Study Title: Brain Small Chain Fatty Acid Metabolism in Bipolar Disorder: Ketones

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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 Bipolar Disorder: Ketones

1.2 Principal Investigator: Nicolaas Bohnen, MD, PhD, University of Michigan, Department of Neurology
1.3 Study Coordinators & Research Staff: Jaimie Barr, BSc & Robert Vangel, BSc

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

To give you more information about this particular study assessing ketone esters, a ketone ester is a supplement that increases the body's level of natural ketone bodies (primarily the compound beta-hydroxybutyrate) when ingested. The term "low-glycemic index diet" refers to a type of diet designed to minimize blood sugar spiking – this is often done by replacing "simple" carbs (such as white rice or white grains) with "complex" carbs (such as brown rice or quinoa). Low-glycemic dietary changes are often used to enhance the benefits of ketone ester supplements. The investigators want to learn whether the intake of a ketone ester supplement (available over the counter as a sports performance and health supplement called "Qitone—Pro-Ketone Powder") combined with a low-glycemic index diet may affect your blood glucose and ketone levels, which may help with mood stability and brain/body health in individuals with Bipolar Disorder. The investigators also want to explore how this intervention may affect other outcomes. Psychological testing and some blood work to check various markers of metabolism will be performed both before and after a 90-day ketone ester and low-glycemic index diet regimen. Functional MRI (fMRI) imaging to assess brain network stability will be performed before and after the intervention. Optional brain/body PET imaging to assess mitochondrial function will be performed before the treatment regimen. Glucose levels will be monitored through the use of wearable sensors for approximately 1 week prior to the start, and during the final (approximate) week of the treatment regimen. Sleep will be monitored with a wearable ring device (called "Oura ring") throughout the supplement intervention. You will

need to download 3 phone apps to enable collection of data for this study: 1) an app for measuring ketones and

glucose at varying times, 2) the app for the "Oura ring" measuring sleep parameters, and 3) an app for mood tracking (brief surveys will be electronically provided each evening at 7 pm; should take no more than 2-5 minutes to complete).

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This research is studying an over-the-counter ketone ester supplement (combined with some dietary changes to minimize blood sugar spiking) in adults with Bipolar Disorder to learn about its safety and its effect on the body and brain as a potential treatment for Bipolar Disorder or other mood-related brain conditions. This study will examine the relationship between these dietary changes and brain network stability (measured with a fMRI scan), as well as sleep quality and continuous glucose monitoring. Optional PET imaging is used at baseline to assess mitochondrial function by taking pictures of the brain/body while you are lying in a camera following the intravenous injection of a so-called "radiolabeled tracer." This term refers to the use of 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). These images will show how active the mitochondria are in your brain/body (mitochondria are sometimes referred to as the "powerhouses of the cell" – research has suggested they may play a vital role in Bipolar Disorder).

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 who have been diagnosed with Bipolar Disorder who are at least 18 years of age can participate in this study. Participants should be willing and able to comply with the study requirements. Subjects with psychiatric contraindications (including active substance use dependency), neurological conditions (including seizures), and/or unstable medical conditions may be excluded. Subjects with poorly controlled diabetes, or subjects being treated with insulin, will be excluded. Persons taking 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 will not be eligible. Subjects with any contraindication for Positron Emission Tomography (PET) imaging, including significant prior participation in research procedures involving ionizing radiation, will not be eligible for the optional PET imaging portion of this study. Radiation is a term that refers to a form of energy that allows us to see inside the body but may damage cells, particularly if excessive exposure occurs. Further details about this scan are explained in Section 5.1 of this document in the PET scan subsection. Pregnant or breastfeeding women are also not eligible for this study. There are some other eligibility requirements that will be reviewed during our screening interview.

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

Up to 20 people with Bipolar Disorder are expected to participate in this 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 begins.

We will first review information in this consent form with you, make sure that your questions are answered, and ask you to sign in the appropriate place(s) at the end of this document (in person or electronically). We will review your medical history, medications, and substance use with you and ask you to provide a urine sample for a drug screen. We will also administer tests about your mood. If your bipolar diagnosis in your medical/psychiatric records is not clear, a trained clinician may administer a confirmation diagnostic interview (lasting about 90 minutes) to confirm your diagnosis. Once your eligibility has been confirmed, you will be enrolled in this study.

Besides the eligibility assessment visit, there will be 5 visits for this study. Your first two visits will consist of the initial imaging and clinical assessments split over 2 days. After the initial visit, you will be instructed to wear a sleep tracker ring (Oura Ring) on your finger and a continuous glucose monitor (CGM) on your lower abdomen. You will wear the CGM for approximately 1 week prior to coming in for Visit 2, when you will start the supplement/diet. You will wear the Oura ring for approximately 1 week prior to starting the supplement/diet and throughout the duration of the intervention period. After the initial baseline monitoring period (approximately 1 week), you will be instructed to start the approximately 90-day ketone ester and low-glycemic index diet regimen.

Specifically, four dietary changes will be required of you:

1) not drinking soda (including diet soda) for the duration of the intervention period,
2) not eating candy/sweets for the duration of the intervention period,
3) not eating white grains/rice during the intervention period (you can replace these with “complex carbs” such as brown rice and whole grains), and
4) if eating fruit with a meal, eating it at the very end of the meal to minimize blood sugar spiking.

You will also be instructed on how to take blood readings of your glucose and ketone levels, and may be asked to measure your glucose and ketone levels intermittently throughout the KE intervention (though doing this yourself will be optional as we can help take the measurements for you).

You will also be asked to regularly complete brief self-reported mood and symptom check-ins and keep a meal photo-diary, both of which will be completed on smartphone apps.

At the mid-intervention point (approximately 45 days into the ketone ester intervention), you will return for Visit 3, where some psychological surveys will be repeated (this visit may be completed over Zoom if needed). The continuous glucose monitor will again be worn during the last week of the treatment regimen. You will return for Visit 4 (repeat clinical assessment) and Visit 5 (repeat imaging), split over 2 days.

After the intervention, you will continue to wear the Oura ring for 7-21 days, after which you can return it via mail or drop-off at the lab. There is no pre-set sequence for which assessment (clinical or imaging) comes first for the first two as well as the last two visits.

The table below provides specific details about these visits.

Table 1: Schedule of activities for ketone ester (KE) intervention

	Visit 1* Baseline Imaging	At-home wearable sensor use (7 days ± 3 days) before starting KE intervention	Visit 2* Baseline Clinical Assessment	At-home KE intervention 90 days ± 10 days (to continue throughout rest of study)[3]	Visit 3 Mid-intervention Clinical Assessment @ day 45 ± 10 days	At-home wearable sensor use (7 days ± 3 days) while on KE intervention	Visit 4* Post-intervention Imaging while on KE intervention @ day 90 ± 10 days	Visit 5* Post-intervention Clinical assessment while on KE intervention @ day 90 ± 10 days	Device follow-up for 14±7 days, after which ring is returned
Overview	Baseline Imaging: fMRI and PET; instructions for wearables	Continuous glucose monitoring (CGM); sleep tracking ring (Oura)	Baseline assessment; psychological and mood surveys; bloodwork; CGM, Oura, & glucose/ketone meter instructions	KE supplement taken twice daily with meals (e.g. with breakfast and dinner)	Repeat psychological testing (may be completed virtually if needed); repeat glucose/ketone meter measurements	Continuous glucose monitoring (CGM); sleep tracking ring (Oura)	Post-Intervention Imaging: fMRI	Post-Intervention Clinical Assessment	Ring and mood surveys continued in isolation (no intervention) → then return Oura ring (by mail or drop off)
Approximate time commitment	3-6 hours	-	4-6 hours	-	2-4 hours	-	2-4 hours	4-6 hours	15 minutes
Test location(s)	North Campus fMRI lab/UM Hospital	Home	Domino's Farms	Home	Domino's Farms	Home	North Campus fMRI lab/UM Hospital	Domino's Farms	Home
Informed consent (or prior eConsent)	X								
fMRI scan	X						X		
OPTIONAL [18F]BCPP Baseline PET scan	X								
Continuous glucose monitoring		X				X			
Sleep Tracking Ring (Oura)		X	X	X	X	X	X	X	X
Glucose/ketone meter[2]			X		X			X	
Blood draw[1]			X					X	
Urine drug screen			X					X	
Neurobehavioral test battery			X		X			X	
Mood tracking (via app on phone)		X	X	X	X	X		X	
Meal Photo-Diary (via app on phone)				X	X	X	X	X	
In lab/at home KE intervention usage			X	X	X	X	X	X	
At home diet modification[3]				X	X	X	X	X	
Weekly phone / email monitoring				X					
Adverse event assessment	X		X		X		X	X	
Drug accountability			X					X	
Pregnancy test in women of childbearing potential (for optional PET)	X (within 48 hours of optional PET)								

Note:
* Visits 1-2 and 4-5: There is no pre-set sequence for which assessment (clinical or imaging) comes first.
[1] Blood laboratory assays will be optional. Participants may be required to fast in the morning prior to blood draw and/or abstain from exercise for at least several hours prior to blood draw.
[2] Glucose/ketone meter measurements will be performed at baseline, during the intervention (approximately mid-way at Day 45 ± 10 days), and at the end of the intervention period. Measurements will be taken before supplementation (morning fasting) and two hours post-supplementation.
[3] Modified diet throughout KE intervention to minimize blood sugar spiking. Participants will be asked to follow a modified low-glycemic index diet in which they cut out soda/sugary drinks, candy, and white grains/rice. If consuming fruit, they will be asked to do so at the end of each meal to minimize glycemic spiking. If they desire more information, participants may be given a recipe sheet with off-limit foods/drinks and alternative meal/snack ideas.

Clinical test days
General clinical tests: You will receive a physical and neurological examination ("medical check-up") including measurements of weight, height, pulse, and blood pressure. This may include a urine drug screening to ensure eligibility for the study and to account for substance use as a confounding health factor when assessing outcomes. We will also ask you questions about your health, medications, and adverse childhood experiences (if applicable). In addition, we will ask you for some general demographic and clinical information.

Psychological surveys: We will ask you questions about your mood, sleep, fatigue, and symptoms. These assessments may be completed via virtual visit at Visit 3 (mid-intervention visit) if needed.

Keto-Mojo samples: We will use a finger-pricking device to measure blood sugar and ketone levels at the baseline clinical visit, mid-intervention visit, and post-intervention clinical visit (this will require one drop of blood per measurement), and will be done in the morning before you eat/take the supplement and 2 hours after your supplement is taken. We will educate you on using this device so that you (if desired) will be able to provide additional data about your blood sugar and ketone levels while you are at home on this diet.

Blood samples: Optional blood samples will be collected at the baseline clinical visit and post-intervention clinical visit, and may be used for analysis of metabolism and other measures. We will collect approximately 40 mL (approximately 2.5 tablespoons) of blood or less. Having your blood drawn is optional, and if you have a contraindication to blood draws or strong preference to avoid blood (for example, if you have a blood phobia) then participation in the study is still allowed without blood draws. The blood draws will be performed at a UM blood drawing station at Domino's Farms, and will be analyzed through the Michigan Medicine clinical labs. You will be able to view the results of your lab tests if you have a patient portal account. Permission for this sub-study will be documented in Section 12 of this consent form.

Genomic testing: With your permission, we may collect and store information about your mitochondrial genes. The DNA contained in these genes holds the instructions that your mitochondria ("powerhouses of the cell") use to function. Genes can also be responsible for some medical conditions. *Genomic* information relates to the structure and function of the genetic material in the body. We will label your genomic information with a code, instead of your name or other information that people could use to directly identify you. Even so, there is a possibility that when your genomic information is combined with other information available to researchers,

either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. Researchers will have *controlled access* to your specific genomic information. Controlled access means that researchers will need approval in order to obtain de-identified genomic information.

To this end, we are collecting saliva or a blood sample to analyze a sample of your mitochondrial DNA. You may decline to provide a sample for genetic analysis. If you decline to participate in the mitochondrial genotyping 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 Department of Human Genetics, University of Michigan, or at other locations. No personal identifiers will be stored in the repository and the samples will be used for preparation of DNA and will be stored indefinitely. Research teams will analyze the genetic samples for variants in mitochondrial DNA sequence. Samples and unidentified data could be used for research into any type of disease and will be available to researchers at hospitals, universities, and commercial organizations. Once analysis is performed, we will break the links between the DNA and your name. There is a risk that someone could use information from the sample you submitted, via DNA, to identify you if it were matched with another DNA samples provided by you. However, any user of this sample must agree not to use it for that purpose, and the risk, while real, is small. You have the right to withdraw from this research sub-study, at any time. If possible, any samples you contributed will be discarded if you request this; however, because of the sample and data-marking, we may not always be able to identify which samples were donated by you. We will not be returning results to donors. You will be asked to document your decision about this sub-study in Section 12 of this consent form.

Imaging (Visits 1/2 and 4/5)

Resting State fMRI scan: functional MRI scans allow the investigators to visualize all the structures in the brain in great detail by using a large magnet. It also allows investigators to assess brain network stability (essentially, how well brain networks are "talking" with each other). Like a traditional MRI scan, a fMRI 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 fMRI scan. During the fMRI scan loud noises may be heard. The fMRI scan will be performed in an FDA-approved MRI scanner at the University of Michigan Hospital or the Functional MRI Laboratory located at the University of Michigan's North Campus Bonisteel Interdisciplinary Research Building (BIRB), 2360 Bonisteel Blvd, Room 1072 BIRB.

_____(Initials) I understand that the fMRI scans (baseline and follow-up) are required for this study.

Optional PET scan: The ^{18}F-BCPP-EF PET scan will allow the investigators to "see" mitochondrial function in the brain/body. To establish this, a radiotracer will be injected into your vein through an IV (intravenous line or plastic "tube" inserted in an arm vein). 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 thighs will be obtained over a period of 60 to 120 minutes. Women of childbearing potential will be required to provide a urine sample for a pregnancy test within 48 hours prior to the PET scan. You will be asked to make your choice to participate in this sub-study in Section 12 of this consent form.

Testing at home

Sleep Tracking: You will wear a ring called Oura ring to track your sleep from the baseline period (e.g. after imaging) until you finish your participation in the study. After the intervention period, you will continue to wear your Oura ring for a 14 (±7)-day post-intervention follow-up period. You will be asked to download the Oura ring app and open it daily to allow the data to sync with the study database. However, the information gathered by the Oura ring will not be shared with you.

Continuous glucose monitor: The continuous glucose monitor will be worn at your lower abdomen. It will be inserted by placing an automatic applicator on your skin and pressing a button. The inserted sensor filament is water-resistant so you can take a bath, shower, or swim as needed. The sensor is contained in an adhesive patch and can be removed the same way as removing a Band-Aid. The continuous glucose monitor will be worn for approximately 1 week before starting the supplement and approximately 1 week during the end of the supplementation period. The information gathered from the continuous glucose monitor will not be shared with you.

Meal Tracking: You will be asked to download an app, FoodView, and use it to keep track of your daily food intake while you follow the dietary modification protocol. You will be prompted to take a picture of your meals using your smartphone and share your FoodView food diary with study staff to facilitate monitoring adherence to the modified diet.

Mood and symptom check in: You will download an app, Care Evolution, that will send a prompt to check in each day around 7pm to rate your mood and symptoms. These surveys are designed for tracking daily fluctuations in your mood and energy levels, and the study team will not have access to these survey results on a daily basis. If you are experiencing a low mood, or having thoughts of suicide, you will need to seek help. Section 5.1, risks for "Daily Mood Tracking," explains this in more detail.

90-day (± 10 days) Ketone Ester Drink Supplementation and Modified Diet Intervention

Ketone Ester Drink: 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. The ketone ester drink used in the proposed dosage in this study has been determined to be Generally Recognized as Safe (GRAS) for use as a food ingredient in the US by the FDA. The ketone ester drink is available over the counter as a supplement. You will take 19 grams of ketone ester drink 2 times per day by mouth (mixed into water, similar to a protein shake). The drink can be taken with meals, with preferably your last meal being several hours before going to sleep. Since ketones have a naturally bitter flavor, you may wish to add Stevia and/or ginger to the drink for taste.

In the event of an availability shortage of the primary study supplement ("Qitone—Pro Ketone Powder"), you may be asked to temporarily use a separate supplement, called "KetoneAid KE4 Pro Ketone Ester" as a replacement. This supplement has the same active ingredient and mechanism of action as the primary study supplement but comes in liquid form. The ketone ester drink used in the proposed dosage in this study has been determined to be Generally Recognized as Safe (GRAS) for use as a food ingredient in the US by the FDA and is available over the counter as a supplement. You will take 10 grams (equivalent to 20 mL) of the ketone ester drink two times per day by mouth. The drink can be taken with meals, with preferably your last meal being several hours before going to sleep. Since ketones have a naturally bitter flavor, you may wish to add Stevia and/or ginger to the drink for taste.

Diet Modification: When you begin the ketone ester supplement, you will also be asked to modify your diet. Specifically, you will be asked to replace foods that spike your blood sugar (such as soda (including diet soda), candy, white grains/rice) with "complex" carbs (such as brown rice, quinoa, blueberries/blackberries). If you eat fruit, we ask that you eat it at the end of your meal to reduce the spike in your blood sugar. If desired, you will be given a recipe sheet with off-limit foods/drinks and alternative meal/snack ideas.

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 supplement and maintaining dietary modifications as directed throughout the intervention period, and reporting 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 any study-related medications/supplements. This will usually be performed at the time of the PET scan before starting the study intervention.

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.

You will return any left-over ketone ester supplement to the research staff upon conclusion of the study.

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 imaging will take place at the University Hospital (Level B1, Reception C) of Michigan Medicine and the fMRI imaging will take place either at the University Hospital or at the fMRI laboratory located at the University of Michigan's North Campus Bonisteel Interdisciplinary Research Building (BIRB), 2360 Bonisteel Blvd, Room 1072.

There will be a total of 5 study 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 sleep, glucose, and ketone monitoring.

4.3 When will my participation in the study be over?

Your participation will end after you have completed all study visits and returned any left-over ketone ester containers to the study, but you have the right to withdraw from this research study at any time.

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.

In Section 12 of this consent form, you will be asked to document your decision to have your coded research data (i.e., data without your name included) saved for future use which could be 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?

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. During the PET and MRI scans you will be able to talk to technologists 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.

- During the course of the study, you may receive several blood draws, intravenous (IV) catheters, and injection 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 bloodborne 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 unless you request to review the exploratory research findings for non-medical purposes. Please note that if you request to review the research findings with the study team this will NOT be used for clinical purposes.

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.

Neurobehavioral tests:

- There is an **infrequent** risk of boredom, frustration, and/or mental and physical fatigue during the 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. If needed, questionnaires may be completed over the phone/Zoom video call.

Ketone ester drink side effects:

- Ketone ester supplements are usually well tolerated. However, possible infrequent side effects may include mild nausea, diarrhea, indigestion, upset stomach, distended abdomen, feeling bloated, heartburn, loose bowel movements, constipation, passing gas, keto flu-like symptoms, headache, dizziness, headrush (feeling of warmth or buzz in the head lasting a few minutes), or sleep changes.
- *If you are having trouble tolerating the ketone ester supplement upon initiating the intervention period, you may reduce each dose by ½ for the first few days to build tolerance gradually.*
- The ketone ester may have a poor or bitter taste.
- *The drink can be diluted, or mixed with a natural sweetener such as stevia or monk fruit.*
- Ketones may affect blood glucose levels (decrease or increase), which could lead to symptoms of lightheadedness or jitteriness.
- *We recommend you eat regular meals and drink plenty of water while on this diet to avoid these symptoms. You should eat a piece of fruit if you are concerned about low blood sugar; or use the Keto-Mojo device to check your blood sugar. If you feel lightheaded, weak, or fatigued and find that your blood sugar is below 70, please eat a piece of fruit.*
- You may also feel more mental or physical energy with supplementation. Theoretically, increased energy availability provided by ketones may be a risk factor for (hypo)mania (which, in turn, is a risk factor for social consequences and impulsive behaviors such as impulsive spending, risk-taking, and sexual promiscuity), though we are not aware of any clinical reports that validate the possibility of hypomania induced by consumption of exogenous ketone supplements to date.
- *You need to be aware of this possibility and complete weekly check-ins with the study team, reach out to our team as needed with any immediate concerns, and consistently complete mood surveys each evening.*
- It is possible that blood laboratory assay values may change while taking the ketone ester. For example, thyroid function tests may change, as the body interprets ketones as a signal for fasting (and, in turn, slowing down metabolism).
- It is theoretically possible that kidney function values may change, as the ketone ester will be excreted via the kidneys.
- *Please follow the diet and remember to drink plenty of fluids (water and green tea are recommended) as in the dietary handout sheet.*
- We will be checking in with you each week to monitor how you are doing. If there are any concerns regarding your health, we may pause or discontinue the study for your safety and to allow for any necessary medical attention.

fMRI scan:

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

- There is an infrequent risk of bruising, bleeding, infection, or soreness associated with intravenous catheter placement, similar to the risks associated with routine blood testing. Also, you may feel dizzy or lightheaded or may rarely even faint when the tube is put in or taken out. We will use highly trained personnel for placement and removal of the IV.
- 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 the [^{18}F]BCPP-EF tracer involves radiation, a term that refers to a form of energy that allows us to see inside the body but may damage cells, particularly if excessive exposure occurs. The dose used for this study is approximately 4.9 % of the annual radiation exposure permitted to radiation workers by federal regulations; more details on radiation safety are included below. 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-CT room for treatment of any adverse reactions that may occur.

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

We will provide pads and blankets to make you as comfortable as possible. You will be able to talk to a technologist 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.

If you opt to complete the optional PET scan in this study, you will be exposed to radiation from the CT scan (embedded in the PET scanner) and the [^{18}F]BCPP-EF radiotracer. The risks associated with the amount of radiation exposure participants receive in this study are considered very rare and comparable to everyday 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 risk of biological effect from radiation exposure 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 CT, and [^{18}F]BCPP-EF PET scan is equivalent to a uniform whole-body dose of 2.48 mSv, which is approximately 4.9 % of the annual radiation exposure (50 mSv) permitted to radiation workers by federal regulations. This amount is approximately equal to the annual exposure received from natural background radiation levels. You will be instructed to use the bathroom and urinate as soon as possible after the optional PET scan in order to minimize bladder exposure.

In the case of technical failure of the scan you may be asked to undergo a repeat [^{18}F]BCPP-EF PET scan. This may expose you to an additional 2.48 mSv of radiation from internal and external exposures.

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 well below the level where adverse health effects are typically observed. 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 or nursing women.

A urine pregnancy test will be performed on all women of childbearing potential within 48 hours prior to the PET scanning session. If the test is positive for pregnancy, you will not be able to complete the optional PET imaging portion of the study and no radioactive tracer will be injected.

In the case of a technical failure during a PET scan necessitating a repeat PET scan, if you agree to repeat the PET scan then an additional pregnancy test will be required within 48 hours prior to the repeat PET scanning session and women of childbearing potential must maintain abstinence or contraception practices to prevent pregnancy between the two PET scans.

It is your choice if you want to complete the optional PET scan or opt out. If you have a contraindication to completing the PET scan (such as major radiation exposure in the past) or a strong preference to avoid the scan, this choice will be respected and you will still be allowed to participate in the study without completing the PET scan.

Genetic testing:

- We will be testing for mitochondrial genes that are related to metabolism. There is a very rare risk that the genetic information we obtain from your samples could prove embarrassing to you, if somebody were able to link the genetic information with you.

We have a system of double-coding the genetic information, so that it is extremely unlikely that the genetic information would be connected with you. Most importantly, we will break the link between the genetic information and you once the study is completed.

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 reaction or skin irritation to the covering tape. Signs of skin irritation will disappear once you remove the sensor.

Results of the continuous glucose monitoring will not be shared with you. However, if monitoring reveals any information that may be clinically relevant to you, we will discuss this with you.

Oura Ring

Wearing the Oura ring sleep/physical activity tracker will not cause any risks beyond those associated with wearing a normal ring. Like with every ring you may wear on a finger, there is a small risk that that it may feel tight or that you may have difficulties removing it. You will be individually fitted for the ring to minimize this risk.

Results of the Oura ring sleep/physical activity tracking will not be shared with you. However, if monitoring reveals any information that may be clinically relevant to you, we will discuss this with you. For example, the ring may reveal low levels of oxygen in your blood, which may could be a sign of underlying illness. If we notice concerning abnormalities, we will discuss them with you and recommend any necessary medical follow-up with primary care provider(s).

See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

Daily Mood Tracking

We do not anticipate the low glycemic index dietary changes or supplements to cause any increase in mood disturbances. However, thoughts of suicide (or suicidal ideation) are more common in people with Bipolar Disorder than in the general population. The daily mood tracking surveys are not a substitute for regular psychiatric assessment and care, and if you begin to experience suicidal thoughts during the course of the study, you should first reach out to your primary/psychiatric care providers, call the Suicide Prevention Hotline (dial 988), and/or seek care at a psychiatric emergency service (such as the Psychiatric Emergency Service at Michigan Medicine).

In the event that suicidal ideation is reported during a weekly phone call check-in with a study coordinator or identified by study staff in the process of reviewing CareEvolution mood survey results, a certified clinician will discuss these feelings with you either in-person or via phone/zoom call. If the clinician determines you are at risk for suicidal behaviors or self-harm, a safety plan will be implemented, which may include a trip to the emergency

department depending on the level of risk. Please note that survey results are intended to be reviewed at the end of the study and that study staff may not be able to review survey results on a daily basis (for example, in the event of a sever outage or update to the secure platform's software) – these mood surveys are NOT a replacement for regular psychiatric assessment and care.

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.

As a notable exception to the above, we are prioritizing recruitment of individuals participating in the Longitudinal Study of Bipolar Disorder. **If you are a participant in the Longitudinal Study of Bipolar Disorder (HUM00000606), signing this consent gives us your permission to use data gathered in the Longitudinal Study of Bipolar Disorder to help us further understand and analyze the data from this study.**

5.4 How could I benefit if I take part in this study? How could others benefit?
You may potentially experience improved thinking, metabolism, sleep, and mood. It is also possible 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 Bipolar Disorder and related mood disorders. This may ultimately lead to the development of new 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 involves nutritional supplements and dietary intervention that may affect your body's chemistry and neural connections in your brain in ways that may help lead to new investigational treatments for Bipolar Disorder. Please note that the combination of ketone ester supplements and low glycemic index dietary changes is not currently an established treatment for bipolar disorder, and our study's primary aim is to better understand the effects of this dietary combination on your brain, body, and metabolism.

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.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

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

You will receive $50 for each of the clinical testing visits (total of $150 collectively for the pre-intervention, mid-intervention, and post-intervention visits).
You will receive $100 per completed PET or MRI scan (total of $300 collectively for imaging with breakdown as follows: $200 for first imaging visit, featuring both MRI and PET at $100 reimbursement each; $100 for second imaging visit, featuring only MRI).
You will receive a total of $50 for each week of using the continuous glucose monitor (CGM) – thus a combined total of $100 for the two weeks.
You will receive $200 for completing the approximately 90-day intervention of ketone ester supplementation combined with a low-glycemic index diet.

You will receive $50 for completing both the pre-intervention and post-intervention blood draws (thus $25 per blood draw).

If you opt in for the optional PET scan and blood draws, compensation for your time and effort after full study completion may total a maximum of **$800**.

You will be paid after completion of each item or in full after your last study visit – per your preference – and, in the 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.

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.

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 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 fMRI 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 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.

As part of this study, you will be required to download 4 apps to your smartphone. These apps include:

Oura Ring—This app is not yet officially HIPAA-compliant, but the company is working towards this. To download this app, you will need to provide an email address along with your height, weight, sex, and birth year and accept their terms and conditions.

MyMojoHealth App—will allow results of your Keto-Mojo (blood glucose and ketone measurements) to be stored and shared with the study team. This app is HIPAA-compliant. To download this app, you will need to provide an email address and accept their terms and conditions.

FoodView—will allow you to keep an organized food diary during the dietary modification period. This app will not be used to collect protected health information. To download this app, you will need to provide an email address.

Care Evolution—this platform will send a prompt each day at 7pm to ask for your mood rating. This platform is HIPAA-compliant. To download this app, you will need to provide an email address/phone number and date of birth and accept their terms and conditions.

These platforms are independent of each other and will not have access to data from each other, or to data collected for other assessments in this research study. If you are concerned about your private information collected in these apps, we recommend that you provide the minimum necessary information for these apps and decline any additional features. Additionally, there is no guarantee that your privacy will be maintained while using these apps.

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.

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.

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

9.3 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 Michigan Medicine, 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

Overseeing physician: 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 & Research Staff: Jaimie Barr & 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: 734-936-1168

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 Michigan Medicine 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 investigate 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): _____

Sig-C

Consent/Assent for Participating in an Optional PET scan.

This project involves optional participation in a sub-study to have a ^{18}F-BCPP-EF PET scan. I understand that it is my choice whether or not to take part in the sub-study. 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 sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

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

Sig-C

Consent/Assent for Participating in an Optional Sub-Study to Collect Blood Samples

This project involves optional participation in a sub-study to collect blood samples at the baseline clinical visit and post-intervention clinical visit, and may be used for analysis of metabolism and other measures.
I understand that it is my choice whether or not to take part in the sub-study. 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 sub-study.

_____ No, I do not agree to take part in the optional sub-study.

Print Legal Name: _____

Signature: _____

Consent for Participating in Genetic Sub-Study Testing

I understand that by signing below, I am also voluntarily agreeing to participate in the genetic testing aspects of this study. 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 sub-study.

_____ No, I do not agree to take part in the optional sub-study.

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): _____