**Participant Name**: _____ Date: _____

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

**Principal Investigator**: Dr. Andrew F. Leuchter **Contact number:** (310) 825-0248

**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

## INTRODUCTION

You are invited to take part in a collaborative research study with the VA Greater Los Angeles Healthcare System and University of California Los Angeles (UCLA) under the direction of Dr. Andrew F. Leuchter and his research team. This study is supported by funds provided by the Department of the Army/United States Army Medical Research Acquisition Activity (USAMRAA). Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

## BACKGROUND AND PURPOSE

*Purpose of the study*

In this study, we will be researching the effects of Trigeminal Nerve Stimulation (TNS) as a therapy used in addition to other therapies in Veterans suffering with Post-traumatic Stress Disorder also known as PTSD. PTSD is an anxiety disorder that results from exposure to a traumatic event and includes symptoms such as flashbacks, nightmares, sad feelings, loss of interest in activities, irritability, avoidance as well as physical symptoms like changes in sleep, energy, or appetite. PTSD is seen in a substantial number of armed service warriors and veterans and the impact of PTSD upon patients and their families is overwhelming. The trigeminal nerve is the largest cranial nerve, offering a pathway for signals to enter the brain. The trigeminal nerve is connected to specific areas of the brain involved in depression and anxiety. We believe that by stimulating the trigeminal nerve, we can change the function of these brain areas, and help relieve some of the symptoms of PTSD. The method of stimulating nerves is called neuromodulation. Neurmodulation in the trigeminal nerve of the head may help with the treatment of mood and anxiety disorders. This study is designed to explore the potential use of Trigeminal Nerve Stimulation as an effective treatment for PTSD.

*Eligibility*

You have been asked to participate in this study because you currently suffer from PTSD and are currently in treatment and have received treatment-as-usual (TAU) for the last 3 months at the PTSD Clinic or Domiciliary Care Program at the VA Greater Los Angeles.

**Participant Name**: _____ Date: _____

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

**Principal Investigator**: Dr. Andrew F. Leuchter **Contact number:** (310) 825-0207

**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

*Background*

There are a number of treatments for PTSD that may lessen its symptoms including psychotherapy treatments and medications. Although these treatments help to improve PTSD symptoms, there is no one treatment that is likely to alleviate all symptoms of PTSD. We believe that TNS may be helpful in addition to these other treatments in relieving PTSD symptoms, and can be performed at little or no risk to you and can relieve mood or anxiety symptoms without the side effects of medication.

*Study Materials*

The device used in this study is known as the NeuroSigma Monarch eTNS™ (external Trigeminal Nerve Stimulation) System. It is a non-invasive medical device that stimulates the trigeminal nerve using an external electric conductive patch placed directly on the forehead. It can be performed at home daily, primarily while asleep.

Trigeminal Nerve Stimulation will be performed using a CE-mark approved neurostimulator, meaning that it has been approved for use in Europe. In August 2012, NeuroSigma received CE mark certification for use of the Monarch as a treatment in epilepsy and Major Depressive Disorder in adults and children age 9 and older. In this country, the Food and Drug Administration has stated that the TNS device poses a non-significant risk for use in research studies.

*Prospective Enrollment*

The study will enroll 74 veterans with PTSD who are currently in treatment and have received treatment-as-usual (TAU) for the last 3 months at the PTSD Clinic or Domiciliary Care Program at the VA Greater Los Angeles. If you enroll in this study, you will be randomly assigned to treatment with either active or sham TNS for eight weeks, with 37 participants in each group. Random assignment is like the toss of a coin, so that you will have a 50-50 chance of receiving TNS or the sham treatment, which the stimulator will turn on but not actually be stimulating your brain. This study is double-blinded, which means that neither you nor the researchers will know whether you are receiving active or sham treatment until after the study is complete at 8 weeks. You will be followed weekly, and your 8$^{th}$ weekly visit will include measuring the change in severity and frequency of your symptoms. Subjects will be followed an additional four weeks after the sham-controlled phase to determine if symptom changes last.

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## DURATION OF THE RESEARCH

This research study is expected to take approximately 4 years. Your individual participation in the project will take 8 weeks with nightly use of the Monarch eTNS system, plus an additional 4 weeks of follow-up without using the system for a total of 12 weeks participation in this study.

## STUDY PROCEDURES

If you decide to take part in this study, you will be asked to complete various study activities. These activities will include an interview to see if you are eligible to participate in the study. If you are eligible for participation and choose to be in the study, your first visit will include tasks such as a surveys and assessments completed with a study coordinator, urine drug and pregnancy test (females only), receiving your device, randomization and safety monitoring to confirm the device is working properly. During your participation in this study, you will interact with your physician(s) at the PTSD Clinic or Domiciliary Care Program, the Principal Investigator, research nurse, and the study coordinators.

Starting Visit (about 6 hours)

The Starting visit will take 6 hours and will be the longest visit out of all the study visits. This is due to time required to complete the initial surveys/assessments and educate you about the device and how it works. This visit can be split up into two 3 hours visits if necessary.

*Collecting Baseline Information.* The study personnel will ask you questions and perform mental status and physical exams. Then, with the help of a study coordinator/investigator, you will complete questionnaires that measure the severity of your symptoms and offer a way to monitor your response to TNS. You will also complete a "quality of life" questionnaire. This questionnaire will give us a measure of the degree of enjoyment and satisfaction you experience in various aspects of your life, such as with work, school and/or family life. Your responses to these questionnaires will be scored, but there are no "right" answers. We will also ask you questions about any physical symptoms you may be having (e.g. upset stomach, pains in your body). Of the many questions we will be asking you once you sign this consent form, a very small portion of the questions will be about whether you have been having thoughts of suicide. If the study investigators think that your suicidal thoughts are severe and pose an immediate threat to your well-being, the study investigators and emergency personnel will escort you to the emergency department for evaluation and care. If your suicidal thoughts are serious but do not need to be immediately addressed by medical specialists, then you will be given a referral to a physician who can appropriately treat you for this.

*Urine drug and pregnancy tests:* To ensure your safety, as well as to determine whether you are eligible for the study, you may be asked to give a urine sample at the beginning to determine if there

are any other medications or illegal substances (drugs) in your body. All females that have the potential to become pregnant will also have a urine pregnancy test at the first study visit. All urine samples will be destroyed at the end of the visit. Women who are pregnant will not be eligible to participate in the study because we have no information proving that the device is safe to use during pregnancy.

*Education.* You will be shown how to place the electric patch of the TNS device on your forehead, and a photo of you wearing the patch will be taken and given to you. This will help guide you in patch placement at home. Once the photo has been given to you, any other copies or forms of the image (for example, a file on a digital camera) will be destroyed/erased and not used in the research project.

*Randomization.* Following the baseline assessment, you then will be randomized to one of the two treatment conditions. Treatment assignment will be randomized based on gender, symptom severity of symptoms, and presence of current medication treatment to avoid any differences between the two groups so that the data is not misrepresented. Random assignment is like the toss of a coin, so that you will have a 50-50 chance of being on the active treatment or the sham. If you are assigned the active treatment, you will receive brain stimulation that we believe will be medically effective treatment for PTSD. If you are assigned the control/sham treatment, the device that you are using will not deliver actual stimulation to your brain, and we believe will have no real effect on your symptoms. This is what is called a double-blind study, which means that neither you nor the research staff will know which treatment you are receiving until after 12 weeks and your participation in the study is over.

*Personalizing Your Stimulation Settings.* The next goal will be to find the stimulation strength (or dose) intended for you to use in the study. With the electric patch placed just above the level of your eyebrows, the stimulation strength will begin at zero. The study personnel will gradually adjust the stimulation strength. The most common sensation may be pressure or tingling in or near the eyebrows but many people do not feel any sensation. If you do feel something, you will be asked to describe it and rate its intensity. If you feel something uncomfortable or painful, the stimulation strength will be immediately decreased and you should not go above that stimulation strength when using the system. It is not uncommon that you may not feel any sensation during stimulation. Lack of sensation with the device does not indicate it is not working correctly. Throughout the remainder of the study, the strength of stimulation will be set by you to the highest level that is still comfortable for you, and this will be under your control when you use the stimulator at home. We will review how and when you can adjust the settings of the device when we show you how to place the electric patch on your head. You will also be given a user manual for the device for at home use. You may ask any questions about the device and how to operate it during this time and throughout the study.

*Safety Monitoring.* The safety of TNS will be monitored at this visit and all following visits. If there are any major safety concerns, these will be addressed and you may be asked to exit the study for safety purposes.

*Continuing or exiting the study.* If the investigators find anything at this initial visit that suggests your continued participation might be hazardous to you, or that you do not fit the criteria established for entering the project, your participation in the study will be ended and you would not be eligible for further participation after this visit.

*Starting TNS.* You will start TNS stimulation at home after the baseline visit. You may use TNS during the hours of the day that interfere the least with your work and social schedule. For example, if you work during the day, you may decide to use TNS eight hours per day from 10 p.m. to 6 a.m. daily. Most people who have used this for depression have used the system while they are sleeping at night. You will be given a logbook and asked to write in your logbook the hours that you used TNS each day and answer a few questions to determine if the device is working properly. You will be asked to bring this logbook with you to every study visit. Please ask the study personnel if you have further questions about any of the procedures involved in this study.

We ask that you use the device for a minimum of 8 hours. To keep your treatment consistent, we ask that you use the device for no more than 8.5 hours per day and no less than 8 hours per day. More hours of use is not necessarily better than 8.

Phone "Check In" Contact

*Tolerability.* A few days after your Starting Visit you will be called to check how you are tolerating the TNS device and to answer any questions you may have.

Week 1-3 Visits

*Education.* At these visits, you will be reminded about how to place the electric patches and operate the TNS stimulator.

*Symptom Measurements.* At each visit, your responses on the symptom questionnaires will be recorded. For your safety will also be asked about whether you are having any suicidal thoughts or any other side effects.

*Stimulation Log.* You will be asked to bring your stimulation log to these visits.

Week 4 Visit: Midpoint

*At this visit, some of the participants will have their stimulators adjusted to a new frequency of pulses, and some will continue with their original pulse settings; you may or may not feel anything different when you use the stimulator.*

*Education.* At this visit, you will be reminded about how to place the electric patches and operate of the TNS stimulator.

*Symptom Measurements.* At each visit, your responses on the symptom questionnaires will be recorded. For your safety will also be asked about whether you are having any suicidal thoughts or any other side effects.

*Safety Monitoring.* We will check for any safety concerns.

*Stimulation Log.* You will be asked to bring your stimulation log to this visit.

Week 5-7 Visits

*Education.* At these visits, you will be reminded about how to place the electric patches and operate of the TNS stimulator.

*Symptom Measurements.* At each visit, your responses on the symptom questionnaires will be recorded. For your safety will also be asked about whether you are having any suicidal thoughts or any other side effects.

*Stimulation Log.* You will be asked to bring your stimulation log to these visits.

Week 8 Visit - Final in-person visit

*Symptom Measurements.* At this visit, your responses on the symptom questionnaires will be recorded. We will also have you answer questions about your quality of life. For your safety will also be asked about whether you are having any suicidal thoughts or any other side effects.

*Safety Monitoring.* We will check for any safety concerns.

*Stimulation Log.* You will be asked to bring your stimulation log to this visit and turn it in to the study investigators.

*Return Device*. We will ask you to turn your device at this time as you will have completed the treatment phase of this study.

Extension Phase (OPTIONAL)

At the end of the 8-week period, you will be asked to continue the study in an extension phase based on symptom improvement. You will be asked to continue using the TNS device in the same manner as you did in the main study. You will remain blinded during this phase. A phone visit will be conducted monthly with a study coordinator to collect assessments and follow up with any issues with the device. At the end of this phase, you will be asked to schedule a study visit with a study coordinator to complete additional assessments and return the device.

Start of 4-week Follow-up Phase

For participants who completed the 8-week period and do not participate in the extension phase, you will be unblinded and begin a 4 week period of follow-up by weekly telephone assessments by a study

coordinator or personnel after the Week 8 final in-person visit. No treatments are conducted during these visits. They are only to monitor treatment outcome. In addition to questions about symptoms, we will also ask you about your treatment, to determine if it has changed (or not) and how effective it may be for you. Each of these calls should take about 15 minutes, depending on how your condition may be changing.

*Participant Responsibilities*

Your responsibilities, should you choose to participate in this study, will be as follows:

- Use the study device as instructed. This includes using the device only under the personal settings and guidelines determined by the study coordinator and/or principal investigator.
- Keep your study appointments. If it you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- For safety reasons, tell the investigator or research staff if you believe you might be pregnant or if your partner may be pregnant..
- Keep the study device in a safe place for your use only and away from children. Do not allow others to use your device. Do not place the electric patch anywhere on your body other than your forehead.
- Fill out your Simulation Log as instructed.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about staying in the study.
- While participating in this research study, do not take part in any other research project without prior approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this research, as well as that of the other studies

Failure to fulfill your participant responsibilities may result in withdrawal from this study at the investigator's discretion.

The main study site for this study is the UCLA Semel Institute. All subject identification, recruiting, and consenting will be obtained at the VA GLA. The Starting Visit –the longest visit of the study, Week 4 Visit – the mid-point visit and the Week 8 final visit--will be performed at VA-GLA PTSD Clinic or Domiciliary Care Program at the VA Greater Los Angeles.

- Weeks 1-3 and 5-7 will be conducted at UCLA unless you request study visits to be performed at the VA PTSD Clinic or Domiciliary Care Program.

**Participant Name**: _____ Date: _____

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**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

Questionnaires and Procedures for the main study will occur as indicated in the table below:

| **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 | | | | |

*6 hr Baseline visit may be broken into 2 visits, 3 hours each within the same week.

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Questionnaires and Procedures for the optional extension phase will occur as indicated in the table below:

| 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 |

Questionnaires:
**MINI:** Mini International Neuropsychiatric Interview for DSM-IV
**CAPS:** 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
**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.
**LEC-5: Life Events Checklist for DSM-5, self-report**
**E-TRIP: Emory Treatment Resistance Interview for PTSD**
**Treatment Blinding Questionnaire**: Survey to assess effectiveness of blinding
**Safety and Compliance**: Assessment will be performed by the research coordinator to assure the device is being used safely and as directed

**POSSIBLE RISKS OR DISCOMFORTS**

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some or none of the risks or side effects listed. Rare, unknown, or unforeseeable (unexpected) risks also may occur. You may stop TNS *at any time* if you experience discomfort and/or wish to do so.

Risk of Transcutaneous Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) devices, such as the Monarch eTNS™ System, have been used for the control of pain for decades. Chronic pain patients use such devices as much as 24 hours per day, every day, without suffering negative side effects. Because of the special characteristics of the electric patches used for TENS and TNS, the risk of skin irritation such as pain, rashes, or itching due to the adhesive/gel on the patch or the stimulation itself is very low. In prior work using TNS in people with epilepsy who used the system 12-16 hours each day, about 10% developed skin irritation where the electrodes were placed; in prior work using TNS in people with depression, with only 8 hours each day of treatment, no one experienced significant skin irritation. In the event that you do have any skin irritation, you should inform the study staff so they can make adjustments in how you use the device and/or recommend the use of a particular skin cream to address the issue; if these steps do not relieve the problem, you may be withdrawn from the study for your own safety.

The stimulation settings of TNS in this study are well within the established limits of safety and are unlikely to produce any injury to your trigeminal nerve or any part of your body.

In the past, there were no serious medical side effects reported by sixty-two subjects treated for epilepsy who have undergone TNS as part of a previous research study and the forty-three who received TNS for depression PTSD, or ADHD. Common side effects were very mild and included mild pressure sensation on the forehead, mild pain on the forehead, and/or a mild tingling sensation on the forehead when the stimulator was in use.. These side effects improved in all cases when the strength of TNS device was lowered, and stopped whenever the stimulator was not active. If you have any of these problems, you should notify the study staff so they can adjustments with you in your system's settings.

Risk of Autonomic Nervous System Side Effects

The *autonomic nervous system* is the part of your body that controls certain automatic body functions, such as how fast heart beats (heart rate) and blood pressure. The trigeminal nerve is not part of the autonomic nervous system, so heart rate and blood pressure changes are not expected with TNS. We will not measure your heart rate or blood pressure for this study. However, if any mental, emotional or physical issues are observed by the investigator or study coordinator, any sign of risk to you will be immediately addressed.

Risk of Interviews and questionnaires

Some of the questions asked during the interview or on the questionnaires may make you feel uncomfortable. During your first visit, you will be asked sensitive questions about past history. You have the right to refuse to answer any questions.

Risk of PTSD

Worsening PTSD: Even when it is treated, PTSD can have serious consequences. Existing symptoms of PTSD such as feelings of sadness and hopelessness, decreased interest in work and other activities, irritability, difficulty sleeping or sleeping too much, thoughts of death, and changes in appetite can become worse, even when a person is taking medication as directed under the supervision of their own physician. If your symptoms worsen during the course of the study, the primary investigator may end your participation in the research project and ensure that your physician is aware of this problem.

Suicide: In the event that you tell the research staff that you are thinking about harming or killing yourself, or if you answer yes to a question about having thoughts of suicide on one of the questionnaires, the study personnel will ask you more questions about these thoughts. Depending on how intense your thoughts are or how much you feel like hurting yourself, the research staff may provide you with referrals for treatment; work with you to contact your personal physician, trusted family member, or therapist to discuss your thoughts of harming yourself; or work with you on a plan that may include getting you to a hospital for safety.

Note to women of childbearing potential

The investigators conducting this study would like to minimize the potential for any harm to an unborn fetus resulting from these investigational procedures. Thus, women volunteering for the study will be unable to participate unless they are using medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) include:

1. Surgical sterilization (such as hysterectomy or “tubes tied”)
2. Approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Depo-Lupron, Implanon)
3. Barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm)
4. Intrauterine device (IUD)

If you do become pregnant during this study, you must tell the researchers immediately and you may be taken out of the study for your own safety, because we have no information proving that TNS is safe during pregnancy.

You will be excluded from the study if you:

- are, or may be, pregnant.
- have significant thoughts of suicide.
- hear or see things that are not there.
- have facial pain
- have a Vagus Nerve Stimulator or other implantable electrical device such as a pacemaker, spinal cord stimulator, or deep brain stimulator.
- currently use a TENS (transcutaneous electrical nerve stimulation) device.

We will employ measures to minimize described risks, discomforts, and inconveniences by complying with rules and regulations outlined for the device, performing constant safety monitoring and follow up with timely reporting to the investigator and Medical monitor when necessary.

Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

**POTENTIAL BENEFITS**

There are no direct benefits to you from taking part in this research study. However, based on experience with the TNS system in other individuals with PTSD and/or depression, researchers believe it may help relieve some symptoms in subjects with your condition. Of course, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case therefore, there is no guarantee that you will receive benefits from participation in this study.

**ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH**

You may choose not to participate in this study. Whether or not you participate, you still will be eligible to receive your usual treatment in the PTSD Clinic or Domiciliary Care Program at the VA. If it is your decision not to participate in the study, there are other choices such as continuing treatment as usual at the VA Greater Los Angeles PTSD Clinic or Domiciliary Care Program or any of the following alternatives:

*Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) group* - discussions of issues

pertaining to readjustment back 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 cognitive resources.

You may discuss these options with your doctor.

**CONFIDENTIALITY**

Taking part in this study will involve collecting private information about you. This information will be protected in the following ways:

- 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 Structured Query Language (SQL) database server will be used 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 to guard against data loss from on-campus catastrophe (e.g., fire, earthquake) and in compliance with HIPAA regulations.

- 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. The principal investigator will oversee data access. No personal identifying information will be available to those analyzing data. This data confidentiality plan will be followed exactly as described and strictly enforced at all times. The only people who will have access to the Informed Consent forms or the data are members of the study research team. Assessments will at no time contain your name or identifiers that may be linked to you. The above data confidentiality plan will be followed exactly as described and strictly enforced at all times.

- This study is funded by the Department of Defense (DoD). Representatives of the DoD will have access to review research including identifiable information or protected health information.

- Should an adverse event emerge, the Research Monitor for this study may also review your identifiable information and/or protected health information to evaluate your safety and possible continuation in the study.

- Your Social Security number is required for payment and compensation purposes only. Should you choose not to provide your Social Security number, you may still participate in this study. However, you will be ineligible for compensation.

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.

- This is a multi-site study and your information will be shared with the main study site, UCLA, via hard copy records and will be handled and transmitted only by the study staff.

Information about you will be combined with information from other people taking part in the study. We will write about the combined data we have gathered. Any talks or papers about this study will not identify you.

We will not share your records or identify you. There are times when we might have to show your records to other people. For example, someone from the Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the Food and Drug Administration, the VA Greater Los Angeles IRB, our local Research and Development Committee, and other study monitors may look at or copy portions of records that identify you.

As part of the study, we may disclose your information to the University of California Los Angeles who administers this research study, the Department of Defense/USAMRAA who sponsors this study and the US Army Medical Research and Materiel Command (USAMRMC) to perform their duties which include assuring patient protection. We will not share any information with these persons unless they agree to keep the information confidential and use it only for the purposes related to the study.

We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. By law, information can be released if we find or suspect child abuse, elder abuse, an intent to harm yourself or others, or if you have an infectious disease. The Certificate of Confidentiality will not be used to prevent disclosure to local authorities of child abuse and neglect, or harm to self or

others. The Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

**COSTS TO PARTICIPANTS AND PAYMENT**

**Costs to Participants***:*
You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

**Payment Offered for Participation:**
Compensation will be provided in the amount of $200.00 plus reasonable expenses for travel costs (bus fare, mileage, etc.) for the 8-week main study via check. The payments commensurate with the amount of time you will be spending in the study ($40 for the screening visit, plus $20.00 for each subsequent study visit).

- You will be given parking passes for any visits scheduled at UCLA and food vouchers may be provided depending on the duration of your study visit.
- If you choose to withdraw or if the Principal Investigator decides to withdraw you from the study, you will only be compensated for study visits completed before your withdrawal.
- Payments will be disbursed via check by the UCLA Accounting Department. We must obtain your Social Security number to issue payments. Checks may be picked up at UCLA or mailed to your home.
- Should you choose to exit or are removed from the study you will be compensated for completed visits and travel costs associated with completed visits ONLY.
- Compensation will not be provided for visits conducted during the extension phase

## MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury was due to your not following the study procedures.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call anytime, 24 hours a day:

| | |
|---|---|
| Dr. Andrew F. Leuchter, M.D. Principal Investigator | (310) 825-0207 |
| Dr. Bruce Kagan, M.D. Co-investigator | (310) 206-2372 |
| Dr. Mark Barad, M.D., Co-investigator | (310) 849-9055 |
| Dr. Aimee Hunter, Ph.D., Co-investigator | (310) 206-2237 |

You may also contact the Principal Investigator and Co-investigators by calling the UCLA Page Operator at (310) 825-6301.

Emergency and ongoing medical treatment will be provided as needed.
If you are injured as a direct result of research procedures not done primarily for your own benefit, you will receive treatment at no cost. The University of California does not normally provide any other form of compensation for injury.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

## PARTICIPATION IS VOLUNTARY

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with the VA Greater Los Angeles, UCLA (or UCLA Medical Center), or your right to health care or other services to which you are otherwise allowed. If you decide to participate, you are free to withdraw your consent and stop participation at any time without prejudice to your future care at UCLA. If you stop your involvement in the research study, it is your responsibility to:

- Let your study doctor know immediately that you wish to stop the research.
- Return to the research center for tests that may be needed for your safety.
- Discuss your future medical care with your study doctor and/or your regular doctor.
- Bring back the TNS equipment and supplies.

Please note that withdrawal from this study may result in a recurrence or worsening of PTSD symptoms.

The investigator may continue to review the data already collected for the study but cannot collect further information, except from public records, such as survival data.

**RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION**

The study investigators may withdraw you from participating in this research if circumstances arise which justify doing so. The investigators may stop your participation without your permission under any one of the following conditions:

- Your PTSD symptoms remain unchanged or worsen.
- Side effects become very severe.
- Your study doctor believes that participation in the research is not safe for you.
- Your study doctor believes that other treatment may be more helpful.
- The investigators stop the research for the safety of the participants.
- You fail to keep appointments or to follow your study doctor's recommendations.

The study investigators may stop your participation in the extension phase as well if one or more of the conditions outlined above are met.

If you become ill during the research, you may have to drop out, even if you would like to continue. The investigator will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate. If the study doctor or the sponsor stops your participation in the research, it is your responsibility to do the following:

- Return to the research center for tests that may be needed for your safety.
- Discuss your future medical care with your study doctor and/or your regular doctor.

**PERSONS TO CONTACT ABOUT THIS STUDY**

***If you have any questions about the research, or if you experience a research related injury or adverse reaction, please contact one of the following investigators:***

| | |
|---|---|
| Andrew Leuchter, M.D., Principal Investigator | (310) 825-0207 |
| Bruce Kagan, M.D., Co-investigator | (310) 206-2372 |
| Mark Barad, M.D., Co-investigator | (310) 849-9055 |
| Aimee Hunter, Ph.D., Co-investigator | (310) 206-2237 |

**Participant Name**: _____ Date: _____

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

**Principal Investigator**: Dr. Andrew F. Leuchter **Contact number:** (310) 825-0207

**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

Michelle Abrams, Study Coordinator (310) 825-0797

If you have questions that arise after normal business hours, you may call Dr. Andrew Leuchter at (310) 825-0207 or (310)825-0511. The address for Dr. Leuchter is the UCLA Depression Research and Clinic Program, 760 Westwood Plaza, Suite 57-456, Los Angeles, CA 90095.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Greater Los Angeles Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Greater Los Angeles IRB toll free at 1-310-268-4437 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

**SIGNIFICANT NEW FINDINGS**

During the course of this research study, new information may become available about the Monarch eTNS™ System that is being studied that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arranges for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

**FUTURE USE OF DATA**

Your data from this study will be retained after the study for future research. The physical research records will be stored in locked file cabinets within locked offices at the UCLA Semel Institute. 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 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.

**Participant Name**: _____ Date: _____

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

**Principal Investigator**: Dr. Andrew F. Leuchter **Contact number:** (310) 825-0207

**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

## AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr. Andrew F. Leuchter and his research team have explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record if applicable.

| **I agree to participate in this research study as has been explained in this document.** | | |
|---|---|---|
| _____<br>Participant's Name | _____<br>Participant's Signature | _____<br>Date |
| _____<br>Name of person obtaining consent | _____<br>Signature of person obtaining consent | _____<br>Date |

**Participant Name**: _____ Date: _____

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

**Principal Investigator**: Dr. Andrew F. Leuchter **Contact number:** (310) 825-0207

**Principal Investigator for Multisite Study**: Dr. Andrew F. Leuchter

## RIGHTS OF HUMAN SUBJECTS IN MEDICAL EXPERIMENTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given an opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.