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CONSENT TO TAKE PART IN RESEARCH

Dartmouth-Hitchcock Medical Center

Study Title: Safety and Feasibility of Accelerated Low-Frequency Transcranial Magnetic Stimulation (LF TMS) for Medication-Resistant Depression in Patients with Epilepsy

Principal Investigators: Krzysztof A. Bujarski MD, Paul E. Holtzheimer MD, Julia C. Knight, MD

Introduction: You are being asked to take part in a research study. Taking part in research is voluntary.

You are being asked to take part in this study because you have been diagnosed with epilepsy and have symptoms of depression.

Taking part in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information to help patients in the future.

Your decision whether or not to take part will not influence your future medical care. Please ask questions if there is anything about this study you do not understand.

Background Information

Transcranial magnetic stimulation (TMS) is a noninvasive method of stimulating the brain and changing the way the parts of your brain communicate with one another. When you get TMS treatment, you sit in a chair and a magnetic coil is placed on the surface of your head. The coil delivers magnetic energy into your brain and you will hear a loud thumping sound as the electrical current turns on and off through the coils. As the magnetic field passes through the skin of the scalp, it activates nerves in the scalp and face, often producing a tingling sensation.

Sometimes this sensation can feel strong and produce moments of pain in the scalp, ear, eye, or face, which stop once the magnetic pulses stop. Other people may feel no sensations at all during the magnetic pulses. TMS has shown potential benefit in treating a number of psychiatric disorders, including depression. Traditionally, TMS is given at high frequencies of more than five pulses per second. Unfortunately, high-frequency TMS is associated with increased risk of seizures. Low-frequency TMS, on the other hand, describes treatment with fewer than one pulse per second and may have anticonvulsant effects while being just as effective as high-frequency TMS in treating depression.

TMS machines, including the machine we will use in the study, have been used since 1985 for

clinical and research purposes. TMS was approved by the FDA for the treatment of depression

in 2008. The device being used in this study is not FDA-approved for the treatment of depression in patients with epilepsy.

What is the purpose of this study?

The purpose of the study is to determine if TMS is safe and effective for treating depressive symptoms in patients with epilepsy. We will also look at the effects of TMS on brain activity measured using electroencephalography (EEG).

Will you benefit from taking part in this study?

Although your depression may improve during this study, you might not personally benefit from being in this research study. We hope to gather information that may help people with epilepsy and depression in the future.

What does this study involve?

Your participation in this study will take approximately 7 months to complete, but it may take longer if any of the appointments need to be rescheduled. You will complete two screening visits: one with the study Neurologist, and the second with the study Psychiatrist and research coordinators. These visits may happen on the same day when possible, but may happen on two different days.

We will ask you to return to the clinic 6 times for imaging, treatment, and follow-up visits. Before you begin the TMS treatment, we will schedule you to receive magnetic resonance imaging (MRI), EEG, and neuropsychological testing. This visit will last approximately four-five hours.

After you have completed all the screening and imaging visits, you will be scheduled to start TMS treatment. The treatment sessions will be held on three consecutive days and each session will take up most of the day. The procedure does not require any anesthesia and you will be fully awake. A family member, friend, or person who knows you well, will be required to drive you to Dartmouth-Hitchcock Medical Center (DHMC) for the treatment sessions and accompany you to a hotel after Day 1 and Day 2 of treatment. This person will stay in the same room as you during the night, and will be educated on how to safely respond if you experience any negative reactions to the treatment. The research staff will assist you with booking your hotel room, and you will not have to pay for the hotel room. When possible, the study team will give you the option of commuting from home. A family member, friend, or person who knows you well, will be required to stay in the same room as you during the nights between treatment days. You will be scheduled to receive a total of 15 TMS treatment sessions over the course of the three days. If you are unable to complete the 15 sessions by the end of Day 3 of treatment, you will be given the option to return for one more day to make up the missed treatment.

The follow-up sessions will last approximately two or three hours for each visit. The complete details of each visit are specified in the Study Visit Guide attached to this consent form.

Screening Tests:
You will need to have the following exams, tests or procedures to find out if you can be in this study.

- Visits with study doctors:
  - Medical and psychiatric history
  - Psychiatric and neurologic evaluations
  - Physical exam, including neurological exam
  - Medication review
- Interviews with research coordinators:
  - Montreal Cognitive Assessment (a test of your cognitive function)
  - Mini-International Neuropsychiatric Interview (an interview about psychiatric symptoms)
  - Antidepressant Treatment History form.
  - Neuropsychological Testing: Quality of Life in Epilepsy, Memory Assessment Clinics Self-Rating Scale, The Repeatable Battery for the Assessment of Neuropsychological Status,
- Self-report questionnaires:
  - Quick Inventory for Depressive Symptomatology (a review of your symptoms of depression)
  - Seizure log
  - Systematic Assessment for Treatment Emergent Events (a review of common physical symptoms you have experienced)
  - Positive and Negative Affect Schedule (A 20 item test that measures both positive and negative affect.)
  - MRI safety form, and TMS Safety Form.

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be assigned to receive TMS treatment.

Before your treatment begins, we will calibrate the machine to your sensitivity by determining your "motor threshold." The research nurse or trained TMS study team member will deliver a series of pulses until you experience a small twitch in your hand. During the beginning of treatment, the power settings of the TMS machine will start low – like starting on a low "dosage" of medication. The TMS power will be gradually increased until the optimal level of stimulation, based on your motor threshold assessment, is reached.

After you reach the optimal TMS power level, you will stay at the power level for the rest of the TMS treatments during the study. It is possible, although unlikely, that the optimal intervention power level will feel uncomfortable for you. If this happens, tell the technician and they will attempt to make it more comfortable.

	VISIT	LOCATION/TIME	PROCEDURES
Screening	1a	DHMC About 2 hours	•Review and sign consent form •Visit with study neurologist and physical exam •Epilepsy medication review
	1b	DHMC About 2 hours	•Visit with study psychiatrist and medication review •Interviews with research coordinators •Self-report questionnaires
Imaging	2	DHMC About 3 hours	•MRI & fMRI •EEG •Photogrammetry •Neuropsychological Testing
Treatment Visits	3	DHMC About 6 hours Within 4 weeks after Visit 2.	•Enrollment •Self-report questionnaires •Motor threshold •4 x 50-minute treatment sessions •Self-report questionnaires.
	4	DHMC About 8 hours	•Self-report questionnaires •7 x 50-minute treatment sessions •Self-report questionnaires
	5	DHMC About 5 hours	•Self-report questionnaires •4 x 50-minute treatment sessions •EEG •Self-report questionnaires
Follow-Up Visits	6	Phone About 30 min 1 week after Visit 5.	•Interviews with research coordinators
	7	DHMC About 2 hours 1 month after Visit 5	•Visits with study doctors •Interviews with research coordinators •Self-report questionnaires •Neuropsychological Testing •EEG
	8	DHMC About 30 min. 3 months after Visit 5	•Interviews with research coordinators
	9	DHMC About 2 hours 6 month after Visit 5	•Visits with study doctors •Interviews with research coordinators •Self-report questionnaires •Neuropsychological Testing •EEG

Diagram of Study Schedule:

What are the options if you do not want to take part in this study?

TMS treatment may be available as part of regular clinical care. You can discuss this with your doctor and the study physicians. If you do not choose to participate in this study, you will continue to receive care from your current physicians and other treatment providers. Whether or not you participate in this study, your ability to receive regular medical care will not be

affected. Other treatments for depression include antidepressant and other medications, psychotherapy, and electroconvulsive therapy (ECT). These other options for treatment have their own risks and benefits. Please discuss them with your doctor.

If you take part in this study, what activities will be done only for research purposes?
All the procedures, tests, and activities described in this consent form are being done only for research purposes.

What are the risks involved with taking part in this study?
We cannot be sure how your body may respond to the TMS used in this study. The research team will discuss possible problems and the chances that they will happen. Unknown problems may happen. Problems may be small, such as scalp pain or headache, or they may be so serious that they result in seizure or fainting. You should report any problems to your doctor or to the director of this study, Dr. Bujarski, who can be reached at 603-650-5104, or Dr. Holtzheimer, who can be reached at 603-650-4914.

RISKS/SIDE EFFECTS OF TMS Treatment

Common

- buzzing sensation at the treatment site
- tapping sensation at the treatment site
- scalp pain
- headache

Rare

- painful sensation at the treatment site
- neck pain
- toothache
- worsening of depression
- transient (temporary) dizziness
- fainting
- brief changes in attention and thinking
- changes in hearing
- transient acute hypomania

Very Rare

- seizure
- fainting (syncope)

Your TMS treatments will be given in an area of DHMC where trained medical personnel and equipment are available to treat you if a seizure occurs. The staff has been specially trained to respond to seizures.

Because the stimulator can emit a loud noise and there is a risk of temporary hearing loss, you will wear protective earplugs during treatment.

TMS cannot be used by anyone who has non-removable magnetic metal in their head or within one foot of the TMS coil. You will be screened before beginning treatment to ensure that the treatment is safe. Ignoring this restriction could result in serious injury or death.

Although TMS has been used for many years, the long-term effects of TMS on individuals are not completely known. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Risks of MRI

There are no significant known risks to MRI. You will be screened for metallic implants or magnetic devices before beginning the scan. The MRI scanner does produce loud banging noises and may be uncomfortable if you experience claustrophobic-like reactions in confined spaces. If this occurs, you may terminate participation at any point.

Risks of Photogrammetry/EEG

There are no significant known risks to dense-array EEG recording. The EEG cap placed on your head uses a saline-type solution and you may have your scalp gently rubbed under the electrodes in order to improve the quality of the recording.

Reproductive Risks and Risks to Pregnant Women:

The risks of TMS to a pregnancy are unknown. Pregnant women may not take part in this research study. All women who could become pregnant will have a pregnancy test during the screening visit. The Diamond Endowment will pay for your pregnancy test.

All women who could become pregnant need to use a medically approved method of birth control in order to take part in this research study. Please discuss options with the researcher.

If you or your partner become pregnant, you should let the study team know right away at 603-650-4506. If you become pregnant, you will no longer receive the TMS treatment.

Other Risks

Other possible risks of study participation include discomfort associated with questionnaires, such as feeling embarrassed talking about suicidal thoughts or other personal topics with non-doctor professionals like the study coordinator and/or device technician. There are also confidentiality risks through greater collection of data than in usual medical practice.

During the study it is possible that your depression could get worse. Your mood and overall condition will be monitored very closely during this study. It is possible that your depression could worsen to the point that you become suicidal and/or require hospitalization. If this occurs, you will be carefully evaluated to determine whether it is safe for you to continue in this study.

MRI is commonly used in medicine for the purpose of diagnosing abnormalities of the brain. The procedures that are to be used in this study are different from clinical MRI scanning. As

researchers, we do not intend to make any medical diagnosis with the MRI as used in this research project, and we are not trained in medical diagnosis. However, if in the course of this research study we observe an anomaly in one or more of the MRI images, we feel ethically obligated to inform you of the observation. We believe it is important to inform you of such observations, because we cannot rule out the possibility that an anomaly may require medical attention. In this event, all information collected as part of this study will be made available to you for further examination by a medical professional. You will be fully responsible for the costs associated with a radiological examination and any further examinations or treatments that may be required for medical purposes. If you prefer not to be informed of an image anomaly, you must choose not to participate in the study.

Other important items you should know:

- **Leaving the study:** You may choose to stop taking part in this study at any time for any reason. If you decide to stop taking part in this study, it will have no effect on the quality of medical care you receive. Even if you do not wish to end participation in the study, the study doctor may choose to terminate your participation if this is deemed appropriate.

- **New Information:** New information related to this research will be made known to you when it becomes available. This may affect your decision to stay in this study.

- **Funding:** The Diamond Endowment provides funding for this research through an interdisciplinary neuroscience grant.

- **Number of people in this study:** We expect 20 people to enroll in this study.

How will your privacy be protected?

This study will involve collecting information about:

- your epilepsy and seizures
- depression and mood symptoms
- other psychiatric symptoms, including drug and/or alcohol abuse
- other health information such as EEG, MRI, and photogrammetry reports

The following information collected as data for this study will be entered into your electronic medical record at DHMC (eDH):

- This consent form, documenting your agreement to participate in the study
- Any changes in health that you may experience
- Any treatment you may receive as a result from an adverse event

Electronic data collected for this study will be maintained indefinitely once identifiable information has been removed. Physical data will be maintained for three (3) years after the study has been completed.

We are careful to protect the identities of the people in this study. We also keep the information collected for this study secure and confidential. Where possible, we will de-identify your data, which means we store your data with your study number instead of with your name. Your name and other facts that might identify you will not appear when study results are published or presented.

The physical, paper data collected for this study will be stored in a locked office in cabinets, and the electronic data will be stored on secure, password-protected research databases. Confidential data are stored on a secure computer hard drive within the Department of Neurology and the Department of Psychiatry and managed by Information Technology Department at DHMC. The department follows industry standard procedures for securing the computers, servers, and networks. Department networks are protected by an internet firewall. Electronic access is restricted by the use of username and password access to authorized personnel only.

The information collected for this study will be used only for the purposes of research as stated earlier in this form.

Who may use or see your health information?

By signing this form, you allow the research team to use your health information and give it to others involved in the research. The research team includes the principle investigators plus others working on this study at Dartmouth-Hitchcock Medical Center and elsewhere. You also permit any health care provider holding health information needed for this study to give copies of your information to the research team.

The information collected for this study may be used by researchers or officials of the following institutions.

- Dartmouth College
- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- Dartmouth-Hitchcock Health IRB (D-HH IRB)

Some of the information used in this study, called Protected Health Information ("PHI"), is protected by federal privacy laws. By signing this consent form, you give your permission to have your PHI collected, used and disclosed for purposes of this study. After the study staff or study doctor discloses your PHI to others, it could be re-disclosed and no longer protected by federal privacy laws.

Your permission to use your health information for this study will not end until the study is completed. During this study, you and others who take part in the study may not have access

to the study data. You may ask for study data once the study is over. You have a right to receive a copy of the information in your medical record at any time.

It is possible for a court or government official to order the release of study data including information about you.

The only time we would give information to anyone other than the individuals and groups listed above is if something happens which leads us to believe that your safety or the safety of someone else, including family members or children, is in jeopardy. If we believe safety is an issue, we will need to talk with someone who can help. You should also know that we are required by law to make a report if we have reason to believe a child or an incapacitated adult has been abused.

What if you decide not to give permission to use and share your personal health information?

If you do not allow use of your health information for this study, you may not take part in this study.

If you choose to stop taking part in this study, you may cancel permission for the use of your health information. You should let the researcher know if you want to cancel your permission. The study team will assist you in putting your wishes in writing. Information collected for the study before your permission is cancelled will continue to be used in the research.

Whom should you call about this study?

If you have questions about this study or need to report a study related injury or problem, you can call your doctor or the research director for this study: Dr. Bujarski at 603-650-5104 during normal business hours.

If Dr. Bujarski is not available, you can call one of the research coordinators for this study, Sandra Snogren RN at (603) 653-9920 or Nicholas Streltzov at (603)-650-5398 to answer your questions during normal business hours.

For urgent matters outside the normal business hours, call (603) 650-5000 and contact the on-call resident neurologist. To speak about urgent mental health concerns, you can call (800) 556-6249 any time of the day.

If you have questions, concerns, complaints, or suggestions about human research at Dartmouth, you may call the Office of the Dartmouth-Hitchcock Health IRB (D-HH IRB) at (603) 650-1846 during normal business hours.

What about the costs of this study?

The TMS treatment will be supplied free of charge. The additional tests, visits, and procedures that are part of the study will be paid for by the Diamond Foundation.

Will you be paid to take part in this study?

You will receive a patient stipend of $50 per TMS visit day and $50 for the final visit, for a total of $200 if you complete the study. To defray the costs of participating in this study, you will receive $20 per day for three treatment days for meals for you and your family member. All study procedures will be provided free of charge.

What happens if you get sick or hurt from taking part in this study?

If you are injured or become ill as a result of research procedures, you will be provided with medical treatment but the following organizations do not plan to pay for this treatment.

- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- Trustees of Dartmouth College

If you have any questions or concerns about the legal responsibility of these organizations, please call the Mary Hitchcock Memorial Hospital Office of Risk Management at (603) 650-1250 during normal business hours.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

CONSENT

I have read the above information about Efficacy and Safety of Low Frequency Transcranial Magnetic Stimulation (LF TMS) for Medication-Resistant Depression in Patients with Epilepsy and have been given time to ask questions. I agree to take part in this study and I will be given a copy of this signed consent form.

Participant's Signature	Date	PRINTED NAME
Researcher or Designee Signature	Date	PRINTED NAME