Cover Page to Accompany ClinicalTrials.gov Document

Informed Consent: October 05, 2018

For Protocol:

Physiological Effects of Nutritional Support in Patients with Parkinson's Disease

Thomas Jefferson University IRB ID: 14D.141

Clinical Trial Number: NCT02445651

Thomas Jefferson University
Informed Consent Document for Human Subjects Research

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Medical Study Title: Physiological Effects of Nutritional Support in Patients with Parkinson's Disease

Lay Study Title: Nutritional Support in Parkinson's Disease

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 Parkinson's disease (PD) which is a disease in which the dopamine system in the brain is damaged. PD usually is treated with medications designed to stimulate the dopamine system in the brain in order to relieve the symptoms such as tremor, rigidity, or slowness of movement. Evidence suggests that an important part of the disease process is damage to the dopamine nerve cells in the brain caused by too much oxygen

(sometimes called oxidative stress) or too much inflammation (or swelling). The purpose of this study is to determine whether oral/intravenous NAC might help to support the dopamine system in the brain. NAC is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine. It is a common over-the-counter supplement and also is available as an injectable pharmaceutical. In the exercise physiology literature, both oral and injectable NAC have been shown to reduce fatigue and improve recovery from exertion which has interesting implications for exploring fatigue related to PD.

Thus, in this study, you may receive one or more supplements that have antioxidant or anti-inflammatory effects. We will provide the NAC supplement to you to take for approximately 90 days. Prior to starting the supplements and at the end of approximately 90 days, you will have your dopamine system evaluated using two special brain scans for PD, (described below) and receive a neurological examination of your movement, tremor, and rigidity to evaluate your PD symptoms. One scan measures the amount of dopamine in your brain while the other measures markers of actual damage in the brain caused by the PD.

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

We hope to enroll up to 65 patients at Jefferson. The entire study will take about 3 years to complete. Your involvement in the study will last about 3-4 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 some questionnaires about your mood, memory, your physical activity level, and how you feel. These questionnaires will take up to 1 hour to complete. You will also undergo a neurological examination evaluating your movement, tremor, and rigidity, in order to determine how much the PD affects you. You will repeat this process including the questionnaires and examination at the end of the study. Throughout the study, you will continue to take whatever Parkinson's medications your doctor has prescribed for you. However, we will ask you to try to remain at the same dosage of your Parkinson's medication throughout the study unless your doctor changes the dose because of worsening symptoms or because of side effects.

Prior to receiving NAC or standard of care treatment, you may receive two different brain scans that may be performed on the same day, but can be performed within two weeks of each other in case of scheduling delays. The order of the scans does not matter. One scan, called single photon emission computed tomography (SPECT), will evaluate your dopamine system. The other scan, called magnetic resonance spectroscopy (MRS) will evaluate the amount of oxidative stress in the brain. On the day of both scans, you will report to either the Myrna Brind Center of Integrative Medicine at Thomas Jefferson University and Hospital or the Marcus Integrative Health at the Myrna Brind Center – Villanova.

Female subjects of child bearing potential will first have a pregnancy test and if negative will proceed with the remainder of the study. Once there, you will be taken to the Division of Nuclear Medicine to undergo the SPECT imaging or the Department of Radiology for the MRS scan. You will receive two of these scans during the study, one each at the beginning and one each after approximately 90 days of receiving the NAC.

The SPECT scan measures the dopamine system in the brain which is where the primary biological problem in Parkinson's disease occurs. The SPECT works by injecting into your vein a radioactive medicine called DaTscan. DaTscan links to the dopamine receptors in your brain so that we can take a picture of the health of the dopamine system. The SPECT scan may be performed on the same day as the MRS scan, but they can be performed within two weeks of each other in case of scheduling delays. The SPECT scan with DaTscan involves drinking 16 drops of a solution called Lugol's solution approximately 30 minutes before injection, which protects your thyroid from radioactive exposure. The use of Lugol's solution is standard practice for these clinical studies. You will then have an intravenous catheter placed in your arm and receive a dose of the commercially approved DaTscan tracer by injection through the catheter. After injection of the tracer, your intravenous catheter will be removed. Approximately three hours after the injection, you will be positioned on the SPECT 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 for approximately 45 minutes.

On the day of the MRS study, you will report to either the Myrna Brind Center of Integrative Medicine at Thomas Jefferson University and Hospital or the Marcus Integrative Health at the Myrna Brind Center – Villanova. You will be taken to the Department of Radiology to undergo MRS which requires an MRI scanner. You will be positioned on the 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 during the imaging procedure, which will last for approximately 60 minutes.

For the treatment component of the study, you will first be placed into one of two groups by chance. The first group will receive a strong antioxidant called N-acetyl cysteine. 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 PD. 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. 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 600mg 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 second group will only receive the DaTscan and the MRS approximately 90 days after the first set of scans with no additional treatment in between other than your current PD medications.

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 either the Myrna Brind Center of Integrative Medicine or the Marcus Integrative Health at the Myrna Brind Center – Villanova once a week for the infusions. However, you are allowed to miss up to 5 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. Rarely, NAC can cause rashes, fever, headache, drowsiness, low blood pressure, and liver problems. It may worsen asthma.

Oral Supplements

General Risks: Any supplement could result in an allergic reaction. You should report any unusual feelings you have while receiving the supplements. In addition, the NAC could interact with different medications. You should tell us if you are taking any of the following:

1. Medications for high blood pressure such as captopril (Capoten), enalapril (Vasotec), losartan (Cozaar), valsartan (Diovan), diltiazem (Cardizem), Amlodipine (Norvasc), hydrochlorothiazide (HydroDIURIL), furosemide (Lasix), and many others.
2. Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) such as aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), alpha tocopherol, and others.
3. Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others.
4. Nitroglycerin can dilate blood vessels and increase blood flow. Taking N-acetyl cysteine seems to increase the effects of nitroglycerin. This could cause increased chance of side effects including headache, dizziness, and lightheadedness.

We will review your medications to determine if there may be some potential. 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.

SPECT Risks

Use of DaTscan SPECT 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 DaTscan 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. The lugol's solution that you will be asked to drink can cause a temporary strange taste in their mouth or a feeling of discomfort in your salivary glands. Some persons may experience some discomfort while lying flat on the table for SPECT scans or may feel uncomfortable or anxious in the scanner. Since the injection of the DaTscan requires inserting a needle into your arm vein, there can be pain and discomfort at the injection site. Bleeding and infection may also occur.

MRS/MRI Risks

You will be asked to complete a MRI Patient Information History form. The MRI scan does not involve any radiation exposure. Due to the strength of the magnetic field of the MRI, there is a risk of being injured 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.

Survey 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 SPECT or MRS 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 215-503-3422 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 DaTscans, 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:

- Nancy Wintering, or designated study staff and nurses 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: Daniel Monti, 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 receive payment for your participation in this study. You will receive $50 for completing the first SPECT and MRS scans, and questionnaires. You will receive an additional $50 for completing the second SPECT and MRS scans, and questionnaires.

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 or your health insurance for any of the SPECT or MRS scan or for the nutritional supplements, or the intravenous NAC 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.

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 Daniel A. Monti, MD Co-Investigator, Andrew B. Newberg, MD Program Manager, Nancy Wintering, LCSW	215-955-4410 215-503-3422 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

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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.

The 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.

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 8/28/20