Brain Small Chain Fatty Acid Metabolism in Parkinson Disease: Tributyrin Supplementation (BUTTER)

NCT05446168

3/9/2023

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

1.1 Study title: Brain Small Chain Fatty Acid Metabolism in Parkinson Disease: Tributyrin supplementation

1.2 Company or agency sponsoring the study: Farmer
Family Foundation

1.3 Principal Investigator: Nicolaas Bohnen, MD, PhD, University of Michigan, Departments of Radiology and Neurology, Functional Neuroimaging, Cognitive & Mobility Laboratory

Study Coordinator: Alexis Griggs, BA, and Robert Vangel, BSc, University of Michigan, Department of Radiology, Functional Neuroimaging, Cognitive & Mobility Laboratory

1.4 Key Study Information
You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

The investigators want to learn whether the intake of tributyrin, a small chain fatty acid that is naturally present in butter, may affect glucose uptake in the brain or body. The investigators also want to explore how the intake of the tributyrin supplement may affect cognitive (thinking), motor or other clinical functions. Clinical, motor, cognitive testing will be performed before and after the treatment with the approximately 30day tributyrin supplement. Optional brain and body glucose and butyrate PET imaging and optional brain MRI will be performed before and at the end of an approximately 30-day period where you will take the tributyrin supplement. Physical activity, sleep, and glucose levels will be monitored for a week prior to the start of the tributyrin supplement intake and during the last week of the supplement intake. Sleep will also be monitored throughout your time taking the tributyrin supplement. Physical activity and sleep will be monitored using wearable sensor. A glucose monitor will also be worn during the same period. If you are a person with

Parkinson's disease the investigators may ask you to hold your Parkinson's disease medications in the morning of the imaging or clinical assessments.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This research is studying an over-the-counter supplement called tributyrin (a prodrug of butyric acid also known as butter acid) in older persons people or people with Parkinson's disease to learn about its safety and its effect on your body and brain as a treatment for Parkinson's disease or other age-related brain conditions that may affect cognitive or thinking functions. This study will examine the relationship between uptake of glucose (sugar) in the brain and body as determined by the use of optional radiolabel PET tracer of glucose. Optional PET imaging is used to take pictures of the brain while you are lying in a camera following the intravenous injection of the radiolabeled tracer. The images will show how much glucose and/or butyrate is used by the brain or body. Optional brain MRI and optional genetic analysis will also be performed before and after using the tributyrin supplement.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Men and women without or with Parkinson's disease or normal adults who are at least 45 years of age, can participate in this study. Participants should be willing and able to comply with study requirements. Subjects with other neurological (including seizures), psychiatric, or unstable medical conditions may be excluded. Subjects with poorly controlled diabetes will be excluded. Persons taking particular medications that might interfere with the research will also be excluded. In addition, subjects who, in the opinion of the investigators, would be at increased risk or who are unable to perform or tolerate the research procedures will be excluded. People who have any contraindication for MRI imaging such as a pacemaker, metal fragment(s) in their body, or severe claustrophobia may not be eligible, as well as subjects with any contraindication for Positron Emission Tomography (PET) imaging, including significant prior participation in research procedures involving ionizing radiation will not be able to complete the optional imaging portion of this study. Patients who take benzodiazepine drugs, such as diazepam, lorazepam or clonazepam regularly are not eligible for this study. Pregnant or breastfeeding women are also not eligible for this study.

3.2 How many people are expected to take part in this study?

Up to 32 people are expected to participate in this study. We will target a minimum of 16 persons with Parkinson's disease and 4 normal older adults.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

After having passed the initial screening process, and if you agree to take part in this study, you will be asked to sign this informed consent form before testing will begin. There will be a total of 5 visits for this study. Your first two visits will consist of the initial clinical assessment and (optional) imaging split over 2 days. After visit 1 you will be instructed to wear physical activity and sleep trackers (called ActivPal a physical activity sensor will be put on your upper leg and a sleep tracker ring called Oura ring, which you will wear at a finger) for 1 week prior to visit 3. You will also wear a continuous glucose monitor during the same time. After you complete the 1 week of physical activity, sleep and glucose monitoring, you will return for visit 3, where the clinical

assessments will be repeated. At visit 3 you will also be instructed to start the approximately 30-day supplementation of tributyrin. You will additionally wear the Oura ring for the duration of the supplement regimen. The physical activity and sleep trackers and the continuous glucose monitor will also be worn during the last week of the tributyrin supplementation. You will return then for visits 4 (repeat clinical assessment) and 5 (repeat optional imaging) split over 2 days. There is no pre-set sequence which assessment (clinical or imaging) comes first.

The table below provides specific details about these visits:

Table 2 Schedule of activities	Visit 1* / Visit 2*: Baseline assessment (clinical)	Visit 1* / Visit 2* Baseline assessment (imaging – OPTIONAL)	At-home wearable sensor use (7 days ± 3 days)	Visit 3 Preintervention assessment	At-home 30 (± 7) days Tributyrin (500 mg tid po) intervention	Visit 4*/ Visit 5* Postintervention clinical assessment (while on tributyrin)	Visit 4* / Visit 5* Postintervention imaging assessment (while on tributyrin, OPTIONAL)
Approximate time commitment	4-6 hours	3-6 hours	-	4-5 hours	-	4-6 hours	3- 6 hours
Test location	Domino's Farms	UM hospital	Home	Domino's Farms	Home	Domino's Farms	UM hospital
Informed Consent (or prior eConsent)	X						
Eligibility	X						
OPTIONAL [^{11}C]butyrate, [^{18}F]FDG PET-CT [1.2] (brain/body)*		X					X (while taking tributyrin)
In case of [^{11}C]butyrate PET, obtain vital signs pre- & post injection of tracer		X					X
OPTIONAL MRI brain*		X					X
DEXA Bone Density Scan	X					X	
Blood/saliva/urine sample collection[1] (optional)	X					X	
Continuous glucose monitor for 7±3 days			X		X (last 7 days)	X	
Sleep tracking ring			X	X	X	X	

Activity tracker for 7±3 days			X		X (last 7 days)		
Motor MDS UPDRS[2]	X			X		X	
Balance test MiniBESTest (sensored)[2]	X			X		X	
Pegboard testing[2]	X			X		X	
Foot Tapping[2]	X			X		X	
Finger Tapping[2]	X			X		X	
Electronic Gait Mat/sensored walk[2]	X			X		X	
Beck Depression Inventory II scale	X			X		X	
Spielberger Trait Anxiety Scale	X			X		X	
Sleepiness scales	X					X	
MoCa, PDCRS (limited cognition)	X			X (optional)		X	
Cognitive test battery	X			X (optional)		X	
PCFRS functional scale	X					X	
Quality of life scale PDQ-39	X					X	
Adverse event assessment	X			X		X	
Phone Call / Email Drug monitoring					X		
Drug accountability				X		X	X
Pregnancy test in women of childbearing potential		X (within 48 hours of PET)		X			X (within 48 hours of PET)

Note

[1]: Fasting in morning

[2]: Dopaminergic off state in people with Parkinson

*Visits 1-2 and 4-5. There is no pre-set sequence which assessment (clinical or imaging) comes first. There may be a time interval of up to one month between Visits 1 and Visits 3, depending on scheduling

If you are a person with Parkinson's disease and taking anti-Parkinson medications, i.e., you will be asked to withhold taking certain dopaminergic medications, such as Sinemet (levodopa) or Mirapex (pramipexole), on the morning of your testing visits at our testing site at Domino's Farms. You also will need to withhold your dopaminergic medications prior to the PET scans. After completion of the clinical motor testing and the scan you can take the morning dose. You will also be asked to refrain from eating breakfast on the mornings of baseline and post-intervention testing and imaging visits.

Clinical test days (Visits 1, 3 and 4)

General clinical tests: You will receive a physical and neurological examination ("medical check-up") including the measurements of weight, height, pulse and blood pressure as well as an evaluation of your ability to move and walk. We will also ask you questions about your health and medications and screen your cognitive abilities. In addition, we will ask you for some general demographic and clinical information. Bone density and body tissue mass will be assessed with a DXA scanner.

Motor tests: Fine movements of the hands, fingers and feet will be examined by finger and foot tapping devices and a pegboard test device (a timed test where subjects put pegs in holes). We will place small sensors at your wrist, ankles, and around your chest to measure your body movements while you perform different balance and gait tasks. Some of the walking may be tested while walking on an electronic gait mat. If you are a person with Parkinson's disease and who is taking Parkinson's medication these assessments will be performed while you are "off" your dopaminergic medications (withholding the morning dose prior to motor testing in the morning). After motor testing has completed (after about 1 hour) you can take your anti-parkinsonian medication.

Cognitive and behavioral tests: The cognitive tests are designed to get an overall estimate of your memory, concentration, and ability to think. These functions will be measured with standard tests. We will also ask you questions about your mood. Other questions are about sleep and fatigue.

Genetic analysis: We are interested in investigating whether some genes may affect the clinical disease presentation. To this end, we are collecting saliva and/or a blood sample to analyze a sample of your DNA. If you decline to participate in the genetic study, you can still do the all the other parts of the study. Your sample will be given a special code, which we will keep separate from your name. In fact, it will only be linked to your name by a second code. The samples may be stored and analyzed in laboratories at the UM Human genetics lab or the UM Functional Neuroimaging, Cognitive & Mobility lab. Researchers will analyze the genetic samples for known variants in the DNA sequence. We will not be sharing the results with you.

Samples: Blood and/or urine samples will be collected for analysis and may be used for analysis of gene expression (see above) and/or metabolic/inflammatory markers. We will collect approximately 80 mL or 5 tablespoons of blood and approximately 20mL of urine.

Optional Imaging (days 2 or 5)

MRI scan: MRI scans allow the investigators to visualize all the structures in the brain in great detail by using a large magnet. An MRI scan of the brain involves lying on a table, which slides into a scanner. You will be instructed to remove all jewelry and other metal-containing objects for the MRI scan. During the MRI scan loud noises may be heard. The MRI scan will be performed in FDA-approved MRI scanner at the Department of Radiology at the University of Michigan Hospital.

_____ (Initials) I agree to take part in the optional MRI scan of the brain.

PET scans: The PET scans will allow the investigators to "see" the uptake of butyric acid and/or glucose in the brain and body. To establish this, in two separate sessions, a radiotracer will be injected into your vein through an i.v. (intravenous line or plastic "tube" inserted in an arm vein). If you choose to participate in the optional imaging, you will have the option of participating in one or both PET scans. A tracer refers to a small amount of a radioactive substance that does not alter body function, but that can be detected (imaged) in the PET scanner. The tracer will be injected as you lie on a table, which will move into a hollow machine resembling an X-ray scanner (CT or CAT). Images of your brain and upper abdomen/lower chest will be obtained over a period of 60 to 90 minutes. Women of childbearing potential will be required to provide a urine sample for a urine pregnancy test within 48 hours prior to the PET scan. If you are a person with Parkinson's disease and who is on Parkinson's medication you will be asked to withhold taking your dopaminergic medications, such as Sinemet (levodopa) or Mirapex (pramipexole), on the morning of your testing. You can resume these after completion of the PET scans. The PET scanning will be obtained after fasting for at least 6 hours. For imaging in the morning this will mean fasting after midnight.

_____ (Initials) I agree to take part in the optional Butyrate PET scan.

_____ (Initials) I agree to take part in the optional glucose PET scan.

Testing at home

Assessment of daily life activity and sleep: You will be asked to wear an activity monitor for a week to monitor your normal overall daily-life movement, so-called "actigraphy". This device is very similar to a pedometer that some people use to count the number of steps that they take every day. We will provide instructions on how to attach this device to your body and when to use it. This requires also keeping track in a logbook when you were wearing the device and document selected activities (for example when you took the device off to take a shower or when you were playing sports). You will also wear a ring called Oura ring to track your sleep before and throughout your time taking the tributyrin supplement. The 1-week activity monitoring will be repeated during the last week of the approximately 30-day tributyrin supplement intake.

Continuous glucose monitor: The continuous glucose monitor will be worn at your lower abdomen. The continuous glucose monitor will be inserted using an automatic applicator that you put over the skin and press a button. The inserted sensor filament will be covered by a water-resistant cover so you can take a bath, shower or swim if you want. The sensor is contained in a bandaid and can be removed the same way as removing a regular bandaid.

30 days (± 7) tributyrin supplementation

Tributyrin is a triglyceride (fatty acid) that is naturally present in butter. Once absorbed tributyrin is broken down in three butyric acid (butyrate) molecules. Tributyrin has been determined to be Generally Recognized as Safe (GRAS) for use as a food ingredient in the US by the FDA. Tributyrin is available over-the-counter as a supplement. You will take 500 mg capsule three times per day by mouth (total of 1.5 grams per day). This daily dosage is equivalent to the amount of tributyrin that is naturally present in approximately two tablespoons of butter.

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments, take your study medication as directed, and report any adverse reactions you may have during the study.

If you are a woman who is sexually active and have not yet gone through menopause, you will need to assure the study team that you will avoid pregnancy through using abstinence or an effective family planning method. We will administer a pregnancy test prior to taking the study medication. This will usually be performed at the time of the PET scans before starting the study medication.

It is important that if you are in this study that you call the study team at your earliest convenience if you experience any unexpected (mild or serious) side effects. If you experience any serious problems that may require immediate attention, please call 911 or go to a nearby emergency room.

We will also contact you during the study to monitor how things are going.

Please bring back any left-over capsules at the end of the study and hand them to the research staff.

Some assessments throughout this protocol may be performed remotely using Zoom for Health at U of M.

4.2 How much of my time will be needed to take part in this study?

Most of the testing for this study takes place at the Functional Neuroimaging, Cognitive and Mobility Laboratory located at Domino's Farms, Suite B1000 in Ann Arbor. PET and MRI imaging will take place at the University of Michigan Health System Hospital (University Hospital).

There will be a total of 5 study visits (or 3 study visits for participants who choose not to participate in the optional imaging visits) as listed in the schedule of activities table above. The table also contains information about the approximate time commitment per study. If all the study procedures cannot be completed in one visit, you may be asked to return to complete the procedures or, if possible, to conduct them by phone. The table also lists information about the 1 week physical activity, sleep and continuous glucose monitoring.

4.3 When will my participation in the study be over?

The study will be over after you have completed all study visits and have returned the left-over tributyrin capsules to the study team.

4.4 What will happen with my information and/or biospecimens used in this study?

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

_____ (initials) I consent to having my coded research data (i.e. data without my name included) shared with researchers and data-repositories inside or outside of the University of Michigan. I understand that if I

withdraw my permission, a reasonable effort will be made by the investigators to remove the research data or prevent it from being used; however, this may not always be possible.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks? risks?

The known or expected risks will be defined as:

Likely - occurring in more than 25% of people (more than 25 out of 100 persons);

Common – occurring in 10% - 25% of people (in 10 to 25 out of 100 persons);

Infrequent - occurring in 1 - 10% of people (1 to 10 out of 100 people); **Rare** -

occurring in less than 1% of people (fewer than 1 out of 100 persons); **Very Rare**

- occurring in less than 0.1% of people (fewer than 1 in 1,000 persons).

General risks:

- There is a **very rare** risk of breach of confidentiality, which may affect privacy, self-esteem, social standing, employability, and insurability.

Section 9.1 will provide more detailed information on how we protect your privacy. In general, study records will be kept in databases maintained by the investigators. These databases are kept separate from medical records, are protected by passwords, and only accessible to personnel involved in the study. If you withdraw from the study at any time, a record of the withdrawal and the reasons given for withdrawing may be kept as part of the study record.

- There is a **rare** risk that you may experience some minor anxiety ('test anxiety'), become worried, or have an anxiety reaction in response to any of these tests and procedures. For example, you become worried about your health, or you may experience a sudden fear of the confined space while in the scanner.

Trained research staff will conduct all tests and procedures. The staff will be prepared to respond to your anxiety, concerns and behavioral changes, by temporarily suspending testing, breaking up testing sessions into several brief visits if needed, and/or answering your questions. During the PET and MRI scans you will be able to talk to technologists throughout the scan and indicate right away if you wish to stop the study and leave the scanner. At the option of your personal physician, (s)he may prescribe sedation with lorazepam (Ativan) or diazepam (Valium) to be taken before the scan in accordance with the prescription directions.

- If you are a person with Parkinson's disease taking Parkinson's medications there is an **infrequent** chance that you may develop "freezing" symptoms when you do not take your dopaminergic medication, which is caused by stiffening of your muscles making movements more difficult. You may require additional assistance from your caretaker during this time.

Any risk of adverse effects will be minimized by careful supervision during test procedures that are being conducted when are withdrawn of your dopaminergic medications. You will be instructed to resume taking your dopaminergic medications after the completion of the testing. If the withdrawal of medication is intolerable, you may resume taking medication and withdraw from this study at any time.

- During the course of the study you may receive several blood draws, intravenous (iv) catheters, and injections for the PET radiotracer. There is an **infrequent** risk of bruising, bleeding, infection, or soreness at the injection site. There is a **very rare** risk for infection. There is a **rare** risk that you may feel dizzy, lightheaded, or faint after an injection.

Blood drawing, iv catheter insertions, and injections will be performed by a certified and experienced research technician or other health care professional who is also trained in blood borne pathogens control. Aseptic techniques will be used in accordance with University of Michigan guidelines. You can lie down if you feel dizzy, lightheaded or faint after an injection.

- None of the test results, brain images, and procedures in this study will be reviewed or interpreted for making a medical diagnosis. For example, there is the potential that the MRI scan may reveal an abnormality that is already in your body, such as a cyst or tumor. Any result or abnormality that would be indicative of current or future disease will most likely not be discovered. Many such abnormalities are not clinically significant, but you may need or want to investigate them further. Such a finding might require additional studies, and maybe even treatment, which would not be paid for by the investigators, the sponsor, or the University of Michigan. The research results of the brain images and genetic testing will NOT be communicated back to you.

You should consult your personal doctor if you have any health concerns.

Clinical tests:

- There is an **infrequent** risk of physical fatigue during the clinical examination.

Trained research staff will conduct all the tests and administer all the questionnaires. The staff will be prepared to respond to your concerns by temporarily suspending testing and/or breaking up testing sessions into several brief visits if needed.

- There is a **common** risk that you may have a dry mouth after providing the saliva sample.

You may drink some water after providing the sample.

- Risks associated with the dual-energy X-ray absorptiometry (DXA) scan are described below under the header “PET scans.”

Motor testing:

- Many of the tests are comparable to normal standing and walking conditions that you may experience in everyday-life. Nonetheless, there is an **infrequent** risk of falling or near falling during these tests which may result in fall-related injuries.

Trained research staff will remain in close proximity to you at all times, and observe (‘spot’) you to prevent you from falling.

- There is a **very rare** risk that the sensors to measure overall movement and balance may become detached and that you may trip. You may also trip on the pressure sensitive mat.

We will regularly check the sensors for appropriate attachment and you will be closely monitored.

Cognitive, and neurobehavioral tests:

- There is an **infrequent** risk of boredom, frustration, and/or mental and physical fatigue during the neuropsychological and neurobehavioral testing.

Trained research staff will conduct all the tests and administer all the questionnaires. The staff will be prepared to respond to your concerns by temporarily suspending testing and/or breaking up testing sessions into several brief visits if needed.

Tributyrin side-effects:

Tributyrin is usually well tolerated. However, possible infrequent side-effects may include mild nausea, indigestion, feeling bloaty, heartburn, loose bowel movements, constipation, passing gas, headache, dizziness/lightheadedness, or sleep changes. There is a rare risk of allergy. Tributyrin may cause a butter-like odor.

MRI scan:

- There is an infrequent risk of finding an unexpected abnormality in the scan. We will discuss this with you and with your permission can also discuss it with your doctor.

- There is an **infrequent** risk of discomfort or anxiety from being in the confined space of the MRI scanner.

We will provide pads and blankets to make you as comfortable as possible. You will be able to talk to a technician throughout the study, and you will be able let him/her know right away if you want to stop the study and get out of the scanner. At your request, you may be provided with a mild sedative; however, you must have made prior arrangements to be driven home by an accompanying adult.

- The MRI scanner makes loud, vibrating noises.

You will wear foam earplugs to reduce the loud noises made by the scanner and prevent any hearing damage.

- Some studies, like this one, have the potential to cause "peripheral nerve stimulation" (PNS). PNS is a light touching sensation on the skin surface, lasting only for a few seconds. It may cause mild discomfort, but is not harmful to you.

The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low.

- Sometimes, subjects report a temporary, slight dizziness, light-headedness or nausea during or immediately after the scanning session.

If you feel dizzy or light-headed, we will have you get up slowly from the scanner.

- Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside your body could be accelerated by the magnetic field and strike you, causing you injury. There is also a risk that the magnetic fields could disturb a metal fragment in your body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in your body to heat up, causing you harm.

We keep the environment around the MRI scanner completely free of loose metal objects that could be moved by the magnetic field, and we will make sure that you have no metal on your body that could be affected by the MRI scanner. We will also ask you questions and have you complete an MRI screening form to make sure that you have no metal inside your body that would cause you harm during the MRI scan. The radiologist may order an X-ray to make sure there are no metallic fragments in your eyes or chest.

PET scans:

- There is a **very rare** risk that you could experience an allergic reaction to the PET tracer. This could involve itching, skin rash or shortness of breath shortly after injection. However, because of the very small tracer amounts used in PET imaging, the risk is very rare.

The use of [^{11}C]butyrate PET is considered to be generally safe and effective as approved by the University of Michigan Radioactive Drug Research Committee in accordance with Food and Drug Administration regulations (21 CFR 361.1). The use of [^{18}F]FDG PET is considered to be generally safe. Certified staff will be in attendance at all times during the study. A physician will be available and an emergency cart is located in the PET Facility for treatment of any adverse reactions that may occur.

During the course of this study, you will be exposed to radiation from the CT scan (embedded in the PET scanner) and the [^{11}C]butyrate PET, [^{18}F]FDG radiotracer PET, and two DEXA scans. The risks associated with the amount of radiation exposure participants receive in this study are considered very rare and comparable to every day radiation exposure risks. **Please inform the investigators if you have had any major radiation exposure in the past, particularly in the past year, such as medical treatment with X-rays or radioactivity, or diagnostic X-rays, CT-scans or nuclear medicine scans.**

The potential biological effect of radiation in humans is measured in terms of Sieverts (Sv) or mSv (1/1000 Sv), which is a unit of uniform whole body exposure. The radiation exposure you will receive from the [^{11}C]butyrate PET, and [^{18}F]FDG PET scan is equivalent to a uniform whole body dose of 21.2 mSv, which is approximately 42.4 % of the annual radiation exposure (50 mSv) permitted to radiation workers by federal regulations. This amount is approximately 7.1 times the average annual natural background radiation exposure, which is 3 mSv per year. You will be instructed to use the bathroom and urinate as soon as possible after the PET scans in order to minimize bladder exposure. The radiation you will be exposed to from each DXA scan is 0.0310 mSv, which is significantly less than 1% of the permitted annual radiation exposure.

There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low. The risk of a side effect from this level of radiation exposure is very rare. The risk from radiation exposure of this amount is considered to be similar to other everyday risks, such as driving a car.

- No PET studies will be performed on pregnant, nursing, or potentially pregnant women.

A urine pregnancy test will be performed on all women of childbearing potential within 48 hours prior to the PET scanning session.

Assessment of daily life and sleep activity:

- There is a **very rare** risk of the movement monitor (actigraphy) detaching, which may result in tripping during the daily life monitoring of overall movement (actigraphy). It should be noted that the actigraphy device only measures overall movement. It does not record your geographical location or

specific activities that you were performing, nor can this be derived at a later point from the data that is stored in the actigraphy device.

You will receive instruction for proper attachment of the actigraphy device.

- Wearing the Oura ring sleep/physical activity tracker is not likely to pose significant risks. Like with every ring you may wear on a finger there is a small risk that the ring may feel tight or you may have difficulties removing it from the finger. You will be individually fitted for the ring to minimize the risk.

Continuous glucose monitoring:

- There is a small risk of pain when applying the sensor. You may occasionally feel a tinge of pain or discomfort when wearing the monitor. There is an infrequent risk of an allergic skin reaction or skin irritation to the covering tape. Signs of skin irritation will disappear once you remove the sensor.

Genetic Analysis

- It is possible that our genetic analysis may reveal a mutation of clinical relevance or unclear clinical significance. However, the genetic testing we will perform will not be utilized for clinical purposes (strictly for research purposes). The results of these tests will not be shared with you.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may potentially receive a benefit of better sleep or better bowel functions when taking tributyrin. Otherwise, you may not receive any personal benefits from being in this study. Participation in this study may provide important new insights into better treatment options of Parkinson's disease. This may ultimately result in development of treatments for this disorder.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You do not have to participate in this study. You may drop out of the study at any time without penalty.

This study will involve investigational treatments for Parkinson disease. Please note that there may be other experimental treatments. Your doctor can tell you more about these other treatments, their risks and their possible benefits. You should have this discussion about the risks and benefits or other alternatives prior to making your decision about whether or not you wish to take part in this research study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

There is no harm in leaving the study before it is finished. However, if you decide to leave the study during some of the procedures we may ask you to stay until it is deemed safe to leave.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Nicolaas Bohnen immediately, at 734-998-8400. The doctor will either treat you or send you to another doctor for treatment. You will get free medical care at the UMHS for any hospitalization or ER visit caused by the study drug, device, or procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study. The UMHS will pay for your hospitalization or ER visit only if the need for treatment has been caused by the study drug, device or procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study. It is not the

general policy of the federal funding agencies to compensate or provide medical treatment for human subjects in federally funded studies.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices Monitoring for side effects or other problems Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

There is the potential that the research evaluations may have caused you anxiety or worries about your health. You may need or want to investigate these health concerns further for an appropriate diagnosis. However, any procedures or tests, including the MRI and PET scan, should be obtained separately if your doctor believes that you require those tests for your diagnosis. These additional studies and appropriate treatment, if necessary, will not be paid for by this study.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $100 for each of the clinical testing visits (total of $300 for visits 1, 3 and 4)
You will receive $50 per completed PET or MRI scan (up to $150 for each of visit 2 or 5; combined total of $300).
You will receive a total of $50 for each week of the physical activity, sleep and glucose monitoring; combined total of $100 for the two weeks.
You will receive $100 for the completion of the approximate 30-day of tributyrin supplementation.
Compensation for your time and effort after full study completion may total a maximum of $800.

Overnight accommodations may be provided depending on personal circumstances or if you live far away. We will discuss with you the need for these accommodations as the research appointment(s) are being arranged. If eligible, overnight lodging can be arranged through the UMHS Patient and Visitor Accommodations Program either by a study team member or by you. However, you may decide to make alternative arrangements. In that case, please discuss with the study team first if you are eligible for reimbursement prior to making any reservations. We can only reimburse for expenses that have been approved in advance by the study team. You will need to provide receipts to the study team before expenses can be reimbursed. We will reimburse to a maximum of $300 for lodging and meals. You will receive a voucher for valet parking at the University Hospital. Parking at Domino's Farms is free.

You will be paid after your last study visit or, in case you decide to withdraw from the study, you will be paid for the parts that you have completed. You will be paid by check, which will be sent to your home address. Alternatively, you may request a payment coupon for cash payment at the University Hospital. We do not keep cash for immediate payment.

If you receive payment of $600 or more for taking part in this study, the University of Michigan accounting department will collect your name, address, social security number, payment amount, and related information. For tax reporting purposes this information must be sent to the Internal Revenue Service (IRS).

8.3 Who could profit or financially benefit from the study results?
Researchers conducting the study, the University of Michigan, and other researchers that obtain your deidentified samples and clinical data will not profit directly from them. However, if research using your samples leads to new tests, drugs, or other commercial products as a result of knowledge gained using your samples, you will not share in any profits.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?
The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
Your research records will be stored in a secure location to which only the investigators have access. All research records will be stored under code numbers, without attached names or other identifying information.

The "key" linking these records to subject names will be stored in a separate, locked (electronic) file. The storage locations for the MRI and PET brain scans will be in protected computer files that are accessible only to investigators within the University who are participating in the research project. If the radiologist orders any Xrays for MRI screening purposes or a urine pregnancy test is ordered, the order requisition and test results may become part of your regular medical record.

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service

- Federal employees receiving care through the Federal Employees Health Benefits Plans

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects ○ Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive payment of $600 or more for taking part in this study, the University of Michigan accounting department will collect your name, address, social security number, payment amount, and related information. For tax reporting purposes this information must be sent to the Internal Revenue Service (IRS).
-
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

A description of this clinical trial may 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, the Web site will include a summary of the results. You can search this Web site at any time.

9.3 Will I be contacted for other studies?

No, unless you indicate by initialing below that you may be contacted by researchers at the University of Michigan for studies for which you may eligible. If you agree to be contacted for other studies we will keep your name and contact information in a separate password-protected database.

_____ (initials) I agree to be contacted about other research studies for which I may qualify. If I cancel my permission for this study, I will not be contacted for other studies.

9.4 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission, or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.5 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Nicolaas Bohnen, MD, PhD

Mailing Address:

UM Functional Neuroimaging, Cognitive, and Mobility Laboratory
24 Frank Lloyd Wright Dr.
Suite B1000, Box #362
Ann Arbor MI 48105
Telephone: 734-998-8400

Study Coordinators: Alexis Griggs and Robert Vangel

Mailing Address:

UM Functional Neuroimaging, Cognitive, and Mobility Laboratory
24 Frank Lloyd Wright Dr.
Suite B1000, Box #362
Ann Arbor MI 48105
Telephone: 1-877-998-1098

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234 e-mail:
irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- ☐ This signed and dated informed consent document, "Consent to be Part of a Research Study"). (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent for Participating in Genetic Analysis

This project involves optional participation in the genetic analysis. I understand that it is my choice whether or not to take part in the genetic analysis. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this genetic analysis.

_____ Yes, I agree to take part in the optional genetic analysis.

_____ No, I do not agree to take part in the optional genetic analysis.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-G

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____