PRINCIPAL INVESTIGATOR: Dr. Dimitrios Kapogiannis

STUDY TITLE: Ketone ester effects on biomarkers of brain metabolism and cognitive performance in cognitively intact adults ≥ 55 years old. A double-blinded randomized controlled clinical trial

STUDY SITE: National Institute on Aging (NIA) Clinical Research Unit, Medstar Harbor Hospital, Baltimore

Cohort: Standard, Adult Consent

Consent Version: January 11, 2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

The purpose of this research study is to look at how a drink containing ketones affects the brain in people with normal cognitive function.

Glucose and ketones are the main energy fuel sources for the brain. Ketones are naturally produced in the body after many hours of fasting or while following a diet very low on carbohydrates/high fat (ketogenic diet).

We know that the brain of people with Alzheimer's disease, and to some lesser extent, the brain of older people or of people with Diabetes Mellitus or Metabolic Syndrome (a condition related to having resistance to the action of insulin, abnormal lipids and high blood pressure) cannot use glucose properly. On the other hand, brain can still make use of ketones, but they are not usually available, since prolonged fasting and low carbohydrate/high fat (ketogenic diets) are uncommon. A convenient way to increase ketones in the body is by taking a supplement drink containing ketones by mouth. Since ketones are the brain's preferred energy fuel, we believe that a ketone supplement could improve brain's function especially in people whose brains have difficulty using glucose.

If we find out that a ketone supplement increases ketone supply to the brain, and improves brain function and cognitive performance in people with Metabolic Syndrome and normal cognitive function, there will be a greater chance that it could also be helpful in Alzheimer's disease.

The study will consist of 4 Visits. All Visits will take place at National Institute on Aging (NIA) Clinical Research Unit located at the Medstar Harbor Hospital in Baltimore.

You will be asked to refrain from: high fat/low carb (<50 g carbs/day) diet or very low calorie (< 500 calories) diet or intermittent fasting or other ketogenic supplements/foods (such as Medium Chain Triglycerides (MCTs), Coconut oil, or Ketone salts).

The remaining document will now describe more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a research study. The purpose of this research study is to test whether a drink that contains ketones (compared to a placebo drink that tastes similarly, provides the same amount of calories but does not contain ketones) can increase ketone supply to the brain and improve brain function.

It is unusual for people to have high levels of ketones in the blood, unless they have been fasting for many hours or have been following a low carbohydrate/high fat (ketogenic diet). A supplement containing ketones can increase ketones in the body quickly. This will allow us to study whether it can increase ketone supply to the brain, improve brain metabolism and function, and cognitive performance. We are asking you to join this research study because you are 55 years old or older, your memory and cognitive performance are normal, and you do have risk factors that together with your age suggests that your brain may not be using glucose efficiently. The results of this study will help us understand how the brain responds to taking ketones as a supplement.

The ketone supplement we are using in this study has not been approved by the U.S. Food and Drug Administration (FDA) to treat any medical condition. It is generally considered safe and has already been tested in healthy people as a supplement to improve their performance during exercise (e.g. long-distance cycling). We are testing it in this research study to see if it can increase ketones in the brain and improve brain function.

WHAT WILL HAPPEN DURING THE STUDY?

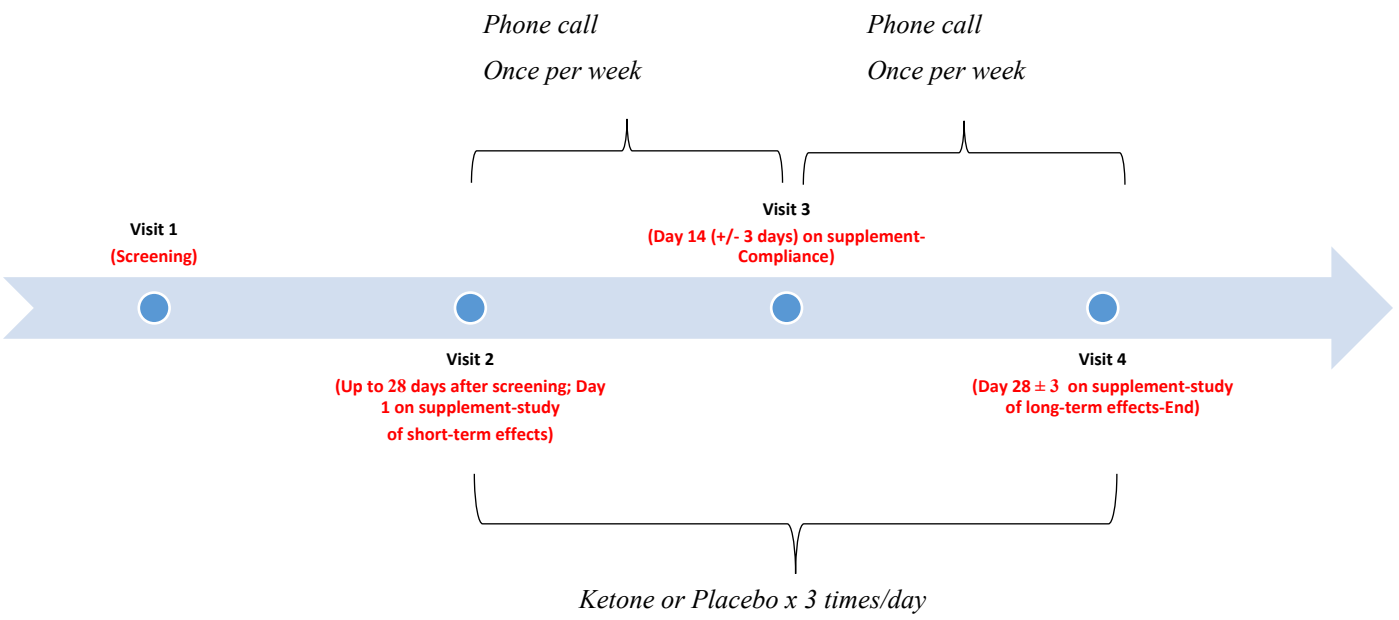
If you decide to take part in this study, you will be asked to come to the National Institute on Aging (NIA) Clinical Research Unit located at the Medstar Harbor Hospital in Baltimore for 4 visits.

- Visit 1 will be a screening visit to determine if you are eligible.
- If you qualify you will be asked to return for 3 more visits over a period of 28 ± 3 days.
- During these 28 ± 3 days we will be calling you once per week.
  For all Visits, you should arrive in the morning after fasting for at least 12 hours. You may have water.

You will be asked to take a drink containing ketones or a placebo drink 3 times per day for 28 days. The placebo drink will be packaged into similar bottles, taste similarly and provide the same number of calories as the ketone drink but will not contain ketones. We will compare the two drinks and to find out which one produces the greater effects on the brain.

<u>All procedures in this study are for research purposes only.</u> No admission to the hospital will be required.

<u>Timeline:</u>



<u>Visit 1 (Screening):</u>

You will arrive after fasting for at least 12 hours. You may have water. During this Visit, one of the study investigators or nurses will review this consent form with you and answer any questions you may have. After signing the consent form, you will go through the following procedures:

- **Eligibility Review**

- **Review of your Medications:** This will include all prescription medications, over the counter-drugs and any vitamins/supplements you are taking. Please bring a list of your medications with the dosages with you.
- **Vital Signs:** We will measure and record your temperature, blood pressure, pulse rate, respiratory rate and oxygen saturations.
- **Anthropometric measurements:** We will measure and record your height, weight and waist circumference (width).
- **History and physical exam:** A doctor or nurse practitioner will meet with you to review your medical history (including your past medical history, current review of systems, as well as family history). You will change into a hospital gown prior to the physical examination. Please note that this examination is for research purposes only and does not replace an examination you may receive from your own physician. You may also be examined if the study physician feels it is needed at any time during the study.
- In addition, you will be asked questions to find out if you are eligible for Magnetic Resonance Imaging (MRI), which is required for this study.
- **Questionnaires:** We will test your memory, language and learning skills to determine your cognitive state.
- **Blood tests:** About 40ml (about 2.5 tablespoons) of blood will be taken during this visit. As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS in addition to Hepatitis B and C. If you are infected with HIV or Hepatitis B or C, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. We will also check your complete blood count, complete metabolic panel (including glucose), HbA1C, insulin levels, lipids panel (including cholesterol and triglycerides).
- **Urine drug screen test:** During this study, we will perform a urine drug screen. If your drug test is positive, you will be told promptly, and you will not be included in the study.
- **Urine Pregnancy test:** If you are a woman who is able to become pregnant, a urine pregnancy test will be performed at the screening visit and prior to the MRI.
- You will receive a meal ticket at this visit.

This visit will take approximately 3 hours. If you are found eligible for the study, you will be assigned into one of two groups. Each group will consist of 25 people. We will use a computer program to assign you into one of the two groups. It will assign you by chance (like tossing a coin). You will have an equal chance of being in either group. You will not know which group you belong to or which one of the two drinks you will be taking.

Group A (ketone group): people in this group will consume a supplement drink that contains ketones and provides 140 calories per dose, three times every day for 28 days (total of 420 calories per day).

Group B (placebo group): people in this group will consume a drink that does NOT contain ketones, but provides 140 calories per dose, three times every day for 28 days (total of 420 calories per day).

If it appears you will be eligible for the study (pending lab results) you will be given supplies and instructions to collect a stool sample. This sample will be collected at home within 24 hours before Visit 2. This sample will need to be kept on ice.

Visit 2 (Initiation and Acute Effects):

This Visit will take place on any day within 28 days from Visit 1. During Visit 2, we will give you the first dose of the supplement drink. During this visit you will drink the first dose of the ketone/placebo drink. You may take the drink with some water or you may drink some water immediately after you take the drink. The drink will have a bitter taste so drinking water will help you swallow it. You can ingest the drink as slowly as you want. Before and after taking the first drink, you will have blood draw, MRI/MRS and memory/cognitive tests.

Specifically, the following procedures take place:

- You will give to us the **stool sample that you collected within the previous 24 hours at home**.
- We will also **collect your urine while you are at the NIA Clinical Unit**.
- **Review of your Medications**
- **Vital signs**
- **Urine Pregnancy test, if applicable.**
- **Blood test:** We will draw your blood before and after the first dose of the assigned study drink. About 40 mL of blood or (2.5 tablespoons) will be drawn at this visit. Blood will be drawn in the morning when you arrive (about 35 mL) and about 5 mL of blood will be drawn 60-75 mins after you take the first study drink. The blood will be drawn to measure some new proteins and chemicals in that could be related to brain health and function (the measurement of those proteins and chemicals is experimental).
- **Memory and cognitive tests:** we will perform cognitive tests that will help us understand your usual memory and cognitive performance to determine if the supplement can improve brain function or not.
- **Magnetic resonance imaging (MRI)/Magnetic Resonance Spectroscopy (MRS):**
  a) Brain: MRI scans give us detailed pictures of various parts of the body, such as the brain and muscles. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. For this study, we will first obtain pictures of your brain with MRI. MRS is a procedure that uses the same MRI scanner, but instead of taking pictures, takes measurements of some chemicals. During the MRI and MRS, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You may be asked to lie still for up to 45 minutes for each brain-scanning session. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs and earphones to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine

at any time. It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

While you are at the same position, we will use the scanner for brain MRS, a procedure that allows us to measure concentration of various substances in your brain. In this case, we are interested in the levels of ketones, glucose and lactate in your brain.

Each brain-scanning session will take about 45 minutes. You will have two of these sessions during Visit 2.

b) OPTIONAL: you may participate in an additional MRS study of the thigh muscle: After finishing the brain MRI and MRS, you will be asked to change position so that we can perform MRS of your thigh muscle while you are doing a leg exercise. Using the same MRI scanner, we will measure some substances in your thigh muscle that find out how the muscle uses energy before, during and after exercise. We will ask you to extend your knee repeatedly while you are lying in the scanner. Each extension cycle will last about 30 seconds, which will be repeated several times depending on the measurements we get. The thigh MRS session will take about 45 mins to complete. If you agree to this optional scan you will have two of these during Visit 2.

This visit will take totally around 8 hours (review of medications, vitals, urine pregnancy test, blood draw, cognitive tests and MRI/MRS before the drink: ~ 3.5 hours; blood test, cognitive tests and MRI/MRS after the drink: ~ 4.5 hours). You will receive meal tickets at this visit.

How to take the study drink (ketone or placebo) at home:

You will be asked to take one dose of the study drink 3 times per day, with doses being approximately 6-8 hours apart from each other. The drinks will provide you with 360 calories every day.

We suggest you take the study drink between 8-10am, 2-4pm, 8-10 pm but these may be modified to fit your schedule. If one or more study drink doses are skipped, you should continue with the next dose(s), as originally scheduled. Do not take more than one dose within a 4-hour period.

Both drinks will have a bitter taste. You may take the drink with some water or you may drink some water immediately after you take the drink. The drink will have a bitter taste so drinking water will help you swallow it. You can ingest the drink as slowly as you want.

The study drinks will need to be stored in a refrigerator.

You must bring back ALL bottles (empty or full) at your next visit.

Communication between Visit 2 and Visit 3:

We will call you once between Visits 2 and 3. During the call, we will ask you if you are taking the study drink and we will ask if you have any concerns or questions. We will also review and discuss the importance of this study. The calls will take about 15 minutes and the time of the call will be based on your availability.

Visit 3 (Compliance Visit):

About 14 days after Visit 2, you will be asked to come for Visit 3. This Visit is done to do the following procedures and review study compliance. This Visit will last around 1.5 hours. You will have the following procedures:

- Review of your Medications
- Vital signs
- Urine Pregnancy test, if applicable.
- Labs: we will take blood to test for ketones before and after you drink the supplement. Some of the blood will be used for experimental testing of proteins and chemicals that are related to brain health. About 40 mL or 2.5 tablespoons of blood will be drawn.
- Review compliance logs. Questions, concerns and the importance of the study will be discussed, as well.
- We will ask you questions about your expectations about taking the supplement.
- You will be given supplies and instructions to obtain a stool sample before the 4th Visit.
- You will be given additional bottles of ketone/placebo drink. You will bring back ALL bottles (empty or full) at your next visit.

Communication between Visit 3 and Visit 4:

We will call you once between Visits 3 and 4. During each call, we will ask you if you are taking the drink and we will ask if you have any concerns or questions. We will also review and discuss the importance of this study. Those calls will last about 20 min. The time of the call will be based on your availability.

Visit 4 (Chronic Effects-End of Study):

About 28 days after Visit 2, you will be asked to return for the last Visit (Visit 4). During Visit 4, all procedures of Visit 2 will be repeated in the same way (see Visit 2 for details). In addition, we will review compliance logs and ask you questions about your experience while taking the supplement. The purpose of this Visit is to test the long-term brain effects of taking the supplement for 28 days.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, you will complete 4 study Visits. You will have a screening Visit followed by 3 additional visits.

Visit 1 will take about 3 hours.

Visit 2 will occur within 28 days of Visit 1 and it will take about 8 hours.

Visit 3 will occur about 14 ± 3 days after Visit 2 and will take 1.5 hours.

Visit 4 will occur about 14 ± 3 days after Visit 3 and will take about 9 hours.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Up to 150 people will be screened and up to 50 people will be enrolled and complete the study. Withdrawals will be replaced.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Risks/discomfort from:

- **Study Drink:** you may experience nausea, but the risk of this is low. Other GI problems such as diarrhea and abdominal bloating are also possible, but they are not common. This drink is also known to have a bitter taste. Drinking water during or after the drink could possibly help lower the risk of the side effects.
- **Medical History and Physical exam and nursing assessment:** There are no significant risks to providing medical history and having a physical exam and nursing assessment. However, you may have some psychological discomfort, if we find any abnormalities that may be significant for your health. In that case, we may advise you to have follow up with your own physicians, which may cause you further inconvenience and costs.
- **Measurement of Blood Pressure, Respiratory Rate, Heart Rate, Temperature, Weight, Height, Waist Circumference:** Some psychological discomfort might result from these procedures, if we find abnormal values (e.g. high blood pressure, abnormal weight)
- **Blood draws:** You may feel some pain and discomfort at the needle entry site where blood is drawn or where the intravenous line is inserted. There is a slight risk of bleeding or bruising around the site. Some people feel lightheaded or dizzy. There is a remote risk of fainting and infection after having blood drawn. To reduce the risk of injury because of a fall, you will be closely monitored and asked about these symptoms before you are allowed to stand up. Clean aseptic technique will be used by experienced staff while drawing your blood.
- **Stored Samples:** The greatest risk from the use of stored samples is an unplanned release of information from medical records. The chance that this information will be given to an unauthorized person without your permission is very small. We will not enter any experimental information (research results) into any other medical record and we will not

release information to a third party unless specifically authorized by you. Possible problems with the unplanned release of information include discrimination when applying for insurance and employment. Some problems may occur if you disclose information or you agree to have your medical records released.

- **Hepatitis Virus B, hepatitis virus C, and HIV testing:** The results of these blood tests, if positive, will be reported to you and the state health department.
- **Stool and urine samples:** There are no known risks to providing stool or urine samples.
- **Urine drug screen**: If you do not want this information in your medical records you should not participate in the study. The medical records can only be released with written agreement by you. However, insurance companies may require individuals to release these records and may not provide insurance if they refuse.
- **Urine Pregnancy test**: There are no known risks to providing a urine specimen for pregnancy testing.
- **Questionnaires:** There are no risks associated with completing questionnaire, but it may take some time and be inconvenient.
- **Compliance logs:** There are no risks associated with completing these logs, but it may take some time and be inconvenient.
- **Cognitive tests (also known as neuropsychological testing):** The tests are not harmful but may be frustrating or stressful. We only ask that you do your best. No one performs perfectly on these tasks. If you get tired you can ask for a break. You may choose not to answer every question, or you may choose to stop testing all together. These tests will take about 90 minutes, which may be inconvenient.
- **Modified Credibility/Expectancy Questionnaire:** There are no risks associated with completing this questionnaire, but it may take some time and be inconvenient.
- **Imaging studies (MRI/MRS):**

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have a pacemaker or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

We will be using the MRI in research mode. This means that the way the MRI is generating the images may be different than what is normally done in a routine clinical scan. This use of research tools in the MRI has not been approved by the FDA and is considered investigational.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

Rarely, you may feel a vibration or tingling of your skin during the MRI due to the magnetic fields. These sensations will stop when the MRI is stopped. Please let the MRI technician know if you have these, or any other sensations and the MRI will be stopped at your request. Because each research MRI is different, participation in future MRIs will depend on the type of MRI that is requested and your previous response. It is not known if MRI is completely safe for a developing fetus. The scan will not be done if pregnancy tests are positive. There are no known long-term risks of MRI scans.

- **Exercise protocol for thigh muscle**. There is a risk that the exercise procedure may cause fatigue, muscle cramping and/or strain. Please report if you have any pain or during the procedure and the procedure can either be modified or stopped.

Incidental findings (brain MRI scan):

All participants in MRI research studies will have an MRI scan read by a credentialed radiologist. Sometimes there are unexpected findings on an MRI scan or on other testing that we will perform. We will inform you about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider.

What are the risks related to pregnancy?

If you can become pregnant, we will ask you to have a pregnancy test before beginning this study and throughout the study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the supplement being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the research team member identified at the top of this document as soon as possible. If you plan to become pregnant in the future, please discuss with the research team how long you need to wait before becoming pregnant after completing the course of this study drug or procedures on this study.

MRI/MRS do not use radiation, however the effects of the MRI/MRS on a fetus or unborn baby are not known. If you become pregnant during the study, you will not be eligible for further participation in the study.

What are the risks of radiation from being in the study?

You will not be exposed to radiation if you take part in this study.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. There is a possibility that you may feel increased levels of energy.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because we will have a better understanding of how increased levels of ketones might affect the function of the brain. Importantly, if we find that this supplement improves memory and cognitive performance, in the future, we and/or other researchers might try to give this supplement to people with Alzheimer's Disease. This is very important since there is no current treatment for Alzheimer's.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose not to participate.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

You may receive a copy of your screening blood work to share with your healthcare provider. All other procedures done are for research purposes only and those reports will not be provided. If we find an incidental finding on the physical exam, cognitive test, clinical labs or MRI we will discuss the abnormal results with you and will provide you with any relevant reports so you can share with your health care provider.

EARLY WITHDRAWAL FROM THE STUDY

You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. We can remove you from the study at any time if we believe that continuation of your participation in the study is not in your best medical interest, you have met an exclusion criterion, or you do not comply with study procedures.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going

on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding the effects of ketones on brain metabolism, brain function and cognitive performance. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether

your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH until there is no remaining sample or the investigators decide to destroy the sample.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

All participants will be compensated for their time and research-related inconveniences via NIA debit cards. Participants will be compensated for each Visit as follows:

Visit 1 (Screening)	$50
Visit 2	$300
Visit 3	$200
Visit 4	$500

Total compensation will be $1050 for participants that complete the study. If you do not complete the study or if the study physician needs to extend your participation due to a missed visit, you will be paid for those visits completed:

In case you are unable to complete a Visit, you will be compensated based on the parts that you completed as follows:

- blood draws (per session) $25; if two sessions are completed per visit, $50
- brain MRI/MRS (per session) $50; if two sessions are completed per visit, $100
- optional Thigh MRI (per session) $20; if two sessions are completed per visit, $40
- cognitive testing $50,
- Stool sample collection $ 10
- Urine sample collection $ 10

- Participants will be offered snacks
- KE/Placebo for one week $50

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

You will also be given snacks and a meal ticket during Visits 1, 2, 3 and 4.

This study does not offer reimbursement for, or payment of, travel, lodging or meals.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose product is being tested.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Research records will be kept at the NIA in a locked room. Some data will be stored on secure computers. These are password protected and maintained on a secure server with access limited to authorized NIA staff members. All NIH investigators and NIA staff members who have access to these databases have the proper training on patient privacy as well as the required Human Subject Protection Training.

Social Security numbers are collected for the purpose of compensation. You may decide at the Screening visit not to provide this information. However, you are required to provide your social security number at Visit 4. If you do not provide your social security number, you may still participate in the study, however, you may not be able to receive compensation.

Blood and lab test records are kept by the Medstar Harbor Hospital on secure computers. Only staff associated with your care have access to these records.

Your samples will be stored in secured freezers at the NIA facility. The only information on the sample is your Study ID number. The key to the ID number will be kept in a separate secure area to which only the Clinical study staff have access.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;

4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

NIA will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, NIA, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dimitrios Kapogiannis, M.D. at kapogiannisd@mail.nih.gov or 410-350-3953 or the Study Coordinator, Sarah Park at 410-350-7315 or sarah.park@nih.gov. You may also call the Clinical Director at (410) 350-3922; the NIA Clinical Research Protocol Office at (410) 350-3947, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date