NEUROLOGY
at The GW Medical Faculty Associates

2150 Pennsylvania Avenue, NW, 7th Floor
Washington, DC 20037
phone: 202.741.2700 fax: 202.741.2721

Informed Consent for Clinical Research

Project Title: Low Frequency Electrical Stimulation of the Fornix in Intractable Mesial Temporal Lobe Epilepsy (MTLE)

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GW IRB Reference number:	111239
Consent Version Date:	14 Dec 2015

Introduction/Purpose

You are being asked to participate in a research study because you are a person who has temporal lobe epilepsy and are a patient at the GW Medical Faculty Associates (GW MFA). The study will be enrolling patients and performing the procedure at the George Washington University Hospital (GWUH) and Thomas Jefferson University; the study will plan to enroll up to 16 participants.

By conducting this research study, investigators are looking at the safety of low frequency stimulation using the Medtronic deep brain neurostimulator device, an extra electrode, and a pulse generator containing a battery pack, all together collectively called the "DBS Device" and its effects on temporal lobe epilepsy. The procedure to implant the DBS Device will require surgery for your brain and monitoring of your brain function and seizure activity, and will last approximately two years.

Implantation of the DBS Device is an investigational therapy in epilepsy. This means that this kind of intervention is not approved by the U.S. Food and Drug Administration (FDA) for treatment of epilepsy. The DBS Device was, however, approved by the FDA for other neurologic disorders, such as Parkinson's disease and Essential Tremor, but in this study, we are using it for epilepsy to investigate its tolerability and ability to reduce seizures.

Before you decide to participate, you should read this document; it is a consent form and it explains why we are doing this study. Ask as many questions as you want so you can decide whether or not you want to be in the study. This consent form may contain words that you do not understand; please ask us to explain any words or information that you do not understand. You should not participate if you are part of another medical research study.

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This consent form and the research study have been reviewed by George Washington University's Institutional Review Board (IRB). The IRB is a committee of scientific, medical, and non-scientific who review research studies involving humans. The committee follows the rules set forth by the United States Government's Department of Health and Human Services (DHHS).

Study Procedures

Screening

As someone who has temporal lobe epilepsy, you've most likely been evaluated as a patient by a physician at The George Washington University Medical Center. You will be asked to return to the hospital so that the study team can verify that you qualify for the study.

The research team will ask that you write down in a diary each day how many seizures you have and how long the seizure lasts; the research team will review this information to get an estimate for the number of seizures you have per month; this is standard of care for all patients evaluated at the GW MFA who have Epilepsy. The research team will need also need you to complete a series of questionnaires; these are designed to determine what your overall quality of life is and if your epileptic seizures have had an effect on your memory and brain function.

Implantation Procedure

Approximately two months later, you will return to the hospital to undergo testing and monitoring to determine the type of seizures that you have and from what section of your brain the seizures are coming from. The testing and monitoring will require that you undergo surgery. Before surgery, your hair will be removed and your head shaved. A metal frame will then be placed on your head, secured, and brain MRIs obtained in the frame, and these procedures and tests are standard of care. The surgery will be done to implant twelve (12) stimulation electrodes (wires) into your brain. This procedure is standard of care for patients with your diagnosis. For the purposes of this research study only, a thirteen (13^{th}) stimulation electrode will also be implanted at the same time that the other twelve are implanted because the additional thirteenth electrode is needed for the DBS Device, and this additional electrode is not standard of care. You will then be brought to the operating room and the areas of the intended incisions will be cleaned and covered in a sterile manner for each electrode (wire) that will be placed in your brain. Local anesthesia (numbing medicine) will be given and a small hole will be made in your scalp through which electrodes will be placed. Normally, as standard of care, 12 electrodes are placed in the brain, however, for this procedure, an extra electrode needed for the DBS Device, will be inserted (for a total of 13 electrodes). This process would only be done for a patient taking part in this research trial.

Epilepsy Monitoring Unit Evaluation

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Once the surgery is finished and the stimulation electrodes (wires) have been implanted into your brain, you will be transported to an area of the hospital called the Epilepsy Monitoring Unit (EMU.) The EMU is staffed with nurses and physicians who understand Epilepsy; you will be monitored there for 5-10 days.

The nurses and physicians will be looking at the type of seizures that you have and from what section of your brain the seizures are coming from. If you were on any seizure medications before the research trial, they will be reduced while you are being monitored in the Epilepsy Unit because the doctors will try to increase the chances of recording seizure activity. The study doctor will monitor for seizure activity in different parts of your brain, including an area called the hippocampus. The hippocampus is responsible for memories. If the seizures are not coming from the hippocampal area of your brain, you will no longer continue with the study. In this case, you may continue your treatment of oral medications, undergo resection surgery if it is recommended, or other standard of care interventions. If resection surgery is considered safe, then all electrodes will be removed from your brain and the resective surgery will be done per clinical standards. If, however, resection is considered by your epilepsy doctors to be risky and might affect your memory, then it will not be recommended. In this case, depth electrodes will also be removed, but your management will ensue with antiepileptic medications alone. Therefore, if your seizures are not originating from the hippocampus, the care will be delivered according to clinical standards alone, and you will not be part of the study.

However, if the doctors determine that your seizures are coming from an area of the brain called the hippocampus, you will then be taken back to the operating room to undergo additional experimental surgery and investigational implantation of the DBS Device. The surgery to implant the DBS Device requires connection of the stimulation electrode to a pulse generator under your collarbone, which contains the battery source so that deep brain stimulation can occur. The remaining electrodes will not be used in the DBS Device system, and will be removed from your brain. These procedures, including the implantation of the DBS Device, will only be done as part of this research protocol. After the surgery, the stimulation DBS Device can be programmed specifically for the research trial. Upon discharge from the hospital, your baseline antiepileptic medications will be resumed and you will see your doctor in one month after discharge to program the device.

Randomization/Study Intervention

You will return home to recover from the surgery, but will be asked to come back to the hospital one month later. At this time, the research team will randomly place you into a group where the settings on your brain stimulation DBS Device will either be placed at 1 Hz (hertz) or 5 Hz (hertz); this process would only be done for a patient taking part in this research trial.

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The DBS Device has been approved by the US FDA for use in other areas of the brain at stimulation settings of 130Hz for patients suffering from Parkinson's Disease and Essential Tremor, and has been used in approximately 1,250 patients in the United States at this level of hertz stimulation with no serious adverse events. The stimulation settings of 1Hz or 5Hz used in the fornix area of the brain (which is the name of the area that we plan to stimulate electrically as part of this research protocol) for this research study are much lower.

The research team will also ask that you continue to complete your seizure diary during this time.

You will then proceed into a treatment stimulation block (stimulation ON) which will last about 2 months. You will be blinded (you will not know) what the setting of your stimulation system is, to either 1 Hz or 5 Hz, and to the intensity setting of your system to.

You will complete one block of stimulation (2 months), and then proceed into a non-treatment block (where all settings will be placed at 0) for approximately 2 months. Altogether, you will go through 6 different blocks, 3 treatment stimulation (stimulation ON) and 3 non-treatments (Stimulation set to 0). During the treatment stimulation blocks, stimulation will be delivered 4 hours on, 4 hours off on a 24 hour cycle.

You will be asked to return to the hospital at the following time points for a follow up visit with the research team; the follow-up schedule is not standard of care, and is followed only for the purposes of this research study:

- Month 1 (post-implantation)
- Month 3
- Month 5
- Month 7
- Month 9
- Month 11
- Month 13

During the research related visits at the above time points, you will undergo the following procedures/tests:

- Adverse Event Evaluation(every visit)
- Neuropsychological Testing (at months 5, 9, and 13)
- DBS Device examination and programming (every visit)
- Review of Seizure Calendars (every visit)
- Psychiatric Evaluation (at months 5, 9, and 13)

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Long Term Follow Up

This phase will last about 12 months, in addition to the 13 months of study visits for a combined study participation of about 27 months. The research team will check in on you and evaluate you on a long term basis; during this time you will no longer be blinded and you will know what your brain stimulation settings are. If you are having problems, the stimulation settings can be changed by a member of the research team as clinically indicated.

A member of the research team will contact you monthly via telephone to discuss any adverse events that may have occurred, any problems with the implanted stimulation system, and to see how your overall quality of life is while at home.

Once the research study is finished, you can follow up with your primary care physician regarding your implanted DBS Device system, or you may continue care with a physician specializing in this area at the GW MFA. The DBS Device and the remaining stimulation electrode will remain in your brain forever, unless complications require their removal.

Risks

Risks associated with the implantation of the 13th electrode may include:

- Memory changes

Risks associated with the surgery to implant the DBS Device include the following:

- Hemorrhage (heavy or uncontrollable bleeding)
- Paralysis (complete or partial loss of function or of sensation in any part of the body)
- Coma or death
- Stroke
- Seizures
- Infection
- Allergic reaction
- Leaking of fluid surrounding the brain
- Temporary and or permanent neurological complication
- Pain at the surgery site
- Headaches

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Risks associated with the implanted stimulation DBS Device include those which are mechanical, electrical, and others related to DBS Device failure. Other risks may include:

- Battery failure
- Electrical shock
- Reactions to various components of the DBS Device
- Shift of the brain wire extension

There is also a risk that you may experience side effects related to stimulation; however these effects are most commonly reversible by adjusting the stimulation parameters or by reprogramming the stimulation settings. In addition to the reprogramming of the DBS Device, if any side effects are experienced, the system can be turned OFF, and you will return to how you were before the surgery. The following risks may be associated with the stimulation:

- Behavioral changes
- Unusual taste or smell sensations
- Mood changes
- Changes in energy levels
- Blurred or double vision
- Speech and visual difficulties
- Weight gain or loss
- Restlessness
- Headache pain
- Pain or discomfort
- Hyperactivity or euphoria (a feeling of well-being or elation)
- Changes in vital signs
- Dizziness
- Motor concentration,
- Facial flushing
- Paresthesia (sensation of tingling, tickling, prickling, pricking, or burning of a person's skin)
- Numbness
- Jolting or shocking sensation
- Muscle weakness
- Nausea
- Gastrointestinal disturbances
- Depression
- Thoughts of suicide

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In addition, some of the questions on the questionnaires may be upsetting, may feel uncomfortable, or cause fatigue when answering them. If you do not wish to answer a question, you may skip it and go to the next question.

If you take part in this research, you will have one or more medical x-ray studies. These x-rays involve a small amount of radiation. To give you an idea about how much radiation you will get, we will compare it to the amounts you encounter in your daily life. There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. Participating in this research gives your body the equivalent of about 1 extra year's worth of this natural radiation. This radiation dose is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests.

The following medical procedures are **not** allowed:

Diathermy—Patients who will be exposed to diathermy (deep heat treatment). Inform any one treating you that you CANNOT have any short
ware diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) anywhere on your body because you have an implanted neurostimulation system. Energy from diathermy can be transferred through your implanted system, can cause tissue damage and can result in severe injury or death. Diathermy can also damage parts of your neurostimulation system. This can result in loss of therapy from your neurostimulation system, and can require additional surgery to remove or replace parts of your implanted system. Personal injury or device damage can occur during diathermy treatment when:

- the neurostimulation system is turned on or off.
- diathermy is used anywhere on your body (not just where your neurostimulation system is located).
- diathermy is used to deliver heat or no heat.
- any component of your neurostimulation system (lead, extension, neurostimulator) remains in your body.

Certain MRI procedures—You should not have certain types of MRI if you have an implanted DBS System or any part of the DBS System implanted in your body. If an MRI is prescribed for you, make sure to tell your doctor that you have an implanted DBS System and that you cannot have an MRI procedure that involves the use of:

- a full body transmit radio-frequency (RF) coil.
- a receive-only head coil.
- a head transmit coil that extends over the chest area.

These types of MRI can cause the electrode tip of the implanted lead or leads to generate heat, resulting in serious and permanent injury (including coma, paralysis, or death).

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Transcranial magnetic stimulation therapy—Transcranial magnetic stimulation therapy (TMS) is contraindicated for patients with any implanted DBS System or system component.

The effect of stimulation on/during pregnancy and on a fetus is not known. For that reason, if you are pregnant, or are planning to become pregnant you may not participate in this study. Before you enter the study, you will have a pregnancy test. If you are a woman of childbearing potential, you may participate only if you are using a reliable method of birth control. The study doctor will discuss appropriate birth control measures with you. If you suspect that are pregnant during the study, you must notify the study doctor immediately. Low frequency stimulation should be discontinued as soon as pregnancy is detected because of concerns about its possible effects on the unborn child.

This treatment or procedure may involve unforeseeable (or unknown) risk to you as a subject.

Consequences of Withdrawing or Being Discontinued from the Research

If you withdraw from the study prior to its completion or are being discontinued from the research for any reason identified in this consent form, you will need to discuss with the research physician the options regarding your stimulation system. The stimulation system can be safety turned to OFF and remain implanted inside your body. The stimulation system can also be removed from your body and taken out permanently, which involves risks such as memory impairment, bleeding, infection and other known risks associated with surgery under general anesthesia.

Benefits

There may be no direct benefit to you participating in this study. You may see a reduction in your seizure symptoms or you may also see a reduction in the number of seizures you have. The information collected in this study could help investigators decide if this procedure is safe and effective; thus giving potential benefit to future patients.

Alternatives to Study Participation

This is a voluntary study and you can choose not to participate. If you choose not to participate in this research, you may continue your treatment of oral medications, surgery, or other standard of care interventions. The DBS Device is not approved for use in patients with epilepsy in the United States; therefore, it is not available outside of this study. Your decision to participate will in no way influence any care you might receive at the GW Medical Faculty Associates or the George Washington University Hospital, nor will it affect how the study personnel treat you.

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Financial Information

You will not be paid for your participation in this study. The DBS Device is being provided by Medtronic, Inc, and therefore there will be no cost to you or your insurance company for the DBS Device. The research portion of the implantation procedure is being paid for by available funds from the Department of Neurology at The George Washington University Medical Faculty Associates, and therefore will also be no cost to you or your insurance company. The cost to remove the DBS Device will be paid for by available funds from the Department of Neurology at The George Washington University Medical Faculty Associates and will be at no cost to you.

Once the research study is finished, clinical visits that may need to be scheduled to program your DBS Device or adjust the stimulation settings for your DBS Device will be the responsibility of you or your insurance company. In addition, if your DBS Device needs to be replaced after the study is finished, this cost will be the responsibility of you and/or your insurance company.

Research-Related Injury

You may have medical problems or side effects from taking part in this research study. If you have any side effects after having the DBS Device implanted or undergoing the study procedures, or are injured during the study, tell your study doctor right away. Once you tell your study doctor, he will either provide you with or refer you to get proper medical treatment.

If you believe that you have been injured or have become ill from taking part in this study, you should seek medical treatment right away. This can be done through:

- GWU Hospital and/or the GWU MFA or
- your physician or
- treatment center of your choice

You and/or your medical insurance will be responsible for the cost of all care and treatment for all research injuries that occur.

In the event that the DBS Device and the electrode must be removed due to complications, only the cost of the procedure to remove the Device and electrode will be paid for by available funds from the Department of Neurology at The George Washington University Medical Faculty Associates.

To help avoid injury, it is very important to follow all study directions. You are not giving up any of your legal rights by signing this form. There are no plans for Medtronic Inc., GWU Hospital and/or the GWU MFA to pay you for any injuries or illnesses.

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Confidentiality

Results of the research testing will be treated as confidential information and the results will not be included in your medical record. Similarly, your medical history will also be treated as confidential with no identifiable information released or shared with individuals outside the study team. If the study results are published, your name will not be used. Once all your results are collected, any identifiers will be removed and the information assigned a code. The date will be identified by a study number and not by your name or identifying information. The code assignment key will be maintained by the principal investigator and clinical research coordinator, on a password secured computer kept in a locked office. Assess to the code key will be limited to the principal investigator and the study personnel on a need only basis.

U.S. NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIAL DATABASE: 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 website at any time to find out information about the trial and basic results.

Termination of Participation

Your participation in this study may be discontinued by the sponsor or investigator without your consent for the following reason:

1) You no longer wish to or stop taking your antiepileptic medication that you were taking before you started the research study
2) You no longer wish to or stop completing the tests designed to monitor your brain functions
3) You no longer wish to or stop completing the seizure diaries
4) You become pregnant
5) Any other situation that the principal investigator/research team deem necessary to remove your inclusion from the research trial

Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of The George Washington University. This Authorization form is specifically for a research study entitled " Low Frequency Electrical Stimulation of the Fornix in Intractable Mesial Temporal Lobe Epilepsy (MTLE)" and will tell you what health information (called Protected

Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can use the information.

In order for the Principal Investigator, Dr. Mohamad Koubeissi and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment at the GW MFA or the GW Hospital. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.

Generally the Principal Investigator and study staff at GW MFA and GW Hospital who are working on this research project will know that you are in a research study and will see and use your PHI. The researchers working on this study will collect the following PHI about you: name, age, medical record number, medical history, comorbid medical conditions, medications, and results from procedures (EEGs, for example). This PHI will be used to help determine if low frequency stimulation will help reduce your seizure symptoms and the how often your seizures occur. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: your healthcare providers (like doctors and hospitals) which are not part of the study, GWU Office for Human Research's Institutional Review Board (IRB) or its authorized representatives who may review your records to ensure your rights as a research subject are protected; Members of the George Washington University, that may review your subject research records, who are responsible for overseeing research safety and compliance; Thomas Jefferson University research team; Case Western University Research Team; Government representatives or Federal agencies, when required by law, and Medtronic Neuromodulation, Inc. (the DBS Device manufacturer).

De-identified study-related health information will also be shared with Medtronic, Inc. (device manufacturer), who is providing funding support for this study. Medtronic will keep your information confidential in accordance with all applicable laws and regulations. Medtronic may use your study-related health information for overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Any reports or publications about the study or any other research will not include your name or a description of you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes. The US Food and Drug Administration's regulations, as well as other applicable laws, control Medtronic's work in developing and assuring the safety and quality performance of its medical devices. Medtronic may disclose your study-related health information to the US Food and Drug Administration (FDA), as well as to other US and foreign government authorities responsible for assuring the safety of medical devices. You agree to allow Medtronic to

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use the study-related health information in these ways. You also agree to allow FDA and other governmental authorities to inspect your study-related health information.

Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to:

Dr. Mohamad Koubeissi, MD,
2150 Pennsylvania Ave., NW
Suite 9-400
Washington, DC 20037.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Please understand that once your PHI has been disclosed to anyone outside of The George Washington University, there is a risk that your PHI may no longer be protected; however other Federal and State laws may provide continued protection of your information.

Summary of your rights as a participant in a research study

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at The George Washington University Hospital (GWUH) or elsewhere; however, GWUH, GWU and the GWU MFA have no plans to provide free care or compensation for lost wages.

Contact information

The Principal Investigator, Dr. Mohamad Koubeissi, can also be contacted at (216)844-1764 during normal office hours, or you may call (202)741-2700 24 hours a day and ask to speak with the Neurology Resident on-call. You can also contact the study coordinator by phone at (202)677-

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6210 or by email at neurostudies@mfa.gwu.edu. If you have a research related injury, any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research- related injury; or other human subject issues, please call the The George Washington University Office for Human Research at (202) 994-2715 or write to 2030 M St., NW Suite 301 Washington, DC 20036 or ohrirb@gwu.edu.

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Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Signature of Participant	Date
X	
Printed Name of Participant	

Study personnel (only individuals designated on the checklist may obtain consent)

X	
Signature of person obtaining informed consent	Date
X	
Printed name of person obtaining informed consent	
X	
Signature of Principal Investigator	Date
X	
Printed name of Principal Investigator	