Study Title: Effects of combined exercise training and Ketone ester on muscle strength and cardiovascular response in Parkinson's disease

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UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Effects of combined exercise training and Ketone ester on muscle strength and cardiovascular response on Parkinson's disease

Company or agency sponsoring the study: There is no sponsor because this is a pilot study.

Principal Investigator: Fay Pongmala, PhD, University of Michigan, Departments of Radiology, Functional Neuroimaging, Cognitive & Mobility Laboratory
Study Coordinator: Austin Luker, BSc, University of Michigan, Department of Radiology, Functional Neuroimaging, Cognitive & Mobility Laboratory

1.1 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 childcare, or make other plans. In your decision to participate in this study, consider all these matters carefully.

This research is studying the use of a supplement in small numbers of people to learn about its safety as a dietary supplement to improve physical performance for Parkinson's Disease. Researchers want to understand how the supplement works in your body and how your body will react to it. This study will measure the changes in muscular strength and aerobic endurance after a cycling training program with ketone ester supplementation, or with a placebo. Some health-related information including blood sampling by finger lancet will be collected for this research study.

This study involves a process called randomization. This means that the dietary supplement you receive in the study is not chosen by you or the researcher. The study design divides study participants into separate groups by a random number generation computer program to compare different treatments or

procedures. If you decide to be in the study, you need to be comfortable not knowing which study group you will be in.

This study may require you to stop taking certain medications during the research study. This includes dopaminergic medication on the two testing/assessment days of the study. If you decide to be in the study, you should understand that some symptoms that were controlled by that medication may temporarily worsen.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include fatigue, soreness, freezing or exacerbated Parkinson's symptoms from being off medication, anxiety, boredom, discomfort or anxiety from being in the confined space of the MRI scanner. More detailed information will be provided later in this document.

This study may offer some benefit to you now or others in the future by potentially improving your PD symptoms and/or physical fitness due to the training intervention, and adding to knowledge about the role of ketone supplementation in exercise and PD. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be 4-6 weeks.

You can decide not to be in this study. Alternatives to joining this study include not participating, and you may drop out the study at any time without penalty.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Exercise is known to have disease-modifying effects on the progression of Parkinson's disease. Research has shown that ketone supplementation improves aerobic exercise endurance significantly in people with Parkinson's disease. This research is studying ketone ester supplementation in an exercise training program in persons with Parkinson's disease to determine if it can improve muscular strength, and aerobic exercise capacity even more than exercise alone. This study will compare the changes in these measures before and after a cycling training program with ketone ester supplementation to a control cycling group.

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 with Parkinson's disease who are at least 45 years of age, without any medical history that would prevent participation in this study such as a history of myocardial infarction or other cardiac event, severe symptomatic leg or back musculoskeletal pain, or poorly controlled diabetes. Individuals who are pregnant or breastfeeding during the study are not eligible for participation. 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. Participants should be willing and able to comply with study requirements.

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

A total of 24 subjects are expected to participate in the study.

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 15 visits for this study. Visit 1 will consist of initial clinical assessments, cognitive testing and questionnaires, and baseline testing for muscular strength and aerobic capacity. Visits 2-6 and 8-14 will be the intervention period of the study, where you will take the ketone ester supplement and exercise on a stationary bicycle for 1-hour. Visit 7 and 15 will consist of follow-up testing for muscular strength and aerobic capacity, and the clinical and cognitive testing will be repeated. On all visit days we will ask you to arrive in a fasted state, and not yet having taken your dopaminergic medication. On visits 1 7, and 15 we will ask you to withhold from your dopaminergic medication until the exercise testing is complete. On visits 2-6 and 8-14 we will ask you to take your dopaminergic medication after arriving, 1-hour prior to exercise. You will be randomized by to either the experimental group or control group by a random number generation computer program. Participants should not make changes to medications or begin taking new supplements while participating in this study. Not all assessments are required to be done in the same day they were originally scheduled.

Clinical test days (Visits 1, 7, 15)
***Each of these assessments will occur at all three of the assessment visits (listed above)of the study period.* (Please note – the optional MRI will not occur at visit 7)**

Exercise Screening: Before beginning any exercise testing or training you will be asked to complete a Physical Activity Readiness Questionnaire (PARQ+), and undergo a 12-lead ECG screening to detect cardiac arrhythmia (irregular heart beat rhythms).

General clinical tests: You will receive a physical and neurological examination ("medical check-up") including measurements of weight, height, pulse, blood pressure, and heart rhythm, 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. We will also ask questions to see if you're eligible to undergo MRI. In addition, we will ask you for some general demographic and clinical information. Bone density and body tissue mass will be assessed with a DEXA scanner.

(Optional) MRI scans: 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. You may decline to participate in the portion of the study, and it is not required in order to participate in the rest of the study.

Motor tests: We will place small sensors on your wrists, ankles, and around your chest to measure your body movements while you perform different balance and walking tasks. Some of the walking may be assessed on an electronic gait mat. If you are a person 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).

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, sleep, and fatigue. (Optional) In addition, there are a series of optional assessments to further assess cognition in this study to provide a more comprehensive understanding of cognition in relation to the ketone and cycling intervention. The additional optional assessments will take ~60-90 minutes to complete at both the pre and post-intervention visits.

Maximal Strength and Aerobic capacity testing: You will be asked to perform maximal knee extension assessment with each leg individually on a Biodex dynamometer. After sufficient time to fully recover, you will perform a graded aerobic capacity exercise test on a stationary cycle ergometer, followed by an endurance test with a personalized intensity drawn from the baseline test. The cycling tests may vary in their starting point depending on measured physical ability and researcher discretion. After another rest period, you will perform a 1-minute anaerobic threshold test at a personalized intensity. After exercise testing is completed (about 1-hr) you may take your dopaminergic medication.

Blood samples: Blood samples will be collected by finger prick to evaluate blood levels of ketones, glucose, and lactate on a portable meter before and after exercise. Each analysis requires only a single drop of blood. No blood samples will be saved from these tests.

Continuous glucose monitoring: You will be asked to monitor your glucose levels using a wearable device that will be worn on the stomach for 10 days. This will be placed during your first study visit.

Exercise intervention days (Visits 2-6, 8-14)

Cycling training session: During each exercise training session we will ask you to complete 1-hour of stationary bicycling, including warm-up and cool-down time. The cycling will be at a personalized intensity based on a percentage of your maximum heart rate. You will be asked to arrive 1-hour before the exercise session to take your dopaminergic medication, followed by either the ketone supplement or the placebo (depending on the group you have been randomized to).

Blood samples:
Blood samples will be collected by finger prick to evaluate blood levels of ketones, glucose, and lactate on a portable meter before and after exercise training. Each analysis requires only a single drop of blood. No blood samples will be saved from these tests.

Ketone or Placebo supplement:
Ingestion of the ketone ester drink results in the production of a ketone body called beta-hydroxybutyrate (βHB), which is naturally present during fasting or when adhering to a so-called ketogenic diet. Once absorbed, ketone ester drink is broken down in two βHB molecules. The Ketone ester drink is available over-the-counter as a supplement. You will take 25 grams of ketone ester + an electrolyte solution diluted in water, or an electrolyte only drink dissolved in the same amount of water. You will consume this beverage once per day on your exercise training intervention visits. You will not be asked to change your diet while taking the ketone ester drink.

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 your scheduled appointments, taking your study medication as directed, and reporting any adverse reactions you may have during the study.

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.

For some research studies, such as the one you are being asked to join, it is important that you do not learn whether you have been randomized into the experimental group or the control group. Whether you intend it or not, sometimes learning this information may make you change your actions and behaviors in ways that could impact the outcome of the study.

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

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. MRI imaging will take place at the University of Michigan Health System Hospital (University Hospital).

There will be a total of 15 study visits as detailed in the study activities above. All 15 visits will be spaced out over a 4-6-week period. Visits 1 7, and 15 are expected to last 6 hours (7 hours if including optional assessments), and visits 2-6 are expected to last 2 hours. The MRI scans will take approximately 60 minutes.

4.3 When will my participation in the study be over?

The study will be over when you have completed all study visits.

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.

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?

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 are 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 may 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.* If you are a person taking Parkinson's medications there is an **infrequent** risk 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. *During the 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.*

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.

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

- For participants taking Parkinson's medications: In most patients, temporary withdrawal can be accomplished safely on an outpatient basis and may result in inconvenient reduction in functional abilities, but not result in inability to conduct essential activity of daily living. There is an infrequent chance that you may develop "freezing" symptoms, 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 the morning after the overnight withdrawal of the 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.

- 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 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.

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.

Ketone ester drink side-effects:

- Ketone ester drink is usually well tolerated. However, possible **infrequent** side-effects may include mild nausea, diarrhea, indigestion, distended abdomen, feeling bloated, heartburn, shakiness, lightheadedness, sweating, loose bowel movements, constipation, passing gas, keto flu-like symptoms, headache, dizziness, sleep changes, other symptoms of low glucose, or increased glucose. The ketone ester may have a poor or bitter taste, but the drink can be diluted. A clinician may recommend an anti-acid if you begin developing symptoms of nausea or an upset stomach.

Glucose/ketone body/lactate monitoring:

- There is an infrequent risk of pain or infection at the finger prick site when using the blood lactate, glucose, or ketone devices.

Continuous Glucose Monitor:

-There is an infrequent risk of bruising, bleeding or soreness associated with the CGM. There is a very rare risk of infection. There is an infrequent risk that you may feel dizzy or lightheaded or may even faint.

The FDA safety information for the CGM includes the following contraindications:

1) Sensor and transmitters need to be removed before Magnetic Resonance Imaging, Computed Tomography scan, or diathermy treatment. It is unlikely that you will have any of those tests for

personal reasons while enrolled in this study because we will be carefully selecting research participants. If you do however need one of these tests, then you will be scheduled to participate in this research study during different days than you would have those tests. We will also remind you regularly about this contraindication.

2) Taking medications with acetaminophen while wearing the sensor may falsely raise glucose readings. We will remind you to avoid acetaminophen during the study and to use alternative painkillers if needed.

The safety information for the CGM system also contains the following possible adverse device effects of inserting a sensor and wearing the adhesive patch:

- local infection
- inflammation
- pain or discomfort
- bleeding at the glucose sensor insertion site
- bruising
- itching
- scarring or skin discoloration
- hematoma
- tape irritation
- sensor or needle fracture during insertion, wear, or removal

All these adverse events are considered minor and easy to resolve. We will train you on the insertion of the sensors and we ask that you communicate with us immediately in the event of any adverse effect.

Exercise testing and training:

- When measuring muscle strength with the Biodex system there is a common risk to feel some pressure against the muscle that is tested as well as some fatigue afterward.
- There is a common risk for some minor muscle pain after testing, which can appear 1-3 days afterwards and should resolve by itself.
- There is a common risk for shortness of breath when performing aerobic exercise.
- There is a **very rare** risk of a cardiac event when performing aerobic exercise testing.
- There is a **rare** risk of exercise induced hematuria (defined as visible blood in urine) when performing exercise testing or training, which typically resolves within 72 hours and is non-serious. Hematuria lasting more than 72 hours may indicate a more serious condition. Please report hematuria at the first instance. The study team will monitor your condition, and If hematuria continues more than 72 hours from first occurrence, please contact your primary care physician.
- There is a common risk of experiencing some pressure when pushing against the handheld dynamometer for the muscle strength assessment.
- *The pressure will disappear if you release the dynamometer.*

DXA Scan:

- During the course of the study, you will be exposed to radiation from the DXA scan
- *The biological effect of radiation in humans in measured in terms Sieverts (Sv) or mSv (1/1000 Sv), which is a unit of uniform whole-body exposure. All subjects will undergo a DXA scan. The*

exposure for the DXA scan is 0.5 mSv. Thus your total exposure for this study will be 1.0 mSv for two DXA scans in this study. Your life-time radiation risk includes the background radiation you are exposed to naturally like everyone else living on this planet, which is on average 3 mSv per year. The exposure resulting from the two DXA scans is about 3 times lower than the natural background radiation. The effects on the body of this radiation exposure will be added to your overall lifetime radiation risk. The US Federal Government requires that the annual amount of radiation exposure of radiation workers does not exceed 50 mSv per year; the radiation you will be exposed to in this study is a maximum of 2.0% of this amount.

- Your lifetime radiation risk also includes any radiation you may have received in the past for diagnosis or treatment, and any such radiation you may be exposed to in the future.
- *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.*
- No DXA 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 DXA scanning session.*

MRI scan:

- 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.

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 experience improved thinking, metabolic, and sleep functions. In addition, you may experience improved physical capacity. 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 to improve physical performance in Parkinson's disease and related conditions. This may ultimately result in development of treatments for these disorders.

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.

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 certain 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 that you think is wrong, contact the researchers 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.

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, 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 $50 for each of the assessment visits (total of $150 for visits 1, 7 and 15)
You will receive $25 per completed exercise training session ($300 total for visits 2-6, 8-14)
Compensation for your time and effort after full study completed may total a maximum of $450.

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.

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 de-identified 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 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 scan will be in protected computer files that are accessible only to investigators within the University who are participating in the research project. If any X-rays, urine tests, or blood tests are ordered for screening purposes, the order requisition and test results may become part of your regular medical record but you should not receive a bill for these.

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 any payments for taking part in this study, the University of Michigan finance department will need your name and address for tax reporting purposes. In a calendar year if: 1)

your payments total greater than $400 for this study or 2) if you receive payments of greater than $400 for being in more than one study, the University of Michigan finance department will also require your Social Security Number for tax reporting purposes. If you do not wish to provide your Social Security Number, you may continue to participate in research studies, but you will not be able to receive payment for the remainder of the calendar year. 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.

This trial may be registered 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: Fay Pongmala, 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 Coordinator: Austin Luker

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

Sig-A

Consent/Assent 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 [NAME OF STUDY TEAM MEMBER OBTAINING CONSENT] _____. 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.

Print Legal Name: _____

Signature: _____

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

Sig-C

Consent/Assent for Participating in an Optional MRI Scans

This project involves optional participation in MRI scans before and after the intervention I understand that it is my choice whether or not to take part in the imagingI 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.

_____ Yes, I agree to take part in the optional imaging portion of the study

_____ No, I do not agree to take part in the optional imaging portion of the study

Print Legal Name: _____

Signature: _____

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

Sig-C

Consent/Assent for Participating in an Optional Neuropsych Testing

This project involves optional participation in additional neuropsych testing before and after the intervention, as a possible addition to the required portions of neuropsych testing. I understand that it is my choice whether or not to take part in these assessments. 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.

_____ Yes, I agree to take part in the optional neuropsych assessments

_____ No, I do not agree to take part in the optional neuropsych assessments

Print Legal Name: _____

Signature: _____

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

Sig-D

Consent/Assent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. 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.

_____ Yes, I agree to let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print 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): _____