INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are an NIH employee, a Clinical Research Advocate (CRA) from the Human Subjects Protection Unit (HSPU) will be present during the informed consent. Informed consent is the discussion between you and the research team about this study. The CRA ensures you have the information you need to make an informed decision about participating in this study. The HSPU is part of the NIMH Office of the Clinical Director. They are not part of the research team.

Purpose of This Study
The purpose of this study is to learn more about myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that starts after an infection.

Background
Chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME), also called systemic exertion intolerance disease (SEID) by the Institute of Medicine, are terms used to describe extreme fatigue and post-exertional malaise along with
other symptoms like pain, sleep problems, depression and anxiety. “Post-exertional malaise” is a feeling of profound exhaustion after exercise. The cause of ME/CFS is not known. At times, this condition is triggered by an infection. The purpose of this study is to learn more about ME/CFS that starts after an infection. To study ME/CFS, participants will have physical and psychological examinations about their symptoms and ME/CFS effects on many aspects of their lives. There will be tests of blood and various body fluids and magnetic resonance imaging. Some participants will have exercise stress testing.

For this technical development sub-study, we are testing two new ways to measure how physical and mental activity create the feeling of fatigue. The first way is functional magnetic resonance imaging (fMRI), which measures which parts of your brain are being used during physical and mental activity. The second way is transcranial magnetic stimulation (TMS), which measures how your brain controls the movement of your muscles as you get tired. Both fMRI and TMS have been widely used in research. During these tests we may also collect electroencephalography (EEG), which measures your brain waves. In this study, we want to test the measures in up to 10 healthy volunteers and in up to 10 people with ME/CFS.

This consent form describes the technical development sub-study. Healthy volunteers in the technical development sub-study may also participate in other parts of the study, including visits to the NIH and research examinations. ME/CFS volunteers in the technical development sub-study cannot participate in other parts of the study.

The study is run by the National Institute of Neurological Disorders and Stroke (NINDS), within the NIH.

Study Population
Up to 206 people will participate in this study. There will be 5 groups of participants.
- PI-ME/CFS group - People with ME/CFS whose fatigue started after an infection
- Lyme group - People who had Lyme disease, were treated, and don't have symptoms anymore
- Healthy Volunteer group - Those in good general health
- Focus Group - Those with ME/CFS participating in a phone conference only
- Technical Development Sub-Study - Healthy volunteers and ME/CFS patients having functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) testing only.

Who Can Be In This Study
You may be eligible to participate in the technical development sub-study if you are:
1) An adult between 18 – 60 years of age
2) Able to speak, read, and understand English
3) Willing and able to complete all study procedures
4) Right-handed
5) Able to give informed consent for yourself

If you are a ME/CFS participant, you also must:
1) Have been diagnosed with ME/CFS by your health care provider

Who May Not Be In This Study
You may not be eligible to participate in the technical development sub-study if:
1) You have an active infection at the time of study enrollment.
2) You have or have had a disorder that can cause psychosis, such as depression with psychosis, bipolar disorder, or schizophrenia
3) You have a psychiatric disorder (such as major depression, anxiety, or post-traumatic stress disorder) and your
symptoms have not been well-controlled on a stable dose of medication for at least 6 months.
4) You have ever abused drugs or alcohol
5) You have thoughts about harming yourself or committing suicide.
6) You have had a head injury that caused you to lose consciousness or have memory problems.
7) You are taking any drug (including prescription, over-the-counter, or illegal drugs) that may affect the study results and that you cannot safely stop during the study, based on our evaluation. Drugs that might interfere with the study include (but are not limited to) antidepressants, mood stabilizers, pain medications, muscle relaxants, and sleeping medications.
8) You are pregnant, trying to become pregnant, or were pregnant in the past year.
9) You have or have had cancer, other than certain skin cancers.
10) You have an immune disorder such as Type 1 diabetes or rheumatoid arthritis.
11) You ever used medications that suppress the immune system such as steroids and biologic immune modifying agents.
12) You have any medical condition that would make taking part in this study risky or difficult for you or that may affect the study results, such as heart disease, severe arthritis, poorly-controlled asthma, or untreated sleep apnea.
13) You are participating in another research study in which you receive treatment that may affect results of this study.
14) You work directly for one of the study investigators.

If you have ME/CFS, you also may not be able to take part if:
1) You have a significant neurological disorder (e.g. neurodegenerative disorder, stroke, epilepsy).
2) You have ME/CFS disease severity that makes it impossible for the volunteer to leave the home or requires inpatient treatment.
3) You are being currently treated for underlying illness that may cause fatigue such as thyroid dysfunction, hepatitis, or other systemic diseases.
4) You are a participant in other parts of the research study.

Procedures
If you participate, you will have 1 or 2 outpatient visits at the NIH Clinical Center in Bethesda, MD. During the visits, you will have a medical evaluation and screening to ensure that it is safe for you to have TMS and MRI scans. If you are healthy enough to volunteer, you might have an MRI scan of your brain, then have TMS testing, and then have MRI scanning. During both tests we might also perform EEG. After you complete all these tests, your participation in the study ends.

All of these tests are being done for research purposes, not for your medical care. If you have had any of these procedures recently at NIH, you may not have to repeat them for this study.

History and physical examination
We will ask you about your and your family's medical history. We will examine you. If you have ME/CFS, we will ask you detailed questions about your symptoms. This exam will take 1-2 hours. This physical exam is for research purposes only and does not replace any exam you may have from your own doctor.

Urine collection
You will provide a urine specimen by peeing into a cup. We will check the urine to see if you are eligible to take part in this study. We will use the urine for screening for drug use. If you are a woman that is able to become pregnant, we will perform a pregnancy test as well. Collecting a urine sample takes up to 5 minutes.
Magnetic Resonance Imaging (MRI) and Functional MRI (fMRI)

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the inside of your body. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie still on a table that can slide in and out of the cylinder. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.

Functional MRI (fMRI) is a type of MRI that allows us to see what parts of the brain are used when you do a task. In this study, you will have an fMRI done at rest, during an exercise task, and during a thinking task. The fMRI exercise task will ask you to move your wrist against resistance until your wrist gets tired. The thinking task will ask you to solve addition and subtraction math problems. You will be told about the tasks that you will do during the scan and you may have the opportunity to practice.

You will have either one or two MRI scans. If you have not had an MRI scan of your brain at the NIH within the last year, you will have a 30 minute MRI scan before having your TMS session. After having the TMS session, you will have a 90-120 minute MRI scan including the functional scans.

Transcranial Magnetic Stimulation (TMS)

We will use transcranial magnetic stimulation (TMS) to look at how your brain controls the movement of your muscles as you get more tired. For transcranial magnetic stimulation (TMS), a wire coil is held on the scalp. A brief electrical current passes through the coil and creates a magnetic pulse that affects brain activity. You will hear a click and may feel a pulling sensation on the skin under the coil. There may be a twitch in muscles of the face, arm or leg. We may ask you to tense certain muscles or perform simple actions or tasks during TMS. The TMS will last about 1 ½ hours.

Electroencephalogram (EEG)

During fMRI and TMS, we may record an electroencephalogram (EEG). The EEG records the electrical activity of the brain (“brain waves”). For the EEG, small electrodes will be put on your scalp with an electrode cap. A gel may be placed in the space between the electrodes and your scalp, to make sure there is good skin contact. The electrode cap will be taken off once the EEG is complete.

Questions about fatigue

We will ask you about how tired you are at different times before, during, and after the TMS and MRI sessions.

Storage and Sharing of Samples and Data

If you are enrolled in other studies, your data may be shared with investigators of those studies. The data may be shared with your name and identifying information. Sharing these data and samples will help minimize your need to repeat procedures if data is already collected.

Your data, including images from MRI scan, measurements from TMS, and answers on rating scales, will be stored securely on the NIH campus. Your name and identifying information will not be on the samples and data. The samples and data will either have a code that links to your identifying information or will be stored without a code linking them to you. If they are coded, the key to the code will be kept at NIH in a separate, secure area and will not be shared.

Your data may be shared with others, including those not at NIH. Your data may be sent to a repository for storage and may be released for research purposes. Some repositories restrict access to the data they contain to researchers and projects they approve. Some repositories permit unrestricted access. The data may be used for other research projects,
including those not related to ME/CFS. If you do not want your data used for other projects, you should not participate in this study.

Research using data from this study may lead to new tests, drugs, or devices with commercial value. You will not receive any payment for any product developed from research using your samples and data.

If you withdraw from this research study before it is complete, you may ask that data that can be identified as yours be destroyed. Results obtained before you withdraw will be kept. Your privacy will be protected as much as possible. We will not be able to remove data that have already been sent to a repository or distributed to others.

**Risks, Inconveniences and Discomforts**

**History and physical examination**
There is minimal medical risk and discomfort from providing your medical history and the physical examination.

**Urine Collection**
There is minimal medical risk from providing urine specimens. Collecting urine while in the metabolic chamber may be inconvenient.

We will tell you if you test positive for drugs of abuse and you will be withdrawn from the study. The results of the drug testing will be in your NIH medical record. If you do not want this information in your medical record, you should not participate in this study. Your medical record can only be released with your written agreement. However, insurance companies may require you to release these records and may not give you insurance if you refuse.

Women who are able to get pregnant will have urine testing before any procedure that might be unsafe for pregnancy or fetal development. You will not be able to participate in the study if you are pregnant.

**Magnetic Resonance Imaging (MRI) and Functional MRI (fMRI)**
You may be at risk for injury from the MRI magnet if you have some kinds of metal in your body. It may be unsafe for you to have a MRI scan if you have a pacemaker or other implanted electrical device, brain stimulator, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for such metal before having any scan. If you have any, you will not receive an MRI scan. If you have a question about metal in your body, you should inform us. You will be asked to complete an MRI screening form before each MRI scan you have.

All magnetic objects must be removed before entering the MRI scan room. This includes items like watches, coins, jewelry, and credit cards.

It is not known if MRI is completely safe for a developing fetus. Therefore, all women who are able to get pregnant will have a pregnancy test done no more than 24 hours before each MRI scan. The scan will not be done if the pregnancy test is positive.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.
You will be asked to complete a MRI screening form for each MRI scan you have. There are no known long-term risks of MRI scans.

Transcranial Magnetic Stimulation (TMS)
TMS can cause strong contractions of scalp muscles leading to discomfort or a headache. If you find TMS too uncomfortable, you may stop it at any time. Headaches usually go away by themselves or with nonprescription medication. The noise of the TMS magnet can damage hearing, so you will be fitted with earplugs which must be worn during TMS. TMS can interfere with implanted medical devices. You will not be able to have TMS if you have a pacemaker, implanted pump, a stimulator (such as a cochlear implant) or metal objects inside the eye or skull. Please let us know if you have any of these or hearing loss.

Electroencephalogram (EEG):
There is minimal medical risk from having an EEG. The electrode cap may be uncomfortably tight and cause a headache. The EEG gel sometimes causes mild irritation. You may not like the smell of the paste or the glue remover, but they are not harmful.

Questions about fatigue
There is minimal medical risk from answering questions about how tired you are.

Risk of Banking and sharing of data:
Even though we will remove information that could identify you from data that are sent to repositories or shared, there is a very small chance that the samples and data could be identified as yours.

Anticipated Benefits
There is no direct benefit to you from participating in this research study, however, we hope to learn more about how our TMS and fMRI tests work. We hope this information will help us learn more about ME/CFS.

Right of Withdrawal and Conditions for Early Withdrawal
You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. We can remove you from the study at any time if we believe that continuation is not in your best medical interest or if you are unable to comply with the requirements of the study.

Discussion of New Findings with You
Sometimes there are unexpected findings on tests we will perform in this study. We will tell you about any finding from this study that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider. We may not inform you about minor abnormalities that do not have importance for your health or well-being.

The information we obtain from this study will not provide information on your health. You will not receive any individual results.

Alternatives to Participation or Treatment
This study does not provide treatment and does not replace any therapy that your own doctor is giving you. You may choose not to participate.
Certificate of Confidentiality
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you. The Certificate cannot be used to resist a demand for information from personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of
- We will report certain contagious diseases, information about child or elder abuse or neglect and threats to yourself or others.
- Information needed for your care during a medical emergency may be given to those who are treating you.

Compensation and Travel costs
Participants who are not NIH employees will be compensated for research-related discomfort and inconvenience in accord with NIH guidelines.

For employees of the NIH, in order to receive compensation for the study, participation must occur outside of work hours. Participation during duty hours, requires permission of your supervisor and you cannot receive compensation.

Compensation for completing the technical development sub-study is $120. If you are unable to finish the study, you will be paid for those parts you complete. Travel expenses to NIH from up to 50 miles will be compensated.
OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Avindra Nath, MD Building 10/7C-103, Telephone 301-496-1561, or the Lead Associate Investigator, Brian Walitt, MD, Building 10/3B-19, 301-509-6825.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient’s Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative ___________________________ Date ____________
Print Name ___________________________

B. Parent’s Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor’s Assent, if applicable.)

Signature of Parent(s)/Guardian ___________________________ Date ____________
Print Name ___________________________

C. Child’s Verbal Assent (If Applicable)
The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian ___________________________ Date ____________
Print Name ___________________________

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM OCTOBER 26, 2016 THROUGH OCTOBER 25, 2017.

Signature of Investigator ___________________________ Date ____________
Signature of Witness ___________________________ Date ____________
Print Name ___________________________
Print Name ___________________________

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)

- Adult Patient or - Parent, for Minor Patient
NIH-2514-1 (07-09)
P.A.: 09-25-0099
File in Section 4: Protocol Consent