INSTITUTE: National Institute of Neurological Disorders and Stroke

STUDY NUMBER: 16-N-0058 PRINCIPAL INVESTIGATOR: Avindra Nath, MD

STUDY TITLE: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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ME/CFS

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.

This study will take place at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. The study is run by the National Institute of Neurological Disorders and Stroke (NINDS), within the NIH.

Study Population

Up to 186 people will participate in this study. We will include 3 main study groups:

- 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

The study will also include ME/CFS focus groups- The focus group will include people with ME/CFS who will be interviewed but not otherwise participate in the study. Those in the focus group will sign a separate consent form.

Who Can Be In This Study

You may be able to participate in this study if:

- ☐ You are at least 18 years old, and no older than 60 years old at the time of study enrollment.
- ☐ You completed 7th grade or higher in school.
- ☐ You are able to speak, read, and understand English well enough to complete the study procedures.
- ☐ You are well enough to complete all required study procedures based on our assessment.
- ☐ You have a primary care provider who can provide your medical care while you are in the study.
- ☐ You are able to give informed consent for yourself.

To take part in the PI-ME/CFS group, you must:

- ☐ Have been diagnosed with ME/CFS by a medical care provider
- ☐ Have fatigue that started right after an infection, as documented in your medical records.
- ☐ Have been having fatigue for more than 6 months, but less than 5 years at the time of study enrollment.
- ☐ Currently have substantial and persistent fatigue and post-exertional malaise.

To take part in the Lyme group, you must:

- ☐ Have had Lyme disease diagnosed by a medical care provider
- ☐ Have medical documentation of Lyme disease that meets standard criteria.
- ☐ Have received antibiotics to treat Lyme disease between 6 months and 5 years before the time of study enrollment

Who May Not Be In This Study

You may not be able to take part in this research study if:

- ☐ You have an active infection at the time of study enrollment.
- ☐ You have or have had a disorder that can cause psychosis, such as depression with psychosis, bipolar disorder, or schizophrenia

- ☐ 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.
- ☐ You have ever abused drugs or alcohol
- ☐ You have thoughts about harming yourself or committing suicide.
- ☐ You have had a head injury that caused you to lose consciousness or have memory problems.
- ☐ 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.
- ☐ You are pregnant, trying to become pregnant, or were pregnant in the past year.
- ☐ You have or have had cancer, other than certain skin cancers.
- ☐ You have an immune disorder such as Type 1 diabetes or rheumatoid arthritis.
- ☐ You ever used medications that suppress the immune system such as steroids and biologic immune modifying agents.
- ☐ 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.
- ☐ You are participating in another research study in which you receive treatment that may affect results of this study.
- ☐ You are not able to perform the bicycling exercise stress task.
- ☐ You work directly for one of the study investigators.

You may not be able to take part in the ME/CFS group if:

- ☐ You have a neurological disorder such as stroke, epilepsy, or multiple sclerosis.
- ☐ Your ME/CFS is so severe that you need to be treated in the hospital or cannot leave your home.
- ☐ You have been diagnosed with Lyme disease.
- ☐ You have another illness that can cause fatigue, such as thyroid disease or hepatitis.

You may not be able to take part in the Lyme group if:

- ☐ You have symptoms or signs of chronic fatigue.
- ☐ You have a neurological disorder such as stroke, epilepsy, or multiple sclerosis.
- ☐ You have symptoms or signs of or have been diagnosed with Post-Lyme Disease Syndrome
- ☐ You currently have substantial daily fatigue based on measurements we will obtain

You may not be able to take part in the Healthy Volunteer group if:

- ☐ You have symptoms or signs of chronic fatigue.
- ☐ You have a neurological disorder such as stroke, epilepsy, or multiple sclerosis.
- ☐ You currently have substantial daily fatigue based on measurements we will obtain

Procedures

Study Overview:

If you participate, you will have 1 or 2 inpatient visits at the NIH Clinical Center in Bethesda, MD. Visit 1 will usually take 2-5 days. Visit 2 will usually take 5-10 days but may take longer for some people.

The first visit includes many evaluations and tests (described below) that provide information on the signs, symptoms and biology of those with ME/CFS and the other study groups. The 2nd visit includes exercise stress testing. Not all participants will have the 2nd visit.

Screening:
If you are entering the study as an PI-ME/CFS or Lyme Disease participant, we will ask you to send us your medical records. At your first study visit, we will evaluate you to see if you are eligible to participate in just one or both study visits. You will have some or all of these tests:

Visit 1: This inpatient visit will usually take 2-5 days. If may last longer if needed to complete all the tests.
The tests will provide us with information about how your condition affects you. You will have some or all of these tests. The tests are described in more detail below:

- History and physical examination with medical record and medication review
- Blood collection
- HIV testing
- Urine collection
- Interviews and completion of questionnaires about your symptoms
- Psychological assessment including interviews and completing questionnaires
- Tests of your memory, attention, and thinking
- Magnetic Resonance Imaging (MRI) of the brain
- Muscle strength testing
- Saliva collection
- Stool sample collection
- 24-hour heart (Holter) monitoring
- Lumbar puncture (spinal tap)
- Immune cell collection
- Autonomic nervous system testing of blood pressure control and sweating.

PI-ME/CFS participants only:

- Occupational Therapy evaluation

If you have signs or symptoms that could be better evaluated by particular specialists, we may consult with others and you may be asked to have additional tests.

For PI-ME/CFS participants: After you complete the Visit 1 evaluation, we will be able to determine if you are eligible for the 2nd (exercise stress) visit. A committee of doctors who are experts in ME/CFS will review your medical records and results of the first study visit tests. If you are not eligible for the study exercise stress visit, your participation is complete at the end of the first visit.

Healthy volunteer and Lyme Disease participants will all participate in the 2nd (exercise stress) visit.

Visit 2: Exercise Stress visit
The exercise stress visit will take place within 6 months of the first visit. It will include an inpatient stay of about 5-10 days, but may take longer.

In preparation for the 2nd visit, we may ask you to gradually decrease the dose or stop taking some medications you are on, if they can be stopped safely. Do not stop any medications until we instruct you to do so. We will work with your own doctors if medications are to be stopped.

About 1 week before the exercise stress visit, we will give you an activity monitor to wear at home. We will show you how to keep a diary of your fatigue and ask you to complete the diatry at home for one week.

During the inpatient part of the exercise stress visit, you will spend part of the time in a hospital room specially designed to measure how you use energy. This room, called a "Metabolic Chamber" is described below.

During the exercise stress visit, you will have the following procedures:

- History and physical examination with medication review
- Blood collection
- Urine collection
- Saliva collection
- Completion of interviews and questionnaires about your symptoms
- Activity level monitoring
- Bone density x-ray (DEXA scan)
- Exercise stress Testing
- Tests of thinking, concentration and memory
- Heart monitoring
- Functional Magnetic Resonance Imaging (fMRI) of the brain
- Transcranial Magnetic Stimulation (TMS) of the brain
- Lumbar puncture (LP) (spinal tap)

Many of the procedures in Visit 1 will be repeated during Visit 2. You will do some tests twice during visit 2, once before, and once after exercise stress testing.

Description of Study Procedures

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. This exam will take1-2 hours. This physical exam is for research purposes only and does not replace any exam you may have from your own doctor.

Blood Draw

We will collect blood from you up to 10 times during the study, including (3-4 times at the first study visit and 4-6 times at the 2nd visit. We will measure your blood count and blood chemistries and look at your immune system. We will use the blood for genetic testing. Woman who are able to get pregnant may have a blood pregnancy test. We will also analyze the blood to help us understand ME/CFS better.

Blood will be drawn through a needle in your arm. We will draw no more than 130ml (about 1/2 cup) in a single day. We will draw no more than 550ml (2 and 1/3 cups) total over 8 weeks. A blood draw takes about 10 minutes.

You will have an intravenous (IV) catheter in place at the time of the immune blood collection during the first study visit and during your entire hospital stay for your second visit. For the IV, a needle will be used to guide a thin plastic tube (catheter) into one of your arm veins. We will remove the needle, leaving only the catheter in the vein. The catheter will be taped to the skin to hold it in place. The IV line will be changed every few days to prevent infection. IV placement takes between 5-30 minutes. The IV will be used to draw blood during the study.

HIV Testing

As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

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 a urinalysis, pregnancy testing, and screening for drug use. Collecting a urine sample takes up to 5 minutes.

We will test your urine for illegal drugs. If your drug test is positive, you will be told and you will be removed 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.

Interviews and completion of questionnaires about your symptoms

You will complete many questionnaires during each study visit. The questionnaires will ask about many issues including fatigue, pain, sleep, fibromyalgia (a pain disorder), behavior, activity, and which hand you use for different tasks. Some questionnaires may be completed on paper and some on a computer. We may ask you to fill out the questionnaires yourself, or we may interview you. The questionnaires will take 30 minutes to 2 hours a day.

Psychological assessment including interviews and completing questionnaires

We will ask you questions about your mental health and emotional state. We will ask about anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms. You may be asked to complete questionnaires. These assessments take up to 2 hours.

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. You will be in the scanner between 45-60 minutes. You may be asked to lie still for up to 30 minutes at a time. 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. During part of the MRI scan, you may receive gadolinium, a contrast agent through an intravenous (IV) catheter.

Functional MRI (fMRI) allows us to see what parts of the brain are used when you do a task. You will have an fMRI done 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. The fMRI will take about 90-120 minutes. You will have fMRI scans twice during the second study visit.

Muscle Strength Testing
We will test the strength of your grip and other muscles. Muscle strength testing will take up to 30 minutes.

Activity Level Monitoring
Participants in the 2nd visit will need to wear an activity monitor, similar to a wrist watch, at home for one week before the 2nd visit We will mail the monitor to you and give you instructions. The activity monitor will be worn on your wrist or ankle, or around your chest. Please keep the monitor on at all times except when you take a shower or bath. You will continue to wear the activity monitor during your 2nd visit.

Fatigue Diary: You will be asked to keep a diary of your symptoms, including fatigue, pain, sleep and daily activities while you are home during the week that you wear the activity monitor. You will need to bring the diary with you when you come for your exercise stress visit.

Saliva Collection
We will collect saliva once during Visit 1 and several times during Visit 2. For the saliva collection, you will be asked to chew on a piece of sterile cotton for one minute. We will collect the cotton. We will test the levels of cortisol (a stress hormone) in the saliva.
Cheek Swab
We will rub a cotton swab inside of your cheek for about 10 seconds. We will look at the skin cells collected and the bacteria in the mouth.

Stool Collection
We will collect stool samples during Visit 1. We will look at the types of bacteria that live in the gut and how you absorb different nutrients.

Medication Review and possible withdrawal of medications:
If you are eligible for the exercise stress visit and if you are taking medications that change brain activity, you may be asked to gradually lower the doses, one at a time, and stop taking them temporarily if they can be stopped safely. We will not ask you to stop medications that are necessary for your well-being. Any medications changes would be made during the time between the 1st visit and 2nd study visits. We will work closely with your physicians to taper and stop medications. During this period, we will phone you at least weekly to see how you are doing. You will stay off of these medications until completion of the 2nd study visit. If you cannot not tolerate having the dose of a medication lowered or stopped, let us know right away. If you have an urgent or life-threatening problem while the medication is being stopped, do not wait to call us. Go immediately to the nearest emergency room. Tell the emergency room staff that you are in this study and ask them to call us and your regular physicians. If you have a non-urgent problem, call us at the number below or your regular doctors. If you are not able to stop certain medications that affect brain activity, you will not be eligible for the 2nd study visit.

Autonomic testing

Autonomic testing takes about 90 minutes and may include these procedures:

- Breathing testing: We will place straps around your chest and a monitor on your nose. We will ask you to take several deep breaths in 1 ½ minutes. We will monitor your heart rate when you are taking deep breaths.
- Blood pressure testing with a tilt table: We will look at how your blood pressure changes with changes in position. You will lie on a table that tilts. We will tilt the table in different directions, with your head down and with your head up. We will monitor your blood pressure, breathing, heart rate and other functions and draw blood when you are in different positions on the table. We may also collect urine samples before and after tilt table testing. Tilt table testing usually takes up to 40 minutes.
- Valsalva maneuver: You will blow into a tube against resistance for several seconds and then relax. We will measure your blood pressure, heart rate, and other body functions.

Occupational Therapy Evaluation

An occupational therapist will interview you about your symptoms and how they affect your life. You will be asked about how you do different activities using a card sorting task.

Immune Cell Collection:

We will collect immune cells from your blood.

We usually collect immune cells from the blood by cytapheresis. Cytapheresis lets us get more blood cells than by drawing blood. For cytapheresis, you will sit in a reclining chair. Blood will be removed through a needle in an arm vein and run through a machine. The machine will separate and collect the parts of the blood we need. The rest, mostly red blood cells, will be returned to your body through the same needle or a second needle in a vein of the other arm. This will take about 2 ½ hours.

If you are unable or do not want to have cytapheresis, we can obtain immune cells from a blood draw. We will draw of 100mL (about 7 tablespoons) of blood from an IV line. This blood draw may take up to 30 minutes.

Metabolic Chamber

During the exercise stress visit, you will spend most evenings and nights in a "metabolic chamber." During the times you are not in the metabolic chamber, you will be in regular hospital room. Healthy volunteers and Lyme group participants will spend up to 4 evenings in the metabolic chamber. PI-ME/CFS participants will spend up to 6 evenings in the metabolic chamber.

The metabolic chamber is a specialized room that measures the amount of oxygen that you use and the amount of carbon dioxide you produce. We will also collect your urine while you are in the metabolic chamber. The metabolic chamber room is private. It is small but comfortable. The room has a toilet with a privacy screen, a sink, stationary bicycle, bed, desk, telephone, and television. You may bring a computer and access the internet while in the chamber. You will be given food and fresh water through an air-lock drawer system.

You will be in the chamber for up to 20 hours at a time. While in the chamber, you will be able to eat, rest, read, watch television, use the internet, wash at the sink, and sleep. You will not be able to exercise or have company while you are in the chamber.

For the chamber to work properly, the door to the room must remain shut for the entire time you are in the room. You will be able to communicate through an intercom and you will be able to see the nursing staff through a two-way

window. The nursing staff will be able to see you through a camera linked to a monitor at the nurse's station. We will measure your movement while you are in the room.

If you become uncomfortable or anxious, you can leave the metabolic chamber at any time by just walking out of the door. The door will remain unlocked at all times. You will not be able to stay in the study if you cannot tolerate being in the metabolic chamber.

Bone density and body mass (DEXA) scan

The DEXA scan uses x-rays to measure your body mass and bone thickness. For the DEXA scan, you will lie on an exam table while the scanner moves over you. The DEXA scan takes about 30 minutes.

Exercise Stress Testing

We will look at the effects of exercise on fatigue and body metabolism. You must not smoke for at least 4 hours before exercise stress testing. We will do many tests before, during, and after the exercise stress test.

For the exercise stress test, you will pedal a stationary bike. We will monitor your oxygen intake and carbon dioxide output. We will fit you with a nose-clip that will prevent you from breathing through your nose and a mouthpiece (like a snorkel) or a lightweight mask. We will monitor your heart by placing small metal disk electrodes on your chest. We may put a clip on your finger to measure your blood pressure. You will have an IV line in place during the exercise stress test so that we can draw blood.

Once all of the monitors are in place, you will begin exercising by pedaling the bicycle. We will adjust the resistance of the bike pedals. The exercise stress test will start off very easy and gradually become harder. We want to see how much exercise you can tolerate. We will ask you to keep going until you tell us that you feel you have reached the point at which you cannot continue. You will then be able to rest. The exercise stress test will take about 1 1/2 hours.

We will interview you about how you feel before and after the exercise stress test. The interview will be recorded.

Blood samples will be collected through the IV line before, during, and after exercise stress testing. 26mL (about 2 tablespoons) of blood will be drawn before the exercise, a few hours after exercise, and then daily for up to four days.

Tests of thinking, concentration, and memory

To test these functions, we may interview you, ask you to complete forms and questionaires, have you take pen-and-paper or computerized tests and ask you to perform simple actions. During Visit 1, you will have about 2 hours of this cognitive testing. During visit 2, cognitive testing will be done before and after the exercise stress test and will take about 15 minutes. One of the tests you will do during Visit 2 is a computer game that requires you to quickly press buttons with your left or right hand at different times. You can earn up to $8.60 in rewards by playing the game.

24-hour Heart (Holter) Monitor

The Holter monitor collects information on your heart rate and rhythm over the course of a day. You will wear the monitor for about 24 hours during each study visit. We will place small metal disk or sticky pad electrodes on the skin of your chest. The electrodes have wires that attach to a small monitor box that you will wear. You will not be able to shower while the Holter monitor is in place. Please avoid getting the monitor wet.

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.

During 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. Your brain waves will be recorded during the TMS session. The electrode cap will be taken off once the EEG is complete.

You will have two sessions of TMS during the exercise stress visit. Each session will last about 1 ½ hours.

Lumbar puncture (LP)
For the lumbar puncture, you will lie on your side, curled up with your knees at your chest, or you will sit upright. Your lower back will be cleaned. A medicine will be injected into your back to make the area numb, which may sting for a few seconds. A needle will be inserted through the numbed skin and into the space between the bones in your back. You may feel a sensation of pressure. About 1.5 tablespoons of cerebrospinal fluid (CSF) will be removed. It usually takes 5 to 20 minutes to collect the CSF. After the fluid is collected, the needle will be removed and you may get up and move around as soon as your doctor says you may.

Some people have anxiety about having a lumbar puncture. You may ask for a single dose of an anti-anxiety medicine, such as lorazepam, before the LP.

Other medical consultations
To help us care for you during your participation, we may have you see internal medicine, mental health, rehabilitation, or other specialists.

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

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

Research using blood, DNA, other samples and 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 your remaining samples 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 samples or data that have already been sent to a repository or distributed to others.

Risks, Inconveniences and Discomforts

This study includes a large number of procedures and a significant investment of time and effort. You may find that your fatigue and other related symptoms are made worse by being in this study.

History and physical examination

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

Blood Draw

You may have some discomfort and bruising from the needle insertion. Some people feel light-headed or faint.

With IV line placement, you may have some discomfort and bruising from the needle insertion. Some people feel light-headed or faint. The risks of an intravenous catheter also include bleeding, infection, or inflammation of the skin and vein with pain and swelling. These will be treated if they occur. If you need an intravenous line in place for an extended period of time, the line location will be changed at least every 3 days to prevent infection.

We will collect a large amount of blood from you over the course of this study. You should not donate blood for at least eight weeks before participating until eight weeks after completing the study.

HIV testing

As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

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 these tests if you are pregnant: MRI scanning, TMS, DEXA scan, and lumbar puncture.

Interviews and completion of questionnaires about your symptoms, Psychological assessment including interviews and completing questionnaires, and Tests of thinking, concentration, and memory
There is minimal medical risk from these assessments. They will, however, ask personal questions about your life, including questions about traumatic events. Some of the questions may be upsetting. You may choose not to answer any question that makes you uncomfortable.

During this study, we may find that you have psychiatric symptoms or a psychiatric condition that you were not aware of. If so, we will inform you and your own doctors. We will not be able to provide psychiatric treatment or hospitalization for any such condition at NIH. We will refer you to health care providers or facilities if needed. If you are in danger of harming yourself or someone else and insist on leaving the hospital, we may need to arrange for your involuntary hospitalization somewhere else. If you are transferred to another hospital, NIH cannot provide payment. You or your insurance provider will be responsible for payment.

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.

Symptoms from the MRI gadolinium contrast infusion are usually mild. Symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number of people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not should not receive gadolinium if you previously had an allergic reaction to it. If you have never had gadolinium during an MRI before, you will not get it in this study. You will also not get gadolinium if you have ever had a severe allergic reaction called "anaphylaxis" with any medication or you have had chronic asthma requiring treatment. You will be asked about such allergic reactions and your medical history before gadolinium is administered.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis," which has resulted in a very small number of deaths. If you are older than 60 or have diabetes, kidney disease

or liver disease, a blood test of your kidney function will be done within 4 weeks before any MRI scan with gadolinium contrast. You may not receive gadolinium for a research MRI scan if your kidney function is not normal.

Muscle Strength Testing
There is minimal medical risk of strength testing.

Activity Level Monitoring and Diaries
There is minimal medical risk of activity level monitoring and in completing the diaries. Some of the questions may make you feel uncomfortable or anxious. You may refuse to answer any question for any reason.

Saliva collection, Cheek swab, Stool collection, and Heart (Holter) monitoring
There is minimal medical risk from these procedures.

Medication Review and possible withdrawal of medications
If you need to stop medications for the 2nd study visit, your symptoms could worsen. You may have more severe depression, sleeplessness, irritability, or agitation. You may require hospitalization for worsened symptoms. You may be at an increased risk for suicidal thoughts if you stop anti-depressant medications. We will discuss a safety plan with you and your physicians before lowering dose of any of your medications. We will be in close contact with you during any medication tapering or withdrawal. We will call you at least once a week. We will also work closely with your own health care providers in stopping any medication. If we, you or your doctors find that you cannot safely be off of any medication, it will be restarted. You will not be able to continue in the study if you need to stay on a medication that will interfere with study tests.

Autonomic testing
Breathing test: You may feel lightheaded during the breathing test.

Tilt-table test: Being tilted may make you feel lightheaded or weak or cause fainting. We will monitor your blood pressure and heart rate throughout the procedure. If you have symptoms related to the tilting, or if your blood pressure or heart rate changes too much, we will immediately bring you back to the lying position. We will continue to monitor you until any symptoms improve and your blood pressure and heart rate are back to your regular values.

Valsalva maneuver: Blowing against a resistance takes a moderate amount of effort and may make you lightheaded.

Occupational Therapy Evaluation and other medical consultations
There is minimal medical risk or discomfort from the occupational therapy evaluation or other medical consultations.

Immune Cell Collection
Immune cell collection by cytapheresis can cause lightheadedness or fainting. Some people have tingling in the fingers or around the mouth. The blood thinner used to prevent blood clots during apheresis can cause mild muscle cramps. Let us know if you have side effects. We will slow down the blood flow or use a different blood thinner if participants complain of symptoms. If the symptoms do not go away, we will stop the apheresis. You may also have some pain or get a bruise where the needle is placed.

Metabolic Chamber
Being in the metabolic chamber may make you feel uncomfortable or anxious. If you become uncomfortable or anxious during your stay in the room, you can leave the room at any time by walking out; the door will be unlocked at all times.

Bone density and body mass (DEXA) scan

The DEXA scan involves exposure to radiation. The amount of radiation exposure is less than a dental xray. If you are pregnant, you may not have a DEXA scan.

Please tell your doctor about any radiation exposure in the past year including from other research studies or from medical tests. We want to be sure that you do not receive too much radiation. Examples of tests that expose you to radiation include x-rays, cardiac catheterization, fluoroscopy, and nuclear medicine scans.

Exercise Stress Testing

Exercise stress testing can be risky for people with heart disease. People with known heart disease may not take part in this study. Although we will check heart function in all study participants, it is possible that you could have an unidentified heart disease. Such hidden heart disease could lead to chest pain, irregular heartbeat, or death during stress exercise. The risk of death for healthy adults who undergo maximum exercise stress testing is between 0 and 3 deaths/100,000 tests. We will monitor your heart rhythm continuously during the exercise stress testing and will stop the test immediately if there is any concern or if you have heart symptoms, breathing symptoms or another serious effect.

Other risks of exercise stress testing include muscle or joint soreness. Muscle soreness and fatigue could last several days. You may be given mild pain relievers if needed for soreness.

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.

There is minimal medical risk from having an EEG. The electrode cap may be uncomfortably tight and cause a headache. You may have mild scalp irritation.

Lumbar puncture (LP)

You may have a brief pain or tingling sensation in your legs during the lumbar puncture if the needle brushes against a nerve. If this happens, please let us know immediately and the needle will be adjusted. Some people get a mild backache at the site of needle insertion. About one-third of people have a headache for a few days after a lumbar puncture. Usually the headache is not severe and improves without treatment other than a mild pain reliever. Headaches lasting longer than 7 days develop with one in 50 to 200 lumbar punctures and usually improve gradually over 2 weeks. In rare cases, headaches persist longer. Prolonged headaches may be due to persistent leakage of CSF from the area of the lumbar puncture. If your headache is prolonged, you may get a "blood patch." For the blood patch, we will remove blood from a vein in your arm and inject it into the area of your back where the lumbar puncture was performed to seal off the leak of CSF.

If you receive anti-anxiety medication, such as lorazepam, before the LP, the medication will cause sedation. Other possible side effects include confusion, dizziness and agitation. You will be monitored while you are sedated.

If your lumbar puncture is done in the radiology department, x ray fluoroscopy will be used to direct needle placement.

Radiation Exposure
This research study may involve exposure to radiation from up to 2 lumbar puncture under X-ray and a DEXA scan. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you may receive in this study is up to 0.046 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant, you will not be allowed to take part in this research study. It is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults.

Risk of Banking and sharing of samples and data:
Even though we will remove information that could identify you from samples and 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 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 results from this research study will be preliminary. Further research may be necessary before they are fully understood. We do not plan to provide you with research results.

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.

Alternatives to Participation

This study does not provide treatment. You may choose not to participate. You may have to stop medications in order to participate. You may prefer not to stop any medications but to remain on them under the care of your own physicians.

Compensation and Travel costs

NIH will cover travel expenses to and from the Clinical Center in Bethesda, Maryland within the United States. Reimbursement for meals may be offered consistent with NIH guidelines. Accommodations will be provided if an overnight stay is necessary.

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 first study visit will be $490. Those who have cytapheresis will receive an additional $110.

Compensation for completing the exercise stress visit will be $1,005. You may earn an additional $4.00 - $17.40 from the Effort for Reward task.

If you are unable to finish the study, you will be paid for those parts you complete.

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.

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 Principal Investigator, Avindra Nath, MD Building/Room 10/7C-103, Telephone 301-496-1561, or the Lead Associate Investigator, Brian Walitt, MD, Building/room 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 DECEMBER 16, 2015 THROUGH DECEMBER 15, 2016.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____