Official Title: High-Resolution, Relational, Resonance-Based, Electroencephalic Mirroring (HIRREM) for Stage 1 Primary Hypertension
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Wake Forest®
School of Medicine

Department/Section of Neurology

HIGH-RESOLUTION, RELATIONAL, RESONANCE-BASED, ELECTROENCEPHALIC MIRRORING (HIRREM) FOR PRIMARY HYPERTENSION: A RANDOMIZED, CONTROLLED CLINICAL PILOT TRIAL

Informed Consent Form to Participate in Research

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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 hypertension, or elevated blood pressure (BP). Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask the 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 hypertension. HIRREM uses scalp sensors to monitor brain electrical activity, and computer 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 to eight milliseconds, providing the brain an opportunity for self-adjustment of its electrical pattern. HIRREM is not a medical device, and is not intended to treat, cure, heal, or diagnose any disease, mental illness or symptom, and individual results and duration of effects may vary. The HIRREM technology was created by Brain State Technologies, LLC, Scottsdale, AZ, and is FDA-exempt when used for relaxation and self-regulation. 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 improve your blood pressure by using auditory tones that are played back based on readings of your brain's electrical frequencies, to support a shift towards a more balanced pattern. Adults, age 18 and above, who have documented blood pressures between 130-159 systolic, and 80-99 diastolic, who have no other identifiable cause for hypertension, who have a cardiovascular risk score that is ≤ 10%, who are not taking medications for control of hypertension, who have not previously received HIRREM intervention, and who have no other exclusions are eligible to participate in the study.

This study will compare acoustic stimulation linked to brainwave activity (HIRREM, along with continued current care, HCC), or continued current clinical care, 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?

The goal is to have 20 participants complete all study procedures. Since blood pressure eligibility cannot be confirmed until after informed consent is provided, there may be a need to consent up to 100 people in order to identify up to 24 people eligible to be randomized to receive a study intervention. Half of the participants will randomly be assigned to receive HCC, and the other half will be assigned to CCC before being able to cross over and receive HCC.

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 four 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. Your blood pressure will then be taken using an automated device in order to confirm that you qualify for the study. If your blood pressure is too low or too high, you will be excluded from the study, and your participation will be complete.

If the blood pressure qualifies, 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. 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). If assigned to the HCC group, HIRREM sessions will begin within 0-14 days of the enrollment visit. You will also continue your other current care. Those assigned to the CCC group will continue other current care. HCC sessions will be administered over the four week period that follows. Blood pressure and heart rate recording will be repeated prior to the start of the 7th session. Within 1-14 days after your final HIRREM session, the HCC group will complete Visit #2 to collect additional data; 4-6 weeks after V1 visit for the CCC group. Follow up data collections for HCC will also be done about 1 month (Visit #3, 4-6 weeks), and about 3 months (Visit #4, 12-14 weeks) after the last HIRREM session. Those in CCC will have follow up data collections at Visit #3 (8-10 weeks after V1), and Visit #4 (16-18 weeks after V1). Following Visit #4, those assigned to the CCC group will be offered an opportunity to receive a course of HCC within 3 months, and will continue to be followed for data collections at 1-14 days (Visit #5), 4-6 weeks (Visit #6), and 12-14 weeks (Visit #7) after completing their crossover HCC sessions.

At Visit #1 (V1, enrollment, blood pressure measurement, and if you qualify for the study, baseline data collection):

- You will be asked to provide informed consent to participate in the study.
- Your blood pressure will be taken with an automated blood pressure device to see if you qualify for the study. If you do not qualify, you will be given a $10 gift card for your time.
- If you qualify for the study, you will continue with the rest of the enrollment visit data collection.

- A brief medical history will be obtained.
- Women of child bearing years will be asked to take a urine pregnancy test before randomization since pregnancy can have an effect on blood pressure.
- You will be asked to complete 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 regarding your sleep pattern, general daily practices, physical activity, and overall health.
- 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.
- 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.
- All activities for Visit #1 will take about 120 minutes to complete.

At Visit #2 (V2, for repeat data collection, 1-14 days after the completion of your last session of HCC, or 4-6 weeks after V1 for CCC), the same questionnaires and tasks, except for the brainwave assessment, will be repeated.

- Your blood pressure will be taken.
- You will be asked to complete some electronic questionnaires on a computer.
- You will be asked questions regarding your sleep, general daily practices, physical activity, and overall health.
- You will complete a questionnaire where you will be asked questions that have no right or wrong answers. You will simply respond to how strongly you agree or disagree with something. The questionnaire will be explained to you.
- 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.
- Testing at Visit #2 is expected to take up to 45 minutes.

At Visit #3 (V3, 4-6 weeks after last session for HCC, or 8-10 weeks after V1 for CCC):

- Your blood pressure will be taken.
- You will again be asked to complete electronic questionnaires on a computer.
- You will be asked questions regarding your sleep, general daily practices, physical activity, and overall health.

- 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 #3 is expected to take about 90-120 minutes.

At Visit #4 (V4, 12-14 weeks after last session for HCC, or 16-18 weeks after V1 for CCC):

- Your blood pressure will be taken.
- You will again be asked to complete electronic questionnaires on a computer.
- You will be asked questions regarding your sleep, general daily practices, physical activity, and overall health.
- 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.
- 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 #4 is expected to take up to 45 minutes.

All baseline measures, along with a brainwave assessment, will be obtained during the enrollment visit (Visit #1). HCC sessions will begin 0-14 days following Visit #1. You will receive 8-16 sessions of HCC over a 4 week period, although we hope that at least 10 sessions can be completed within 2 weeks. HCC intervention 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 7-14 days, but in no longer than four weeks. You should 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, some with eyes open, some with eyes closed. 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 can fall asleep if you would like, just relax.

Sometime between 1-14 days after HCC sessions are completed, you will have a data collection visit (Visit #2). All measures will be repeated, but no brainwave assessment will be obtained. For CCC, this will occur 4-6 weeks after V1. Between 4-6 weeks after completion of the HCC sessions there will be another data collection visit (Visit #3, CCC will be 8-10 weeks after V1). The same measures as Visit #2

will be repeated, as well as a brainwave assessment. A final data collection visit (Visit #4) will occur 12-14 weeks after completion of the sessions, with repeat of all of the outcome measures, other than the brainwave assessment. The CCC Visit #4 is 12-14 weeks after V1. Although official involvement in the study will be completed at Visit #4 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. Before crossing over, participants will come back for a brainwave assessment 0-14 days before starting HCC 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 computer software also uses the frequencies to determine which musical tones you will hear in the earbuds. This is done to provide an opportunity for your brain to improve balance in its frequencies, which may lead to improvement in your blood pressure 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 share any information with 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, 2-4 weeks of sessions, up to 2 weeks before your Visit #2, 4-6 weeks until the Visit #3, and a final study completion Visit #4, 12-14 weeks after completion of sessions. Those assigned to the CCC group, who following Visit #4 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 #5, up to 2 weeks, Visit #6, 4-6 weeks, and Visit #7, 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, and somewhat paradoxical effects have been reported by some study participants. 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 your blood pressure.

WHAT OTHER CHOICES ARE THERE?

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

WHAT ABOUT PREGNANCY?

Since pregnancy may affect blood pressure, women who are pregnant cannot participate in this study. Prior to randomization, women of childbearing potential will have a urine pregnancy test performed at the WFBH Outpatient Laboratory, 2nd floor, Piedmont Plaza 1 Building. Sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

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 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. Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution, or at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, test results, and information from study visits, phone calls, and surveys.

For the purpose of scheduling your study visits and HIRREM sessions, a medical record number for Wake Forest Baptist Health will be assigned when you enroll, and a record created in the WFBH electronic medical record (WakeOne), 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, 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.

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.

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. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research.

2) Other people or laboratories providing services for this research project on behalf of Wake Forest Health Sciences and Wake Forest Baptist Medical Center.

3) Representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS).

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 might 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 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.
[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.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

This authorization does not expire.

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."

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 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. 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 four enrollment/data collection visits). If you do not qualify for the study based on your initial blood pressure reading, and thus do not complete the remainder of the enrollment visit, you will still receive a $10 gift card for your time.

To receive payment, which will be in the form of a check, 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 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] or the Research Advocate 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.

_____

Participant Name (Printed)

_____ _____

Participant Signature Date and Time, am / pm

_____ _____

Study Personnel Signature Date and Time, am / pm