Transcutaneous Vagal Nerve Stimulation Improvement of Sleep Quality in Veterans with PTSD with or without History of Mild TBI

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U.S. Department of Veterans Affairs, Brain Rehabilitation and Research Center

Department of Veterans Affairs | VA RESEARCH CONSENT FORM

Subject Name: _____ **Date** _____

Title of Study: Non-invasive vagal nerve stimulation and sleep Phase 2

Principal Investigator: John B. Williamson **VAMC:** North Florida/South Georgia Veterans Health System

UF Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any VA or other benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research subject, concerns, complaints, wish to discuss problems or talk to someone independent of the research staff, obtain information, or offer input, please call either of the following offices: (1) the University of Florida Institutional Review Board (IRB) office at (352) 273-9600; or (2) the North Florida/South Georgia Veteran's Health System Research Service Office at (352) 548-6069.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

Department of Veterans Affairs

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For PI Use:

Participant Social Security Number: _____

SSN should be written on this consent form by the research team prior to scanning into the VHA health record; if the subject does not have a VHA health record, this requirement is N/A.

2. What is the Title of this research study?

Non-invasive vagal nerve stimulation and sleep

3. Who can you call if you have questions/concerns, or complaints about this research study?

Principal Investigator: John B Williamson [redacted]

Other research staff: Damon Lamb [redacted], Eric Porges [redacted], Michael Jaffe [redacted]

4. Who is paying for this research study?

The sponsor of this study is the Department of Veterans Affairs.

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board **(IRB) office at (352) 273-9600** or the North Florida/South Georgia Veteran's Health System Research Service Office at (352) 548-6069.

a) In general, what is the purpose of the research, how long will you be involved?

The purpose of this research study is to understand sleep problems in people with chronic stress including PTSD and how non-invasive nerve stimulation may work to help people sleep. The protocol involved three or four sessions, an approximately 1 hour interview in which we will explain the project to you and assess you for inclusion in the study, and two or three sleep visits at a sleep clinic.

In the morning of each sleep visit, we will test aspects of thinking and autonomic (e.g., heart) functions.

b) What is involved with your participation, and what are the procedures to be followed in the research?

You will perform an intake session, where you will sign an informed consent. You will be given a health history questionnaire, as well as questionnaires on your mood and sleep quality. We will assess your cognition and memory. You will be asked to wear an actigraph (a watch like device that measures your sleep at home) for the week after each sleep visit.

During the sleep studies, you will be hooked up to electrophysiological and other passive monitoring equipment. You will receive non-invasive nerve stimulation for the first hour of sleep. We will assess your mood and cognition the following morning with an additional hour of testing.

c) What are the likely risks or discomforts to you?

You will receive nerve stimulation, which can occasionally cause discomfort at the stimulation site. This usually goes away quickly by turning down the stimulation. Please tell us if it is uncomfortable. You will undergo polysomnographies, which involve the application of gel electrodes. These can cause minor skin irritation. Hair samples will be taken from your head. Saliva samples will be taken from your mouth. The collection happens by placing a swab underneath your tongue. You will be given questionnaires about mood and cognition These methods may cause mild and temporary discomfort.

d) What are the likely benefits to you or to others from the research?

This is an experimental research study. No long term benefits are expected from participation in this study. In the short term (during and perhaps a little bit after), you may experience a good night's sleep and better cognitive and mood functioning the next morning/day. Ultimately, our purpose is to develop a treatment for sleep problems in PTSD and thus, others may benefit in the future.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

PTSD and sleep problems can be treated through a variety of psychological or pharmacological interventions, if necessary. You should consult with your primary care physician to determine the best avenue for treatment for your specific case, if necessary.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study.

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

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

Normal clinical care is medical or other treatment or services that you would receive even if you did not participate in this research study.

This is a research study and will not affect your normal clinical care. Parts of our evaluation are sometimes used in clinical settings. All data collected in this study are intended for research purposes. Though some tests that we use are also used in clinical assessments, we are not evaluating the tests in that manner and, thus, no clinical judgments will be made. If you have any issues that you need to address, clinically, please contact the appropriate professional. If, in the course of examining the data, one of the researchers notices something that may be clinically significant, we will attempt to notify you and suggest action. For example, you will be asked about thoughts regarding self-harm (suicide). If you say you are thinking about suicide, we may refer you to emergency services.

7. What will be done only because you are in this research study?

You will be asked to complete two or three sleep studies. At the beginning of each sleep study, we will collect your saliva. During each sleep study, you will receive electrical stimulation of your skin around your ear for part of the time. Before the sleep study, we will ask you to answer some questions about your sleep via interview and filling out forms. We will also ask you about your mood and we will assess aspects of your thinking abilities. We will review your medical history including health status (e.g., high blood pressure) and alcohol and drug use. In the morning of each sleep study, we will assess your thinking and mood (Behavioral) again using a few different kinds of tests. We will also collect your saliva once more in the morning, making two

samples per sleep study. We will only collect one hair sample during the entire duration of the study. It will be a part of the proceedings of one of the sleep studies.

1) **Behavioral (thinking) Assessments**: These tasks will consist of paper and pencil tests of things like how fast you can complete tasks with numbers, test of memory skills, drawing skills, or organizational skills. Emotional and other tasks will consist of questionnaires that will assess things like depression, anxiety, sleep, headaches, personality traits (e.g., if you like being amongst large groups of people, or by yourself), and your opinion of the intensity and mood (e.g., happy, sad) of pictures and faces. If you have already participated in one of the research studies in the Brain Rehablitation Research Center (BRRC) we may use some of the measures you hve already completed to shorten the time to complete these study visits. Likewise, we may share data from psychological assessments with other studies in which you enroll to shorten the assessments used in those other studies.

2) **Sleep study/autonomic**: Aside from non-invasive vagal nerve stimulation, we will complete a standard sleep study as well as ask to wear an actigraph (watch form factor that measures sleep) for a week after each sleep study. Sleep studies require that you sleep in a sleep laboratory while being monitored by electrophysiological equipment. This includes electroencephalogram (EEG, brain activity measurement) and autonomic and muscle activity indicators. These signals are detected with electrical sensors such as electrodes that are placed on the body. All of the electrodes are passive, meaning that there is no electric current or stimulation that will pass through the electrode. We will also measure these signals while you perform some of the behavioral tasks. Video monitoring is also part of a standard sleep study. Tehcnicians use it to monitor you while you sleep in case you need to get up to use the bathroom and also to note activity during sleep to interpret the physiological data. We will not keep the video with the research records.

3) **Non-invasive Nerve Stimulation:** If you are a woman of child bearing potential, we will perform a pregnancy test and the result must be negative to receive stimulation. If you decide to take part in this study, you will receive electrical stimulation of two different locations on your ear.

   Stimulation will be completed with an external/transcutaneous vagal nerve stimulator (tVNS). You will receive stimulation for up to 60 minutes continuously (e.g., during the sleep study). A small stimulating electrode similar to an earbud headphone or a soft earplug will be placed in your ear canal and on your ear lobe. This stimulus intensity will be adjusted from 0 (nothing) up to a level which is

Subject Name: _____ Date _____

Title of Study: Non-invasive vagal nerve stimulation and sleep Phase 2

Principal Investigator: John B. Williamson VAMC: North Florida/South Georgia Veterans Health System

effective but not painful or particularly uncomfortable, described as “comfortable electro-massaging sensation” in previous studies of this kind of stimulation. You might also feel a slight tingling or prickling sensation during stimulation. Stimulation will be performed during sleep.

4) Saliva collection: During each sleep study we are going to collect two saliva samples from you. One will be at night once we have you situated in the sleep clinic, and the other sample will be taken in the morning soon after you have woken up. The samples require an absorbant cotton swab to be placed under the tongue for 1-5 minutes. After the time is up, the swabs are collected and stored for processing. We will be using these samples to help track your stress levels throughout the study.

5) Hair collection: During one of the sleep studies, we will collect a small hair sample from the back of the head using scissors. We will also be using these samples to help track your stress levels.

6) At the end of the final sleep study: Your participation will be ended in the study. You will not be given any of the results for the measures within the entire study, but we might contact you if we find some concerning details with the results (e.g., unreported sleep apnea). You will be able to relay this information to your primary care physician, if necessary. At the very end of the visit, we will answer any questions that you have about the study. If you have any additional questions or concerns after this visit, you may reach out to the study team at any time. There is a contact number on this form (see item number 3 on page 2).

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information or identifiable biospecimens collected and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

If you have any questions now or at any time during this Research Study, please contact one of the Research Team members listed in question 3 of this form.

8. How long will you be in this research study?

There will be three or four sessions. In the first, we will meet with you, discuss this consent form, and complete screening tools for inclusion in the study. This should take approximately one hour. There will be two or three sleep studies and each will

Subject Name: _____ Date _____

Title of Study: Non-invasive vagal nerve stimulation and sleep Phase 2

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take approximately 8 hours with about an hour each morning for cognitive and mood assessment.

9. How many people are expected to take part in this research study?

We expect approximately 274 people to participate in the study.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

Researchers will take appropriate steps to protect any information they collect about you. However there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass you, or possibly even affect your insurability or employability.

Other possible risks to you may include:

Behavioral (cognitive or thinking) Assessments: Some people find tests of thinking to be frustrating, therefore frustration is a risk. Further, questions about mood and personality can sometimes be uncomfortable (e.g., talking about things that make you sad or anxious). Some of the pictures we will show you depict violence (e.g., military scenes, a growling dog). Though likely little different than what you might find on television, these scenes can, and are intended, to evoke an emotional reaction. Some people may be more sensitive to these kinds of pictures depending on their experiences (e.g., people who have experienced traumatic events).

We will be asking you for information about sensitive issues, such as your mood, thoughts of suicide, and substance use, which may make you feel uncomfortable. You can choose not to answer any of the questions and you may discontinue participation in the study at any time. If you are feeling depressed or suicidal, you are strongly encouraged to tell the Principal Investigator, who will talk to you and can make an appropriate referral to a psychologist or mental health services. If we find that you are at immediate risk for suicide, you will be excluded from further participation in the study and an appropriate referral will be made. If we should discover, based on the questionnaires or formal clinical interview, that you

Subject Name: _____ Date _____

Title of Study: Non-invasive vagal nerve stimulation and sleep Phase 2

Principal Investigator: John B. Williamson VAMC: North Florida/South Georgia Veterans Health System

experience marked depression or suffer from another psychiatric condition, we will offer to make an appropriate medical, psychiatric, and/or psychological referral.

Autonomic/Psychophysiological Assessments: The electrodes are sticky. Removing them may feel like pulling off a bandaid. Further, we use a gel to make it easier for the electrodes to pick up a signal. Though the gel is hypoallergenic, if you experience skin irritation, we will remove the electrodes and rinse off the affected area.

Non-invasive Nerve Stimulator: Previous studies using electrical stimulation found that some side effects may occur including itching, discomfort, and local pain at the stimulation site. These side effects usually end shortly after stopping stimulation. If the electrodes are not well placed then you might experience mild pain, although the researchers will adjust the electrode placement if this happens.

Saliva collection: The placement of the absorbant swab could be mildly uncomfortable for some to hold in their mouth for 1-5 minutes. If you experience irritation or discomfort from the swab, we will have it removed and allow time for discomfort to go away.

Hair collection: The collection of hair samples could possibly create some minor discomfort as a small amount of hair is to be removed. The hair will be cut as close to the scalp as possible, so some irritation or redness could occur.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this consent form or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of any new information that may become available and might affect your decision to remain in this study. This includes, but is not limited to, information that may affect your safety, well-being or medical care.

If you wish to discuss the risks or discomforts described above or any discomforts you may experience, please ask questions now or call one of the research team members listed in question 3 of this form.

11a. What are the potential benefits to you for taking part in this research study ?

This is an experimental research study. No long term benefits are expected from participation in this study. In the short term (during and perhaps a little bit after), you may experience a good night's sleep and better cognitive and mood functioning the next morning/day.

11b. How could others possibly benefit from this study?

The results of this study may help us develop an effective treatment for sleep problems that could improve mood and thinking in people with history of PTSD.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator listed in question may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

Participation is completely voluntary. You can choose not to participate in the study. This decision will not impact your healthcare in any way.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

If you decide to withdraw your consent to participate in this study for any reason, please contact one of the research team members listed in question 3 of this form.

If you have any questions regarding your rights as a research subject, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from this study, your research information will no longer be collected. However, information that has already been collected will continue to be used to the extent that the researchers have used it in this research study.

Subject Name: _____ Date _____

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13c. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- You are unable to understand the directions for the study.
- You do not meet the eligibility criteria for the study including medical history and other aspects necessary for the study.
- You show signs of discomfort from the procedure.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

There will be no costs to you for any procedure, treatment or testing done as part of this research study.

15. Will you be paid for taking part in this study?

You will be paid $325.00 at the completion of the study (allowing for paperwork processing time of the VA). If you come in for the study and sign the informed consent form, but withdraw before completing both sleep study sessions, you will be offered $25.00.

The US Treasury requires that all participants in this study receive their study related compensation as an electronic transfer of money directly to your bank account, or placed on a special debit card. If you are already set up to receive VA benefit payments electronically, then there is nothing that you need to do. If you are not already set up to receive VA benefit payments directly to your bank account then you will be directed to the VA Finance Office.

Your compensation for participation in this research study will come from the VA Finance Office, who will issue payment to you by direct deposit to your bank account. If it is not possible for you to receive payment by direct deposit, you may have payment sent to a pre-paid debit card. If you use a pre-paid debit card you will be required to maintain this card throughout the study as all study payments will be deposited to the card. The study team will provide you with additional information regarding electronic funds transfers.

You may be responsible for paying income taxes on any payments provided by the study. Any payment made to you on a VA-funded study, regardless of amount, has to

be reported to the Internal Revenue Service (IRS) because the payment system cannot distinguish payment from reimbursement for expenses.

16. What if you are injured because of the study?

If you experience an injury or illness as a result of your participation in this VA approved research study, all medical treatment considered necessary by your physician (emergency as well as medical treatment beyond emergency) will be provided by the Malcom Randall VA. There will be no cost to you, (or your insurance) unless you fail to follow the directions of the study procedures. Care will be provided at a VA medical facility unless the VA medical facility is not capable of providing the care. If this occurs, you will be treated by a private facility or physician and the VA will pay the private facility or physician for the reasonable cost of your care. In some cases the VA may approve private care for a non-veteran. If you usually pay co-payments for VA care and medications, these co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If you do not follow study procedures, you may be treated by the VA on the basis of your veteran's eligibility. If you are not a veteran and have not followed study procedures the VA can only provide limited care at your expense.

No additional money has been set aside for pain, suffering or any money losses you may suffer during your treatment. You have not waived any legal rights by signing this form.

In the event of a research-related injury, have questions about any discomforts that you experience while participating in this study or if you experience an adverse reaction, please immediately contact the Principal Investigator listed in question 3 of this form during the day and your local emergency service or 911 after business hours. If you seek emergency hospitalization in a private hospital because you are unable to come to the VA, have a family or friend contact your study doctor so that the VA can coordinate care with the private hospital.

17. How will your privacy and the confidentiality of your research records be protected?

Information collected about you will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the legal right to review these research records, and they will protect the secrecy (confidentiality) of these records

as much as the law allows. These people include the researchers for this study, certain University of Florida officials, the hospital or clinic (if any) involved in this research, and the Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research). Certain federal agencies such as the Office for Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), the Federal Drug Administration (FDA) or the VA Office of the Inspector General (OIG), that oversee human subject research may also have the legal right to review your records. Otherwise your research records will not be released without your permission unless required by law or a court order.

Researchers will take appropriate steps to protect any information they collect about you. However there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass you, or possibly even affect your insurability or employability.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

Department of Veterans Affairs

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SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how privacy will be protected:

_____ _____

Signature of Person Obtaining Consent Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your privacy will be protected. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Person Consenting Date