Cover Page to Accompany ClinicalTrials.gov Document

Informed Consent: January 09, 2019

For Protocol

Defining Neurobiological Signatures for Chronic Traumatic Brain Injury Using PET-MRI Technology

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Thomas Jefferson University IRB
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Thomas Jefferson University
Informed Consent Document for Human Subjects Research

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Medical Study Title: Defining Neurobiological Signatures for Chronic Traumatic Brain Injury Using PET-MRI Technology

Lay Study Title: PET-MRI and the Effect of N-Acetyl Cysteine (NAC) and Anti-Inflammatory Diet in Traumatic Brain Injury

What Is Informed Consent?

You are being asked to take part in a medical research study. As required by federal regulations, this research study has been reviewed and approved by an Institutional Review Board (IRB), a University committee that reviews, approves and monitors research involving humans. Before you can make a knowledgeable decision about whether to participate, you should understand the possible risks and benefits related to this study. This process of learning and thinking about a study before you make a decision is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form, once you understand the study and have decided to participate. If you don't understand something about the study or if you have questions, you should ask for an explanation before signing this form;
- Being given a copy of the signed and dated consent form to keep for your own records.

You should understand that your relationship with the study doctor is different than your relationship with your treating or personal doctor. The treating doctor treats a specific health problem with the goal of improving a medical condition. A study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that you may or may not benefit from being in the study. You should ask questions of the study doctor if you want to know more about this.

What is the purpose of this study?

You have been diagnosed with a chronic traumatic brain injury (cTBI) which means that you have had persistent symptoms for more than three months after a concussion or head injury.

Chronic TBI usually is treated with rest and minimizing further strain on the brain. The goal is to allow the brain to heal by not putting it under any additional stress. The goal is that the brain will heal itself within a few months. However, in some patients, the symptoms persist for 3 or more months. Symptoms can include a variety of problems such as headache, cognitive impairment, brain fog, dizziness, difficulty concentrating, emotional problems, coordination problems, and many others. Part of the difficulty in treating cTBI is to determine how better to diagnose what specific issues are affecting the brain. In order to assess the brain function more effectively, we would like to have you undergo a small battery of diagnostic tests that include magnetic resonance imaging (MRI), positron emission tomography (PET), quantitative electroencephalography (EEG), and serum measures in the blood for detecting inflammation. Scans may be performed at the Marcus Institute of Integrative Health PET-MRI scanner using standard head coils or a 32 channel research head coil (Ceresensa: London, ON) which is medically equivalent to currently available head coils, but designed specifically for the PET-MRI scanner. This head coil poses no additional risk to the patients. In addition, you will receive neurocognitive testing to determine which brain functions are most affected. We hope that this battery of diagnostic studies can be used to best determine what areas of the brain are affected by the cTBI and which diagnostic tests might best determine your potential for recovery. In addition, evidence suggests that part of the process that results in the cTBI is related to inflammation or chronic injury/damage to the brain. Thus, a secondary goal of this study is to determine if the administration of an antioxidant supplement or an anti-inflammatory diet designed to reduce inflammation in your body might help to support the healing process of the brain. Thus, in this study, you may receive detailed support to modify your diet for 90 days to include low inflammatory foods or you may receive a natural supplement called n-acetyl cysteine (NAC) that you will take for approximately 90 days. Prior to starting the supplements and at the end of approximately 90 days, you will undergo the brain scan evaluation and receive neurocognitive testing. A third group will be placed into the waitlist control which will have the initial evaluation and the 90 day evaluation while receiving your standard of care treatment for cTBI. At that point, you will be offered the opportunity to receive the NAC for 90 days. We will perform the scans and tests one more time on all patients approximately 180 days (six months) after your original evaluation.

How many individuals will participate in the study and how long will the study last?

We hope to enroll up to 120 patients at Jefferson. The entire study will take about 3 years to complete. Your involvement in the study will last about 6 months.

What will I have to do during the study?

The informed consent process will be completed with you. You will be asked questions about your medical history and about the medications you are taking. You will also be asked to complete several questionnaires about your mood, memory, your physical activity level, and how you feel that will take approximately 30-45 minutes. These questionnaires will include the Speilberger State Trait Anxiety Inventory (STAI), the Profile of Moods Scale (POMS), the Beck Depression Inventory, and for quality of life, the Epworth Sleepiness Scale, Mayo-Portland

Adaptability Inventory-4, Rivermead Post-Concussion Symptoms Questionnaire, and the TBI-39. Cognitive testing may include the Mini-Mental Status Exam, the Delis Kaplan Executive Function System (DKEFS) color-word interference, Trails A & B, and forward and reverse digit span. You will also undergo a neurological examination evaluating your symptoms in order to determine how much the cTBI affects you. You will repeat this process including the questionnaires and examination at 3 and 6 months. Throughout the study, you will continue to take whatever medications your doctor has prescribed for you and will follow your doctor's standard advice regarding management of your cTBI. However, we will ask you to try to remain at the same dosage of any medication throughout the study unless your doctor changes the dose because of worsening symptoms or because of side effects.

Prior to receiving the anti-inflammatory diet, the NAC, or standard of care treatment, you will receive two different brain scans that will be performed simultaneously in a special combined scanner. One scan, called positron emission tomography (PET), will evaluate your brain metabolism and also the level of inflammation in areas affected by the cTBI. The other scan, called magnetic resonance imaging (MRI) will evaluate the structure and function of the brain, along with the connecting fibers affected by cTBI. On the day of both scans, you will report to Marcus Institute of Integrative Health at 789 E. Lancaster Avenue in Villanova, PA 19085.

Female subjects of child bearing potential will first have to confirm that they are not pregnant or undergo a pregnancy test if unsure, and if negative will proceed with the remainder of the study. Once there, you will be taken to the scanner area in the Marcus Institute of Integrative Health. You will receive these scans at the beginning. You will also receive only the MRI component after approximately 3 months and again after 6 months of receiving the anti-inflammatory diet, receiving the NAC, or receiving standard of care for your cTBI.

The PET scan measures the energy metabolism in the brain which is particularly affected in cTBI. The PET scan works by injecting into your vein a radioactive medicine called FDG. FDG is a form of the sugar glucose that is used by your brain for energy. By injecting the FDG, we can see where in the brain it goes so that we can take a picture of the energy of the brain. After injection of the fluorodeoxyglucose (FDG), you will be asked to rest quietly in a dimly lit room for approximately 30 minutes. At that point, you will be brought into the scanner room and will lie down on the PET-MR imaging table. The remainder of the procedure involves having your head held comfortably in a special head holder as a reminder not to move your head and remain still while the scanner takes pictures of your brain.

The MRI scan is performed simultaneously with the PET scan using a special PET-MRI scanner that can do both at the same time. For the MRI scan, we will ask you a number of questions to make sure you do not have any metal in your body that might affect the scanner. While you are lying on the imaging table for the PET scan, the MRI scan will also be performed. All of this is done over a period of time of about 45-60 minutes with your head in a special head holder surrounded by a head coil that enables us to take pictures of your brain. On the follow up scans, you will only receive the MRI scan and thus will be in the scanner for approximately 45 minutes. However, for the MRI only scans, you will not receive an injection of radioactive FDG.

In addition to the PET and MRI scans, you will receive an electroencephalogram (EEG) which requires electrodes to be placed onto your scalp in order to measure the electrical activity in the brain. The EEG records this electrical activity for about 20 minutes. The EEG will be performed at the beginning of the study, and at 3 and 6 months. The EEG can be performed on the same day as the scans or on a different day, but no more than ±14 days from the scan. Similarly, we will draw a sample of blood to check for markers of inflammation. This will require approximately 2 tubes (4-6 Tablespoons) of blood to be drawn and these will be sent off to the lab.

For the treatment component of the study, you will first be assigned into one of three groups. The first group will receive instructions on following a strict anti-inflammatory diet. In general, this will eliminate/reduce dairy products, carbohydrates, red meats, and saturated fats while enhancing intake of proteins, beneficial fats, and plant based foods such as vegetables and fruits. You will also be required to keep a food diary (using either the computer or written depending on your preference) during this time period. The second group will receive a strong antioxidant called N-acetyl cysteine (NAC). When taken orally, NAC is an over-the-counter anti-oxidant supplement. At higher doses that are given intravenously (IV-through the veins), NAC is a medication approved by the FDA for treating an overdose of acetaminophen. However, NAC has not been specifically evaluated in humans for its effects in patients with cTBI. In order to ensure that you receive an adequate amount of NAC, in this study, you will receive an intravenous infusion of NAC each week and take oral NAC daily for approximately 90 days. Each infusion is given over approximately 1 hour and involves the infusion of a liquid solution of NAC directly into the vein. The oral NAC will be given in 500mg capsules that will be taken twice a day on the days that you do not receive the IV. The dosing for both the intravenous and oral NAC is based on currently established guidelines for the use of NAC.

The third group will only receive the standard of care for cTBI, but will still undergo the scanning, EEG, neurocognitive, and blood testing initially, and then at 3 and 6 months. After the 3 month evaluation, these individuals will be allowed to receive the NAC for 3 months prior to the 6 month scan and evaluation.

What are the risks or discomforts involved?

Risks from taking the supplements

N-acetyl cysteine (NAC)

You might experience fatigue or frustration with having to come in to Marcus Institute of Integrative Health either at Villanova or downtown Philadelphia once a week for the infusions. However, you are allowed to miss up to 4 doses and still remain in the study. Since the infusions of NAC require placing an intravenous catheter in your arm via a needle, there can be pain and discomfort at the IV site. Bleeding and infection may also occur. Reports of side effects related to NAC are uncommon but can include nausea, vomiting, and diarrhea or constipation. In the literature the most frequently reported adverse reactions attributed to intravenous NAC administration were rash, urticaria and pruritus. These are all reported in studies of patients receiving NAC for acetaminophen overdose in which the NAC is given over a period of several

days. The frequency of adverse reactions has been reported to be between 0.2% and 21%, and they most commonly occur during the initial loading dose of NAC. Serious acute hypersensitivity reactions during NAC administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous NAC for acetaminophen overdose and occurred soon after initiation of the infusion. Rarely, NAC can cause rashes, fever, headache, drowsiness, low blood pressure, and liver problems. One patient with asthma developed bronchospasm and died after intravenous administration of NAC and we therefore will not include patients with a history of asthma requiring daily medication for adequate management. In animals, NAC has sometimes been found to be associated with pulmonary hypertension, but this has not been reported in human beings. We will review your medications to determine if there may be any potential interactions. If you are able to participate in the study, we may also discuss with you or your doctor how to closely monitor any changes in your response to your medications while on the study.

Risks from following an anti-inflammatory diet

The diet is designed to be healthy and reduce inflammation throughout the body. However, anytime modifications are made to your diet, gastrointestinal discomfort or changes in bowel habits may occur. You might also be frustrated by having to follow the diet since it restricts certain foods.

PET Risks

Use of FDG PET imaging is commercially approved, and has resulted in very rare adverse effects of skin redness, facial swelling, fever, and short lasting rise in blood pressure. This research study involves exposure to radiation from the FDG PET scan and therefore you will receive a radiation dose that you would not receive if you did not have the scans. The radiation dose obtained as the result of participating in this study is the same as standard clinical brain scans using the same tracers. Therefore, at the doses you will receive, it is very likely that you will see no effects at all. Please inform the investigator of any participation in previous studies involving radiation exposure. Some persons may experience some discomfort while lying flat on the table for the PET-MRI scan or may feel uncomfortable or anxious in the scanner. Since the injection of the FDG requires inserting a needle into your arm vein, there can be pain and discomfort at the injection site. Bleeding and infection may also occur.

MRI Risks

You will be asked to complete a MRI Patient Information History form. The MRI scan does not involve any radiation exposure. You will have the scan performed by placing your head within a standard head coil or a 32 channel research head coil to obtain better images. There is no added risk with either of these head coils. Due to the strength of the magnetic field of the MRI, there is a risk of being injured by receiving a burn on your skin or if an unsecured metal object flies into the MRI scanner. In order to minimize this risk, you will be asked to remove all metal objects from your person. Also, all metal objects will be cleared from the area prior to the scan. This is the standard practice when patients undergo MRI exams. It is important when discussing the study that you inform the staff if you have any of the following:

- Surgically implanted electrical devices

- Pacemaker
- Surgically placed metallic clips (aneurysm clips)
- Ear implants
- Any history of metal fragments in the eye

Some persons may experience some discomfort while lying flat on the table for MRS scans or may feel uncomfortable or anxious in the scanner.

You will also receive an intravenous injection of MRI contrast which is a material that helps show the brain lesions related to cTBI. This is standard of care for MRI imaging in cTBI patients. Side effects from the MRI contrast are mild and rare, but can include a feeling of warmth or flushing, nausea and vomiting, headache, itching, and mild skin rash or hives. With MRI contrast, any side effects are usually mild and we will treat them before you leave the facility. Severe allergic reactions are rare, but can lead to difficulty breathing, cardiac arrest, swelling of the throat or other parts of the body, convulsions, or profound low blood pressure. The Marcus Institute of Integrative Health doctors and technologists are highly trained for managing contrast reactions and have the medications required to treat such reactions on site.

EEG Risks

For the EEG, a cap with electrodes will be placed on your head. This requires a gel to be applied to parts of the scalp and the cap can sometimes be uncomfortable or pull your hair. You will then have to rest quietly for approximately 20 minutes while the EEG is recorded.

Question and Neurological Examination Risks

Some of the questions we will ask you as part of this study, as well as the neurological examination, might make you feel uncomfortable. You can refuse to answer any of the questions and you are free to take a brief break at any time when answering these questions or while undergoing the neurological exam. However, you must complete the questionnaire or neurological exam during the study period.

Risks of Discovering an Incidental Finding

The result of the scans will be reported in a clinical report by a trained specialist. If an unknown abnormality (also called an incidental finding) is discovered on the PET or MRI scan, you will be thoroughly counseled by the study doctor and will have an opportunity to ask any questions. Such a finding may make you feel anxious or depressed. However, the information and scans will be made available to your primary care doctor or referring physician in order to manage the finding as quickly and effectively as possible.

What To Do If You Experience Any Adverse Effects

You should call the study doctor as soon as possible at 215-955-2221 if, during the course of this study, you develop any side effects or symptoms. The study doctor has told you that if your condition worsens, if side effects become very severe, or if it turns out that being in this study is not in your best interest, you will be taken out of the study.

What are the risks to fetuses, infants and pregnant women?

Pregnant women or women who are breast feeding should not be in this study because exposure to investigational drugs may be hazardous to an embryo, fetus or nursing infant. Even medications that are well known and prescribed may have adverse effects on an embryo or fetus. Since this study also includes radiation related to the FDG PET scans, pregnant women or women who are breast feeding should not be in this study. As with any medication, there are unknown risks. To be in this study you and your partner must practice adequate birth control measures. The study doctor will discuss acceptable methods of birth control with you. If you are a woman of childbearing potential, you will have a pregnancy test before making a decision about being in this study. This requires either a urine test or that blood be drawn from a vein in your arm (1-2 tsp.) one or two days prior to the start of the study. The results of this pregnancy test will be made available to you prior to the start of the study.

If you become pregnant during the course of this study, you should notify the study doctor as soon as possible.

If you are a person in a same sex relationship, it is not necessary for you to practice birth control. However, if you are female, you will still have to have pregnancy tests according to the study protocol.

Are there alternatives to being in the study?

You do not have to participate in this study.

How will privacy and confidentiality (identity) be protected?

Federal regulations require that certain information about individuals be kept confidential. This information is called "protected health information" (PHI). PHI includes information that identifies you personally such as name, address and social security number, or any medical or mental health record, or test result, that may have this sort of information on it. The laws state that you may see and review your TJU or Thomas Jefferson University Hospital medical records at any time. However, in a research study, you may not see the study results or other data about the study until after the research is completed unless the study doctor decides otherwise.

If you join this study, the following individuals or entities may have access to your PHI and by law must protect it. These include investigators listed on this consent form and other personnel of Thomas Jefferson University and Thomas Jefferson University Hospitals, Inc. involved in this specific study, the University's Division of Human Subjects Protection and the Institutional Review Board (IRB), and your health insurance company (if necessary for billing for standard medical care).

Your PHI may also be shared with the following entities that, while not obligated by law to protect PHI, will protect it to the best of their ability:

- Principal Investigator or designated research staff, who will oversee the study and review medical records to ensure study-related information is correct,
- With any person or agency required by law.

If you develop an illness or injury during the course of your participation in this study, other PHI about treating and following the condition may be generated and disclosed as it relates to this study. Your PHI may be used/disclosed until the end of the research study.

You may quit the study and revoke permission to use and share your PHI at any time by contacting the Principal Investigator, in writing, at: Andrew Newberg, MD, 925 Chestnut Street, Suite 120, Philadelphia, PA 19107. If you quit the study, further collection of PHI will be stopped, but PHI that has already been collected may still be used.

The results of clinical tests and procedures performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, this Web site will include a summary of the results. You can search this Web site at any time.

What if I am injured as a result of being in this study?

In the event that you experience a research-related injury, necessary and available medical care (including hospitalization) will be provided. A research-related injury is a physical injury or illness resulting to you that is directly caused by any procedure or treatment used in this study that is different from the treatment you would receive if you were not participating in a research study. If you are physically injured due to any drug/substance or procedure properly given under the plan for this study, medical expenses for treating the injury will be billed to your insurance carrier. You should be aware that some costs may not be covered by insurance. There is no plan to provide compensation for loss of wages, lost time from work, personal discomfort, or for injuries or problems related to your underlying medical condition(s).

If you receive a bill related to a research-related injury that seems wrong, please discuss it with the study doctor or research coordinator.

Will I benefit from being in this study?

You may not benefit from being in this research, but we hope that what we learn may be helpful to future patients or society in general.

Will I be paid for being in this study?

You will not receive any additional payment for participation in the study. You will receive parking vouchers for the days that you travel to the downtown Jefferson office for any evaluation or IV. There is free parking at the Villanova office.

Will I be told about any new findings?

Anything learned during the study, beneficial or not, that may affect your health or your willingness to continue in the study, will be told to you and explained.

Disclosure of Financial Interest

None of the investigators has any financial interest in the companies that provide products for this study.

Are there costs related to being in this study?

There will be no charge to you for participating in the study. Some diagnostic studies that are clinically indicated may be covered by your insurance such as for the scans, EEG, or laboratory analyses. However, if your insurance does not cover these in part or in full, they will be covered as part of your participation in the study. The dietary counseling and the NAC are provided as a part of this study.

If you receive a bill that you think is wrong, please discuss it with the study doctor or research coordinator.

Standard Testing Procedures

Procedures, tests and doctor's charges resulting that are considered standard of care will be billed to your health insurance carrier. These are charges that you would have whether or not you were participating in a research study which include standard physical and neurological examinations, medications prescribed by your physician, and any other medical treatment you undergo. It is possible that your insurance company may deny payment. If that happens you may be responsible for some or all of these charges. The study doctor will explain to you which procedures, tests and doctor visits are considered standard of care.

If you receive a bill that you think is wrong, please discuss it with the study doctor or research coordinator.

Can I be removed from the study or quit the study?

Your decision to participate in this research study is entirely voluntary. You have been told what being in this study will involve, including the possible risks and benefits.

Your participation in this research project may be terminated by the study doctor without your consent/assent for any reason that he/she feels is appropriate.

You may refuse to participate in this investigation or withdraw consent and quit this study without penalty and without affecting your ability to receive medical care at Thomas Jefferson University.

If you withdraw from this study, you may continue treatment with your Jefferson doctor, or you may seek treatment from another doctor of your choice.
Should you decide to withdraw from the study, please be sure to inform the study doctor. Additional tests or procedures may be needed to ensure your safety. The study doctor will explain why these tests or procedures are necessary.

If you miss a total of 5 or more days of the oral supplements or 5 doses of the intravenous NAC you may be asked to be removed from the study by the investigators. Similarly, if you are not following the anti-inflammatory diet, you may be asked to be removed from the study by the investigators.

CONTACT INFORMATION

Telephone number for questions about your rights as a research participant	The Jefferson Institutional Review Board	215-503-8966
For questions, concerns or complaints about the research, or if you suspect a research-related injury	Principal Investigator Andrew B. Newberg, MD Co-Investigator, Daniel A. Monti, MD Program Manager, Nancy Wintering, LCSW	215-503-3422 215-955-4410 215-503-3423
If you have difficulty contacting the study staff	Call the Jefferson Office of Human Research	215-503-0203

If you want more information about the Jefferson Institutional Review Board or Jefferson's Human Research Protection Program, please visit our website at http://www.jefferson.edu/human_research/irb/index.cfm

The physician investigator's signature certifies that s/he personally provided the study participant with a description of the study, study procedures, risks, benefits and alternatives to participation.

Non-Waiver of Legal Rights Statement

By your agreement to participate in this study, and by signing this consent form, you are not waiving any of your legal rights.

In order to be in this research study, you must sign this consent form.

You affirm that you have read this consent form. You have been told that you will receive a copy.

Signatures:

_____(Date)
Your Name *(please print or type)*

_____(Date)
Your Signature

_____(Date)
Witness Signature
(Only required if subject understands and speaks English, but cannot read English, or if subject is blind or cannot physically sign the consent form—delete if inapplicable)

_____(Date)
Name of Person Conducting Consent Interview

_____(Date)
Signature of Person Conducting Consent Interview

_____(Date)
Signature of Principal Investigator or Co-Investigator

As Per University Counsel - Do Not Sign This Consent Form After 11-10-22