Official Title: High-Resolution, Relational, Resonance-Based, Electroencephalic Mirroring (HIRREM) for Vasomotor Symptoms (Hot Flashes) in Perimenopausal and Postmenopausal Women: A Randomized, Controlled Clinical Trial
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Wake Forest®
School of Medicine

Department/Section of Neurology

HIGH-RESOLUTION, RELATIONAL, RESONANCE-BASED, ELECTROENCEPHALIC MIRRORING (HIRREM) FOR VASOMOTOR SYMPTOMS (HOT FLASHES) IN PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN: A RANDOMIZED, CONTROLLED CLINICAL TRIAL

Informed Consent Form to Participate in Research

Charles H. Tegeler, M.D., Principal Investigator

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 experience menopause-related hot flashes. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study 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?

The purpose of this research study is to determine the effects of a technique called High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®), for women in any stage of menopause, who are experiencing menopause-related hot flashes. HIRREM uses scalp sensors to monitor brain electrical activity, and software algorithms translate selected brain frequencies into audible tones in real time. Those tones are reflected back to participants via ear buds in as little as four milliseconds, providing 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. It is a computer-based technology that may help reduce the frequency and severity of your hot flashes by using auditory tones that are played back based on readings of your brain's electrical frequencies, to help achieve a more balanced pattern. The HIRREM technology was created by Brain State Technologies, LLC, Scottsdale, AZ, and is FDA-exempt when used for relaxation and self-regulation. HIRREM 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. Women over the age of 40 who are entering, are within, or who have completed menopause, and who have a history of at least 5 hot flashes per day (one of which is moderate or severe) may be eligible to participate in the study. Women who are pregnant, or anticipate becoming pregnant, who have menopausal symptoms due to surgery, medications, radiation, or chemotherapy, or who are using medications, hormone replacement, or supplements for menopause management are not eligible to participate.

This study will compare acoustic stimulation linked to brainwave activity (HIRREM plus continued current care, HCC), with continued current clinical care alone (CCC). Both groups will continue their other current care throughout, including non-pharmacological, and lifestyle modification therapies.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Up to 48 participants will be enrolled in order to reach the goal of having 40 complete the study. Half of the participants will randomly be assigned to receive HCC, and the other half will be assigned to CCC. Participants in CCC group will be offered an opportunity to receive HCC after their initial participation is complete.

WHAT IS INVOLVED IN THE STUDY?

If you choose to participate in this study you will be scheduled to be at Wake Forest School of Medicine, Suite 504, Piedmont Plaza II Building, for three study visits and 8-16 sessions of HCC. Visit #1 is an enrollment and baseline data collection visit that will take approximately 2 hours. 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.

If you meet the inclusion criteria, a brief medical history will be obtained, and you will also complete some questionnaires, have your blood pressure and heart rate monitored, perform a reaction time test, a grip strength test, and have a brainwave assessment. For 7-14 days after your Visit #1, you will keep a daily hot flash diary. 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. You will then begin a course of sessions of HCC (HIRREM, acoustic stimulation linked to your brainwaves) or CCC (continued current care). Sessions will begin within 7-14 days of the enrollment visit. You will continue your other current care. HCC sessions will be administered within the 4 weeks that follow. Follow up data collections will also be done at about 1 month (Visit #2, 4-6 weeks), and about 3 months (Visit #3, 12-14 weeks), after the last session is completed. For 7-14 days before Visit #2 and Visit #3 you will keep daily hot flash diaries. Following V3, those in the CCC group will be offered an opportunity to receive a course of HCC within 3 months. Those who accept will continue to be followed for data collections at 4-6 weeks (V4), and 12-14 weeks (V5) after completing their HIRREM sessions. You will also be asked to keep daily hot flash diaries for 7-14 days before Visit #4 and Visit #5.

At Visit #1 (V1, enrollment, baseline data collection):

- You will be asked to provide informed consent to participate in the study.
- A brief medical history will be obtained.
- You will be asked to complete some online electronic questionnaires on a computer. These questions have no right or wrong answers. You will simply respond to how strongly you agree or disagree with something. The questionnaires will be explained to you.
- You will be asked questions about your hot flashes, your sleep pattern, your mood, your overall

health, your alcohol use, and your general daily practices.

- Your blood pressure and heart rate will be monitored for 10 minutes while you are lying down.
- Your reaction time will be tested by having you grasp a dropped wooden stick.
- Your grip strength will be tested by having you grip a hand dynamometer.
- You will be shown how to complete the daily hot flash diary to keep for 7-14 days after Visit #1.
- A brainwave assessment will be obtained. This assessment will evaluate the electrical frequencies of your brain. For this assessment you will be sitting in a chair and the HIRREM Technologist will place sensors over multiple areas of your head to record data while the brain is at rest, or on task, with eyes closed and eyes open. The sensors look like pads that will be placed with special paste. It will not hurt. The sensors have tiny computer chips that will allow collection of data on the frequencies from the brain. This brainwave assessment takes about 30-45 minutes to complete.
- You will be randomly assigned into one of two study groups.
- All activities for Visit #1 will take about 120 minutes to complete.

At Visit #2 (V2, 4-6 weeks after last HCC session or 10-12 weeks after V1 for CCC):

- You will again be asked to complete some online questionnaires on a computer.
- You will be asked questions regarding your hot flashes, your sleep pattern, your mood, your overall health, your alcohol use, and your general daily practices.
- Your blood pressure and heart rate will be monitored for 10 minutes.
- Your reaction time will be tested by having you grasp a dropped wooden stick.
- Your grip strength will be tested by having you grip a hand dynamometer.
- A brainwave assessment will also be obtained.
- Testing at Visit #2 is expected to take about 90-120 minutes.

At Visit #3 (V4, 12-14 weeks after last HCC session or 18-20 weeks after V1 for CCC):

- You will again be asked to complete some online questionnaires on a computer.
- You will be asked questions regarding your hot flashes, your sleep pattern, your mood, your overall health, your alcohol use, and your general daily practices.
- Your blood pressure and heart rate will be monitored for 10 minutes.
- Your reaction time will be tested by having you grasp a dropped wooden stick.
- Your grip strength will be tested by having you grip a hand dynamometer.
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- If you were in the CCC group, you will then be offered an opportunity to be scheduled to receive a course of active HCC sessions. Testing at Visit #3 is expected to take 45 minutes.

All baseline measures, along with a brainwave assessment, will be obtained during the enrollment visit (Visit #1). HCC sessions will begin 7-14 days following Visit #1. You will receive 8-16 HCC sessions over a 4 week period, although we hope that at least 10 sessions can be completed within 2 weeks. HCC sessions will be about 1.5-2 hours in length. It is possible for you to receive 2 sessions during a half day

period. You must be able to receive the first 6 sessions on three consecutive days during the intervention period. You will be encouraged to complete the remainder of the sessions within two to three weeks, but in no longer than four weeks. You may not go longer than 5 days between sessions. If done as 2 sessions per half day, you would be involved for between 4-8 half days during the intervention period. Following the initial 6 sessions, some sessions may be arranged as singles (1 per day), if needed, due to schedule issues.

The sessions will typically be about 1.5-2 hours in length. For the sessions, you will be comfortably at rest, sitting or reclining. For the HCC sessions, sensors will be placed over the specific areas on the scalp corresponding with brain regions/lobes to be observed. During each session, the sensors may be placed onto 4-10 different locations, with 6 to 40 minutes spent at each location. When eyes are to remain open you will be able to read a book, do a word search, or just relax. When eyes are to remain closed, you will be able to fall asleep if they would like, or just relax.

Between 4-6 weeks after completion of the HCC sessions there will be a data collection visit (Visit #2, 10-12 weeks after V1 for CCC). You will be asked to keep a daily hot flash diary for 7-14 days before Visit #2. All measures will be repeated, as well as a brainwave assessment. A final data collection visit (Visit #3, 18-20 weeks for CCC) will occur 12-14 weeks after completion of the HCC sessions, with repeat of all of the outcome measures, other than the brainwave assessment. You will be asked to keep a daily hot flash diary for 7-14 days before Visit #3. Although official involvement in the study will be completed at Visit #3 for those in the HCC group, those who were in the CCC group will be offered a chance to be scheduled to receive a course of HCC within 3 months. Participants originally in the CCC group who choose to pursue a course of HCC will also get a brainwave assessment 0-14 days before beginning sessions.

As part of this research study, electrical frequencies from your brain will be recorded and analyzed using sensors placed on various locations on your scalp during the brainwave assessment. For those who receive HCC sessions, the instrument also uses the frequencies to determine which musical tones you will hear in the earbuds. This mirroring of brainwaves using audible tones allows the brain an opportunity to self-adjust and to improve the balance in the brain frequencies, which may lead to improvement in your menopause related symptoms and other aspects of brain functioning. You may request that your participation be stopped at any time during the course of the research study.

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 HCC group will be in the study for up to 5 months, to include an enrollment visit, up to 2 weeks before the sessions begin while completing the daily hot flash diary, 2-4 weeks of

sessions, 4-6 weeks until the Visit #2, and a final study completion Visit #3, 12-14 weeks after completion of sessions. Those assigned to the CCC group, who following Visit #3 choose to receive a course of HCC sessions, will be in the study for up to 10 months. This will also include follow up data collection visits after the course of HCC, including Visit #4, 4-6 weeks, and Visit #5, 12-14 weeks after completing the HCC sessions.

You can stop participating at any time. 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?

Among over 480 participants enrolled in one of five IRB-approved research studies at WFSM, no serious adverse events have been reported. Non-serious, temporary effects have been reported by participants in other studies. This includes things such as participant reporting 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 research studies at WFSM, such non-serious, temporary effects were estimated to occur in ten percent or less of participants. Based on analysis of a placebo controlled trial of HIRREM for moderate to severe insomnia, among 107 participants such non-serious adverse effects, that went beyond the intensity, expression, or nature of pre-existing health conditions, were reported during roughly 5 months of study participation 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 lasted less than one week. Skin irritation from the paste used to affix the sensors to the scalp was reported by a single participant.

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.

The risk of harm or discomfort that may happen as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests.

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.

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.

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 the frequency and/or severity of your hot flashes.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment for your hot flashes. You should talk to your health care provider about all the choices you have. Your alternative is to not participate in this study.

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.

The purpose of this research study is to obtain data or information on the safety and/or effectiveness of HIRREM; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

WILL YOU BE PAID FOR PARTICIPATING?

If you complete the entire study, you will be paid $100 compensation for time, travel, and inconvenience related to study visits, and completion of the daily diary entries. If you do not complete the entire study you will receive a prorated portion of this amount ($25 per visit for completion of each of the three data collection visits and for proper daily diary completion).

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 sponsored by 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 HAPPENS IF YOU EXPERIENCE ANY 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 [redacted]

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 [redacted] or the Physician's Access Line at [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you, information we get from your medical records or other facilities about your health or behavior 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.

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; Brain State Technologies; 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.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups, it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will be kept for an indeterminate period of time. 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.
[redacted]

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.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

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.

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 [redacted] or [redacted].

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 [redacted].

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 Signature Date, Time, am / pm