacologic adjunctive therapy for the treatment of PTSD symptoms. Given the substantial residual symptoms that patients have after completing either psychological or pharmacological therapy, there is a great need for novel treatments. TNS could help fill a significant gap in our current treatment armamentarium.

20. Assessment of Risk:Benefit ratio

The objective of this preliminary study is to examine the potential efficacy of TNS as an adjunctive treatment in veterans with PTSD. This method of brain stimulation has shown promise for the treatment of MDD (Schrader et al., 2011; Cook et al., 2013). The treatment is very easy to use; subjects simply apply the two electrodes to their forehead, and the stimulation is provided through wires attached to a stimulator about the size of a deck of cards. Subjects will go to bed so that they can sleep with the stimulator on for approximately eight consecutive hours per night. If

they have difficulty sleeping, subjects may also be awake during the treatment. In early trials, subjects reported no significant adverse events and that the treatment is convenient and acceptable to them (Schrader et al., 2011; Cook et al., 2013). We have conducted preliminary, open-label studies of TNS in subjects with PTSD (described above) and have shown that the treatment is well-tolerated and is associated with a significant improvement in PTSD symptoms.

The risks for the TNS treatment in this study is categorized as a non-significant risk. We have taken all the steps necessary to minimize possible risks/adverse events and have received postive results with this device in regards to efficacy and safety. We are confident that the potential benefits to participants and society outweigh the risks.