Wake Forest®
School of Medicine

RANDOMIZED CONTROLLED PILOT TRIAL OF HIRREM-SOP FOR INSOMNIA

Informed Consent Form to Participate in Research
Charles H. Tegeler, M.D., Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is study is to determine the effects of HIRREM-SOP, an updated version of technology that is based on the HIRREM approach, but includes new hardware and software, a standard series of HIRREM protocols, and a fixed number of sessions.

HIRREM-SOP uses scalp sensors to monitor brainwaves, and computer software translates selected brain frequencies into audible tones in real time. Those tones (acoustic stimulation) are mirrored back to participants via ear buds in as little as four milliseconds, giving the brain an opportunity to self-adjust and balance its electrical pattern. It is noninvasive, which means it will not cause pain or break the skin in any way. The HIRREM technology was created by Brain State Technologies, LLC, Scottsdale, AZ, and is FDA-exempt when used for relaxation and self-regulation. HIRREM-SOP is not an FDA approved medical device, and is not intended to treat, cure, heal, or diagnose any specific disease, mental illness or symptom, and individual results and duration of effects may vary.

You are invited to be in this study because you have trouble sleeping. Your participation in this research will involve three study visits and 10 intervention sessions listening to audible tones that are or are not linked to your brainwaves and will last up to 3 months.

All research studies involve some risks. A risk to this study that you should be aware of is temporary worsening of sleep, awareness of emotions and/or temporary head fullness/mild headache, or fatigue. It is possible that you may benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. You may speak with your doctor about those choices. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, please contact the Study Coordinator at (336) 716-9447 or WFHIRREM@wakehealth.edu.

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at (336) 716-4542 or the Research Subject Advocate at (336) 716-8372.

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have trouble sleeping. Your participation is voluntary. Please take your time in making your decision about whether or not you wish to participate. Ask your doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Prior research studies have shown benefit for use of a technique called High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®), to reduce symptoms of moderate to severe insomnia.

The purpose of this research study is to evaluate the effects of HIRREM-SOP, an updated version of this technology that is based on the HIRREM approach, but uses new hardware and software, a standard series of HIRREM protocols, and a fixed number of sessions. Adults over the age of 18 who have documented sleep trouble that places them in the category of at least mild, or worse clinical insomnia as defined by the Insomnia Severity Index, are eligible to participate in the study. The study will compare the addition of either acoustic stimulation linked to brainwave activity (HIRREM-SOP, BCC), with nonspecific acoustic stimulation that is not linked to brainwave activity (randomly generated tones, NCC), in addition to continued use of your current care for insomnia. Acoustic stimulation, whether based on readings of your brainwaves, or nonspecific tones, may help your brain to achieve a more balanced pattern, and reduce insomnia. In this study you will continue your other current care, but will also receive sessions of either BCC or NCC.

HIRREM-SOP is an investigational device. This means it has not been approved by the U.S. Food and Drug Administration (FDA). Drugs and devices that do not have approval by the FDA cannot be sold or prescribed by your physician.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The goal is to have enroll up to 24 participants so as to have at least 20 complete all study procedures and visits. Half of the participants will randomly be assigned to receive BCC, and the other half will be assigned to receive NCC.

WHAT IS INVOLVED IN THE STUDY?

If you choose to participate in this study, you will be scheduled to be at the Department of Neurology, Suite 504, Piedmont Plaza II Building, for three study visits and 10 sessions of BCC or NCC. Visit #1 is an enrollment and baseline data collection visit that will take approximately 45-60 minutes. During this visit, the study will be explained to you in detail, any questions you have will be answered, and your informed consent will be obtained.

Your brief medical history will be reviewed, and you will also complete some questionnaires, and have your blood pressure and heart rate monitored. You will be randomly assigned into one of two study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group. Neither you, the Study Coordinator, or the Principal Investigator will know which study device you are receiving. This information is available to the researchers if needed in an emergency. You will then begin a course of sessions of BCC or NCC. Sessions will begin within 0-14 days of the enrollment visit. Sessions will be given over the four weeks that follow. Although you are enrolled in the study you will continue your other current care for insomnia. If you are randomized to the NCC group, following Visit #3, you will be given an opportunity to receive a course of BCC, to begin within one month of Visit #3.

At Visit #1 (V1, enrollment, 0-14 days prior to intervention):

- You will be asked to provide informed consent to participate in the study.
- You will be asked to complete some electronic questionnaires on a computer. You will be asked questions regarding your sleep pattern, general daily practices, and stress. These questions have no right or wrong answers. You will simply respond to the questions based on your current experiences. The questionnaires will be explained to you.
- Your blood pressure and heart rate will be monitored for 10 minutes while you are lying down.
- All activities for V1 will take about 45-60 minutes to complete.

At Visit #2 (V2, for repeat data collection, 0-14 days after the completion of your last session, the same questionnaires and tasks from V1, will be repeated):

- You will be asked to complete some electronic questionnaires on a computer. You will be asked questions regarding your sleep, general daily practices, and stress. The questions you will be asked have no right or wrong answers. You will simply respond to the questions based on your current experiences. The questionnaires will be explained to you.
- Your blood pressure and heart rate will be monitored for 10 minutes.
- The V2 visit is expected to take up to 45 minutes.

At Visit #3 (V3, for repeat data collection, 4-6 weeks after V2):

- You will be asked to complete some electronic questionnaires on a computer. You will be asked questions regarding your sleep, general daily practices, and stress. The questions you will be

asked have no right or wrong answers. You will simply respond to the questions based on your current experiences. The questionnaires will be explained to you.

- Your blood pressure and heart rate will be monitored for 10 minutes.
- The V3 visit is expected to take about 45-60 minutes.

Study sessions are typically 1-1.5 hours in length. Participants will must be able to receive the first two sessions on consecutive days when beginning the intervention, and the first three sessions within five calendar days. After the first two sessions (single sessions on consecutive days), sessions may be scheduled with two per day, including a break of at least one hour between sessions. Although circumstances may not allow it, every attempt will be made to complete all ten sessions within a two-week period. There should not be more than 5 days between any sessions.

Sessions will begin with a Technologist checking in to ask how you are doing. During the sessions you will be comfortably at rest, sitting or reclining. For the sessions, sensors will be placed over the specific areas on the scalp corresponding with brain regions/lobes to be observed. Most sessions will last about 60-90 minutes and consist of 4 to 6 protocols. Protocols will be done in pairs to limit interruptions for sensor placement changes, and the pair of protocols will last from 12-30 minutes. The computer automatically switches to the other sensor pair. All sessions are done eyes closed, so both groups will be able to fall asleep if they wish, or just relax.

Sometime between 0-14 days after sessions are completed, you will have a data collection visit (Visit #2). All measures will be repeated. Between 4-6 weeks after completion of the Visit #2 there will be a final data collection visit (Visit #3). The same measures as Visit #2 will be repeated. Although official involvement in the study will be completed at Visit #3 for those in the BCC group, those who were in the NCC group will be offered a chance to be scheduled to receive a course of acoustic stimulation linked to brainwaves.

If you request it, we can provide you with information about your study participation which you may share with your personal health care provider. Even if you do not wish to have any information sent to your health care provider, you can still participate in this research study.

HOW LONG WILL I BE IN THE STUDY?

Those assigned to the BCC group will be in the study for up to 3 months. Those assigned to the NCC group, who following Visit #3 choose to receive a course of acoustic stimulation linked to brainwaves, will be in the study for up to 6 months.

You can stop participating at any time during the course of this research study. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Based on experience reported by Brain State Technologies, including information gathered through case management support, feedback from their clients, and feedback from the HIRREM provider community, as well as results from IRB-approved studies evaluating HIRREM at WFSM (now about 500 participants who have received HIRREM), the study team is not aware of any serious adverse events resulting from HIRREM sessions.

Non-serious, temporary effects have been reported by participants in prior studies. That includes things like being more aware of, or more affected by their feelings, or by those around them, changes in sleep, including dreams, emotions, or energy levels, or a feeling of fullness in the head or mild headache. In the course of provision of HIRREM as part of five IRB-approved studies at WFSM, such non-serious, temporary effects have been estimated to occur in ten percent or less of participants. In a recent placebo controlled trial of HIRREM for moderate to severe insomnia (n = 107), such non-serious, temporary adverse effects that were judged to go beyond the intensity, expression, or nature of pre-existing health conditions, were reported by 10.7% in the HIRREM group, and 13.7% in the placebo group. All episodes were brief, typically resolving in hours to 1-2 days, but at the most resolving in less than one week. Skin irritation at the site from the paste used to affix a sensor to the scalp was reported by one participant (personal communication).

Since HIRREM-SOP uses the same core technology and approach, it is expected that the safety profile for HIRREM-SOP will be similar to that of HIRREM. There are no recognized risks for listening to nonspecific acoustic stimulation not linked to brainwaves.

You may find some of the questions involved in the testing during data collection visits as stressful. If you feel uncomfortable please let your doctor or the research staff know about this.

As part of this study, you will be asked questions about previous physical and non-physical trauma, current stresses, and mood. If we learn that you or someone else is in danger of harm, the study team is required to report that information to the proper authorities.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may

help avoid side effects, interactions and other risks.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Charles Tegeler at (336) 716-9447 or (336) 716-7651.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. A benefit of participation in this study may be improvement in your sleep.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All costs related directly to study procedures, including the sessions, will be paid for by the study.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

WILL YOU BE PAID FOR PARTICIPATING?

Participants in this research project will receive $100 in monetary compensation for time related to study visits. Participants who do not complete the entire study will receive a prorated portion of this amount ($25 each for completion of V1, the interventions, V2, and V3). There is no additional compensation available for those who choose to cross over to receive HIRREM-SOP (visits V4-V5).

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.
The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being supported by a research grant from, The Susanne Marcus Collins Foundation, Inc. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

What About My Health Information?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes but is not limited to, such things as your name, address, telephone number, and date of birth.

Brain State Technologies, LLC (BST) will assist with brain pattern analysis. To accomplish this, BST will be provided with the first 8 characters from the randomly generated, 36 alpha numeric character identifier that the HIRREM software generates for each participant's brain frequency and amplitude data, along

with the participant's age and gender, which are believed important for understanding brain patterns. No other participant-specific information is provided.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept indefinitely. This authorization does not expire. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Charles H. Tegeler that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Charles H. Tegeler, M.D.
Department of Neurology

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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 Web site at any time.

For the purpose of scheduling your study visits and HIRREM sessions, a North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants, if one has not already been created. Your name, address, phone number, email address, gender, race/ethnicity, employment status and date of birth, and the fact that you are participating in a research study, will be entered. No personal health information regarding you, or this research study, will be entered. Only in the case of emergency will other personnel directly involved with your care have access to this information in WakeOne.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because you failed to follow instructions, your condition worsened or the study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

This study may enroll students from the Wake Forest University and/or Wake Forest University Medical

Center campus. In addition to your rights as a research participant noted in the previous section, as a student, you are under no obligation to participate in this study. You may refuse to participate or withdraw from the study at any time and for any reason without affecting your grades, performance evaluations, or assignments. You will not be pressured into participating in this research study by any statements or implied statements that your grades, performance evaluations or assignments will be affected by your willingness to enroll in the study. Your medical records/information will not be used by the faculty, administration or study staff to make decisions regarding the status of your medical benefits. If you have questions regarding your enrollment in the study and your status as a medical student, please contact the Office of Student Services for additional information.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Charles H. Tegeler at (336) 716-7651 or (336) 716-4101.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at (336) 716-4542 or the Research Subject Advocate at (336) 716-8372.

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed): _____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed): _____

Person Obtaining Consent: _____ Date: _____Time:_____ am pm