CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title of Study: NAD therapy for improving memory and brain blood flow in older adults with mild cognitive impairment

Principal Investigator(s): Christopher Martens, Ph.D.

KEY INFORMATION

Important aspects of the study you should know about first:

- **Purpose:** The purpose of the study is to learn about the effects of a form of Vitamin B3 called nicotinamide riboside (Niagen®) on your brain health, including your memory and blood flow to your brain.
- **Procedures**: We will ask you about your overall health and analyze your blood, including your genetic risk of Alzheimer's disease. If you qualify for the study, we will measure your pulse speed and blood pressure, test your memory and thinking abilities, and perform an MRI brain scan. We will also take ultrasound images of the arteries in your head and neck to measure the amount of blood flowing to your brain. These tests will be done before and after taking the Niagen® capsules for 12 weeks.
- **Duration:** Your involvement in this study will require about 16 hours over about 3 months, comprising 7-8 in-person visits (between 30 minutes – 3 hours in length) and 5 virtual visits (between 10-30 minutes in length).
- **Risks**: The main risk or discomfort from this research are discomfort associated with having your blood drawn, and general risks from having an MRI such as claustrophobia.
- **Benefits:** The main benefit to you from this research is receiving copies of your bloodwork results and vital signs. If requested, you may also receive your APOE genotype and a copy of your brain MRI. None of this information will be interpreted by the study staff.
- **Alternatives:** There are no known alternatives other than not taking part in this study.
- **Costs and Compensation:** You will be compensated up to $210 for completing the study.
- **Participation:** Taking part or not in this research study is your decision. You can decide to participate and then change your mind at any point.

Please carefully read the entire document. You can ask any questions you may have before deciding If you want to participate.

You are being invited to participate in a research study. This consent form tells you about the study including its purpose, what you will be asked to do if you decide to take part, and the risks and benefits of being in the study. Please read the information below and ask us any questions you may have before you decide whether or not you want to participate.

PURPOSE OF THE STUDY

The purpose of this study is to learn about the effects of a form of Vitamin B3 called nicotinamide riboside (Niagen®) on your brain health, including your memory and blood flow to your brain.

As you get older, your blood vessels become stiffer, and some people experience an increase in their blood pressure. These changes may contribute to memory loss and risk of Alzheimer's disease (AD) and other types of dementia by decreasing the blood flowing to your brain. We are interested in learning the effects of Niagen® on your brain function because our previous work indicates that this vitamin lowers blood pressure and improves blood vessel health in older adults.

To test this, we will have you consume either Niagen® or placebo (sugar) capsules twice a day for 12 weeks. We will measure your blood vessel and brain functions at the beginning of the study and after 12 weeks of taking the study capsules.

This study may help provide information about a potential treatment for improving memory and brain health in people with mild cognitive impairment, which may lower the risk of developing Alzheimer's disease and other forms of dementia.

WHO IS BEING ASKED TO PARTICIPATE?

You will be one of approximately 73 participants in this study.

You are being asked to participate because you have noticed a decline in your memory, have tested lower than normal on several memory tests, and have indicated that you are willing and able to participate in a research study to determine if a form of vitamin B3 improves your memory and brain function.

If you agree to take part in this study, you will first have several tests done to make sure that you qualify for the study and that it is safe for you to participate. You may not qualify if you have been diagnosed with a major psychiatric or neurological disorder (e.g., dementia, schizophrenia, bipolar disorder, Parkinson's disease) or other chronic disease (e.g., cardiovascular disease or stage 4-5 chronic kidney disease). In addition, you must be willing and able to go into a MRI scanner.

PROCEDURES: WHAT WILL YOU BE ASKED TO DO?

This study will take place at the University of Delaware (UD). Most of the visits will take place in the Neurovascular Aging (NOVA) Laboratory, which is located in the UD STAR Health Sciences Complex. Some of the visits will take place at the Center for Biomedical Brain Imaging (CBBI), which is located on the UD main campus. Additionally,

some visits may be completed through virtual means. If you qualify for the study, more measurements will be made to assess your baseline blood vessel and brain functions and you will be randomly assigned to one of two treatment groups (Niagen or Placebo).

We will measure your blood vessel and brain functions before and after you take your assigned pills for a total of 12 weeks. Your actual involvement in the study may last up to 15 weeks depending on your availability for scheduling. In total, your participation will require about 16 hours of time.

During the study, it is important to avoid major lifestyle changes including large changes in your physical activity, body weight, diet and medication use.

Brief Overview of Study Visits						
	Week	**Visit #**	**Duration**	**Location**	**Visit Description**	**Blood**
Screening	Week -1	Visit 1	2 hours	NOVA Lab or Zoom	Informed Consent & Screening	---
		Visit 1.1	1 hour	NOVA Lab or LabCorp	Blood Draw	~5.0 Tbsp
Baseline Testing	Week 0	Visit 2	3 hours	NOVA Lab	Vascular Testing	---
		Visit 3	1.5 hour	Virtual (Zoom)	Cognitive Testing	---
		Visit 4	2 hours	CBBI	Neural Function Testing (MRI) & Receive Initial Capsules	---
		Randomization & Receipt of Study Capsules *Group A: Niagen® or Group B: Placebo*				
Intervention Period	Week 2	10 minute Phone Check-In				
	Week 4	Visit 5	0.5 hours	Zoom Check-In		---
	Week 6	10 minute Phone Check-In				
	Week 8	Visit 6	0.5 hours	Zoom Check-In		---
	Week 10	10 minute Phone Check-In				
Follow-Up Testing	Week 12	Visit 7	3 hours	NOVA Lab	Vascular Testing	~4.0 Tbsp
		Visit 8	1.5 hour	Virtual (Zoom)	Cognitive Testing	---
		Visit 9	2 hours	CBBI	Neural Function Testing (MRI)	---
	Total Time		**16 hours**		**Total Blood**	~9 Tbsp

Below is a description of the study procedures in the order in which they will occur:

***VISIT 1* – Informed Consent and Screening Visit (NOVA Lab or Zoom; 2 hours)**

Visit 1 consent and screening may be completed in person or online via a private video conference. If informed consent and screening forms are performed through online video, there is also the option to complete the blood and urine collection using an outside laboratory rather than visiting campus; however, if you choose to do your bloodwork at an outside laboratory, a second blood draw will be needed during your baseline testing visit to collect additional blood.

- **Informed Consent** – We will explain all of the study procedures to you and answer any questions you may have. Prior to signing the informed consent, we will ask you a series of questions to confirm that you understand the study procedures and potential risks.
- **Family History Questionnaire** – We will ask you about your family history of chronic diseases such as Alzheimer's disease, cardiovascular disease, diabetes, and cancer. This questionnaire should take less than 10 minutes to complete.
- **Menstrual History Questionnaire (Females only)** – We will ask you about the date of your last period to determine whether you have undergone menopause.
- **Patient Reported Outcome Measures** – You will complete a series of self-guided questionnaires on an iPad in which you will answer questions about your perception of your overall quality of life including questions about your sense of fatigue, pain, sleep disturbance, anxiety, depression, alcohol consumption and social engagement.
- **Medical History** – We will ask you some questions about your health and medical history to make sure you are healthy enough to participate in the study.
- **COVID-19 Questionnaire** – We will ask you questions regarding your history with COVID-19 and if you ever tested positive, had symptoms and if you were ever hospitalized from COVID-19. You will also be asked about specific information related to the COVID-19 vaccine.

VISIT 1.1 – Blood draw (NOVA Lab or LabCorp; 1 hours)

Restrictions: No food or beverages (including caffeine) other than water for 12 hours, only if Visit 1 blood draw is being performed on site.

- **Blood Draw** – You will be provided with a form to take with you to your local LabCorp facility to have your blood and urine collected for screening purposes at no cost to you. You may schedule an appointment directly with LabCorp or visit your nearest testing center as a walk-in. If you prefer to have your blood and urine collected at the University of Delaware, we can also schedule a time for you to come in for testing. A nurse or trained phlebotomist will place a small needle in a vein in your arm to collect ~5 tablespoons of blood. Blood will be analyzed for basic clinical values (e.g., blood sugar and cholesterol), COVID-19 related antibodies, and to find out your genetic risk of Alzheimer's disease. You should avoid food (including supplements) or beverages (including caffeine) other than water for 12 hours before your blood draw. If we are unable to obtain enough blood from you or if we are unable to measure all screening markers, we may ask you to come in for a repeat blood draw.
    - **COVID-19 Antibody Test** – We may also perform a blood test to help identify whether you may have previously been exposed to the virus that causes COVID-19 and, if so, whether or not your body has developed antibodies. The results of this test will not impact your ability to be in the study, but we are

collecting this information to test whether prior COVID-19 infection affects the final results of the study. We will only perform this test if you indicated that you have not been vaccinated for COVID-19

- **Urine Sample** – You will be required to provide a small amount of urine to make sure it is safe for you to take the study medication and to monitor factors in your urine that may change with the vitamin intervention.

- **Brain Blood Vessel Screening**: We will place a small ultrasound probe on the top of the skin above your temple to determine if we are able to image a specific blood vessel in your brain. This is being done for planning purposes only. Whether or not we can image your artery will not affect whether you qualify for this study. If we are unable to locate your artery, you will not be asked to repeat this test on future visits.

Randomization: Based on the results of Visit 1 and Visit 1.1, we will determine if you qualify for the clinical trial. If you qualify, you will be randomly assigned to receive either Niagen® or placebo. You will not know what group you are in nor will any member of the research team; however, an independent study monitor who is unaffiliated with the study will know. If you are found to be ineligible after screening, any information that we have already collected will be kept and stored.

BASELINE TESTING:

VISIT 2 – Baseline Vascular Function (NOVA Lab; 3 hours)

Restrictions: *No over the counter medications for 48 hours, no strenuous exercise or alcohol for 24 hours; No food (including study pills) or beverages (including caffeine) other than water for 12 hours.*

- **Body Height and Weight** – Your body height will be measured using a tall ruler and your weight will be measured using an electronic scale.
- **Blood Pressure and Heart Rate at Rest** – Your blood pressure and heart rate will be measured as is done in your doctor's office with a cuff wrapped around your upper arm.
- **Pulse Speed –** We will measure the "stiffness" of your arteries by measuring how fast your pulse travels from your neck to your groin (a faster speed indicates stiffer blood vessels). We will place a small pencil-like probe on your neck and a standard blood pressure cuff around your thigh to measure your pulse. We will also place 3 adhesive electrodes on your chest and abdomen to measure your heart rate. To calculate the speed of your pulse, we will measure the distance between these sites using a measure tape.
- **Neck Ultrasound** – An ultrasound sensor will be placed on the surface of the skin to allow us to measure the amount of blood moving through the arteries in your neck that supply the brain with blood. A video of this ultrasound image will be recorded.
- **Brain Blood Vessel Function** – If we were able to obtain a good image of the blood vessel in your brain during your screening visit, we will perform a more extensive test of your brain blood vessel function. A small ultrasound probe will be placed on top of the skin above your temple, and we will record how fast the blood is moving through a major artery in your brain. You will wear a rubber face mask and will be asked to switch between breathing normal air and air that contains slightly higher or lower amounts of carbon dioxide (CO_2) than you normally breathe. You will wear the face mask for about 20 minutes but will only breathe the air containing CO_2 for a total of 5 minutes. This will cause the artery in your brain to constrict and relax. The exact

amount of CO_2 that you receive will be determined by a computer and will depend on how fast you breathe and the amount of CO_2 that is already in your lungs.

- **Brain and Blood Flow Coupling** – We will test how well your brain increases blood flow in response to a thinking task. A small ultrasound probe will be fixed in place over the skin above your temple. We will then measure the blood flow in your brain at rest and after a series of mental challenges on a computer that require you to remember and count a set of letters or stare at a visual stimulus (alternating black and white checkerboard). We will also measure the amount of CO_2 in the air that you exhale by placing a soft flexible tube placed in front of your nose with ~1 cm extensions inserted into the tips of your nostrils.
- **Blood Draw** – We will collect additional blood to measure factors that may be related to your blood vessel and memory functions or change with the vitamin intervention. If you elect to have your screening blood drawn in our lab, you will not need a blood draw during this visit as we will collect this additional blood at the time of screening.

VISIT 3* – *Baseline Cognitive Function (Virtual Visit over Zoom; 1.5 hours)

Restrictions: *No over the counter medications for 48 hours, no strenuous exercise or alcohol for 24 hours; Eat a light meal or snack.*

- **Memory and Thinking Tests** – Your memory and ability to process information will be measured with 2 tests that involve recalling lists of words or details of stories by listening to voice recordings. These tests may be completed in person or may be completed online via a private video conference.

VISIT 4* – *Baseline Neural function (CBBI; 2 hours)

Restrictions: *No over the counter medications for 48 hours, no strenuous exercise or alcohol for 24 hours; Eat a light meal or snack.*

MRI Scan – This study involves measuring the anatomy and activity of your brain using magnetic resonance imaging (MRI). Although the visit is scheduled for 2 hours, you will only be in the scanner for ~ 1 hour.

- **Repeat MRI Screening Form**. We will ask you questions about your ability to have a MRI brain scan, including questions about any metal implants you may have.
- Before you enter the scanner room, you will need to remove all metal objects, like jewelry, watches, and hairpins. If you need to remove clothing that contains metal, a gown will be provided to wear during the scan.
- You will be required to lie completely still on the scanner bed, which will slide into the center (bore) of the scanner. An MRI head coil will surround your head (a head coil is an apparatus that is used to measure signals emitted from your brain). Your head will be supported with foam pads to make you more comfortable and to help you to keep your head still. The magnet can be noisy. You will usually hear knocking, buzzing and beeping sounds. We will give you ear protection to block most of the noise. You will still be able to hear us give you directions.
- Functional MRI (fMRI) is an MRI scan of your brain that measures the activity of your brain while you do specific tasks. Several scans will be taken and you will need to remain still on the table for about 10 minutes at a time. During the scan you will also perform a mental challenge by following instructions on

a screen in front of you in the scanner requiring you to remember and count a set of numbers. You will be given a clicking device to indicate your answer. You will be given periodic breaks in which you will be able to relax but you will be asked to remain on the scanner bed for the duration of the session, which should last about 1 hour. The entire visit will take about 120 minutes because we will spend some time beforehand preparing for the scan.

- You will also be asked to wear a small clip on your finger to measure your heart rate, and/or a belt around your torso (over the clothing) to measure your breathing rate. You will be able to communicate with us via a built-in intercom. You will also be holding an emergency bulb that you can squeeze at any time to let us know you want to come out of the MRI scanner. If at any time you feel uncomfortable or unwilling to continue, no matter what the reason, you can request to immediately stop the study, and the operator will remove you from the scanner. Stopping the procedure will not disqualify you from the rest of the study. All scans are conducted by certified MRI Technologist or other experienced personnel with relevant safety training.

- **Memory and Thinking Tests** – Additional information about your memory and ability to process information will be measured with 1 pen and paper test and seven computerized tests. These tests involve recalling lists of words or drawings, matching pictures, ordering words, letters, pictures and numbers.
- **Receive Study Capsules** – You will be sent home with a 12-week supply of study capsules. You will be asked to take a dose of the capsules twice a day (2 pills in the morning and 2 pills in the evening). The instructions will be clearly marked on the pill container. If you forget to take a dose, you will be instructed to skip that dose and take your next regularly schedule dose.

This is not a medical evaluation. The images of your brain collected in this study are not intended to reveal illness, in part because this research protocol is not designed for medical diagnosis. Your images will not be routinely examined by a radiologist. The personnel at the MRI Center are not qualified to medically evaluate your images. However, if, in the course of collecting images, we have any concerns, we may show your scans to a clinical radiologist, who may suggest that you obtain further diagnostic tests. Do not rely on this research MRI to detect or screen for abnormalities. At the investigator's discretion, you may view your images and receive digital copies of them. These images will show the inside of your body and you should be aware of the potential distress or discomfort that may occur by viewing these type of images.

***INTERVENTION* - Weeks 2-12**

- ***Monthly Phone Check-In (weeks 2, 6, & 10)*** *– A member of the research team will call you to discuss any concerns that you may have related to the study pills. These phone calls will usually be brief (<10 minutes).*
- ***VISIT 5 & 6 – Check-In (Virtual Visit, 30 minutes each)***

  During this time, a member of the research team will ask you questions about how you have been feeling recently. During this check-in meeting, you will complete a brief survey about your general health and well-being using a private video conference. If you are unable to complete this survey using remote means, you will be required to travel to campus to complete this survey.

***FOLLOW-UP TESTING*: (We ask that you NOT take your study pills the morning of testing)**

- ***VISITS 7, 8, & 9*** will the identical to the baseline visits (Visit 2, 3, and 4). We will ask you to follow the exact same general restrictions that you followed during your baseline testing. During Visit 7, we will also draw blood (~ 4 tablespoons) and collect a urine sample to determine if any markers have changed as a result of the vitamin. We will also retest your blood for COVID-19 related antibodies in case you became infected during the course of the study.

Experimental Procedures: It is important to note that all of the measures in this study are considered experimental. We will not be able to determine your risk of Alzheimer's or other forms of dementia based on the results that we obtain.

WHAT ARE POSSIBLE RISKS AND DISCOMFORTS?

Possible risks of participating in this research study include:

Nicotinamide Riboside (NR) and Placebo Capsules – You will either be given nicotinamide riboside (NR) capsules (Niagen®; 500 mg 2x/day) to raise your blood levels of NAD+, or placebo capsules that contain inactive ingredients (microcrystalline cellulose within vegetarian capsule). Potential side effects associated with NR may include mild-to-moderate cases of headache, feelings of warmth, hot flushing sensations, gastrointestinal discomfort, and fatigue. There are currently no reports of serious adverse side-effects to NR supplementation; however, all adverse events will be closely monitored. While there is strong evidence that NAD+ boosting compounds may prevent cancer in animals there are also a few reports that NAD+ boosting compounds may be linked to cancer growth in animals that already have cancer. The relevance of these animal studies to our clinical trial is unclear and there are currently no reports of increased cancer risk in human with Niagen® supplementation. Out of an abundance of caution, we will ask you about your medical history, including any history of cancer and you may be excluded from the study if you currently have or previously had cancer with an exception to complete remission of basal cell carcinoma. To lessen the risk of gastrointestinal discomfort, we will have you take capsules twice a day instead of all at once. If you miss a dose, do not double the number of capsules that you take; just take the next dose at the regularly scheduled time. If you are allergic to or have had an adverse event after taking one of the above-mentioned drugs or supplements, please notify the investigator before participating. Niagen® is related to niacin (vitamin B_3), which has been shown to cause heart palpitations in some individuals taking high doses. While there have been no reports of Niagen® causing similar side effects, you will not be enrolled in this study if you have previously experienced heart palpitations (heart pounding or racing) and we will ask you to notify us if you experience these symptoms while taking the study pills.

- Blood Draw – When the needle goes into a vein, it hurts for a short time and there may be redness or swelling around where the needle goes into the skin. There is a small chance you may feel lightheaded or faint. In about 1 in 10 cases, a small amount of bleeding under the skin will cause a bruise. A risk of a blood clot forming in the vein is about 1 in 100. The risk of infection or significant blood loss is less than 1 in 1,000. The total amount of blood being drawn over the entire study is approximately 9.0 tablespoons (less than 1/3 pint). You should not donate blood 8 weeks before or after taking part in this study.

- COVID-19 Antibody Test – Your test results may help identify if you were exposed to the virus that causes COVID-19 and, if so, whether or not your body has developed antibodies. Although having antibodies usually gives immunity from further infection, there is not enough evidence at this time to suggest that people who have antibodies against SARS-CoV-2, the virus that causes COVID-19, are protected against future infections from the virus. Results from this test also will not provide information on whether you can spread the virus to others and is not used as a basis for diagnosis. A variety of factors can impact the results from the antibody test, including the time the test was taken after experiencing COVID-19 symptoms, the absence of or time since exposure to the virus, or the lack of an adequate immune response, which can be due to conditions or treatments that suppress immune function. Additionally, serology (antibody) tests may detect IgG antibodies from previous exposure to coronaviruses other than SARS-CoV-2 (COVID-19). This can cause a false positive result.

- Alzheimer's Genetic Test – There are minimal risks associated with learning your genetic risk for Alzheimer's disease; however, some people may experience emotional difficulties (e.g., mild anxiety, depression…etc.) after learning their test results. People with this gene have a higher chance of developing AD compared with people who do not carry the gene. Some people who carry the gene may never develop AD. Others may develop AD even though they do not carry the gene. This test will be performed in our lab for research purposes only and are not meant to make a conclusion about your risk for AD. Whether or not you receive the results of this test is entirely up to you. We will not interpret these results for you; however, you are encouraged to discuss these results with your primary care practitioner (PCP). This will likely require scheduling an appointment which may be billed to your private health insurance.

- Brain Blood Vessel Function Test – There are no risks associated with breathing small amounts of carbon dioxide. This protocol has been used in human studies clinically and in the research setting for decades without any adverse events. You may feel an increase in heart rate, flushed skin, and minor disorientation while breathing the carbon dioxide mixture. A mild headache is also possible. You may experience a dry mouth and jaw discomfort due to the use of the mouthpiece during the test.

- MRI Scan – MRI is an imaging technique that uses radio waves and magnetic fields to produce images of internal structures in your body. Unlike X-rays, the MRI does not use any ionizing radiation, and it does not use radioactivity, so there is no radiation related risks from having an MRI scan done on you. Below there is a description of MRI related risks and what is being done to reduce any possible risks associated with them:
    - **Metal:** The MRI scanner produces a constant strong magnetic field, which may cause any metal implants, clips, or implanted medical devices within your body to shift position or malfunction. You will not be allowed to participate in this study if you have any implanted metal, clips or devices. You will be screened to make sure that it is safe for you to enter a strong magnetic field. Please provide us with as much information as you can, for example if you had surgery in the past, so that we may decide whether it is safe for you to be a participant. Metallic objects brought into the MRI environment can become hazardous projectiles and can also interfere with the data quality. To minimize this risk, metal earrings, other piercings, necklaces and any other metal in contact with your body must be removed prior to the study. You must also remove all items from your pockets, including coins, electronics (including cell phones and hearing aids) and wallets. You must remove belts with metal buckles, and you may be asked to change into a gown that we will provide if your clothing contains significant metal, including metal underwire bras.

- **Inner ear damage:** MRI scanning produces loud noises that can cause damage to the inner ear if appropriate hearing protection is not used. Earplugs and/or headphones will be provided to protect your ears.
- **Claustrophobia:** When you are inside the MRI scanner, the "bore" of the scanner will surround the part of your body that is being scanned. In the case of fMRI, which we will be using in this study, we are interested in brain activity, and your head will be centered inside a close-fitting scanning coil positioned in the bore of the scanner. If you feel anxious in confined, spaces you may not want to participate. If you are unsure, you can try our "mock" scanner to evaluate your comfort level with the enclosed space of the magnet bore. If you decide to participate and begin to feel claustrophobic, you will be able to tell us via the intercom or the squeeze ball and we will discontinue the study immediately.
- **Burns:** In rare cases, contact with the MRI transmitting and receiving coil, conductive materials such as wires or other metallic objects, or skin-to-skin contact that forms conductive loops may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize this risk. Tattoos with metallic inks can also potentially cause burns. In addition, please let the MRI operator know immediately if you experience any heating or burning sensations during a scan. The scanning session will be stopped as soon as you tell the operator.
- **Nerve or muscle stimulation:** While the scanner is operating, there is a small chance that the rapidly changing magnetic fields could cause a slight tingling sensation or a muscle twitch, usually felt in the upper arms or torso. While these sensations may be startling, they are not dangerous or a health risk, and they have no lasting consequences. The sensations should stop when the scan ends. Because these sensations may nevertheless be distracting or even possibly uncomfortable, please squeeze the signal bulb to alert the scanner operator if you feel tingling or muscle twitching, and we will immediately stop the scan. You will then have the opportunity to choose to withdraw from the study or to continue.
- **Other Risks:** Besides the risks listed above, there are no other known risks from the magnetic field or radio waves at this time. Although functional MRI scanning has been used for more than 20 years, long-term effects are unknown.

WHAT ARE POTENTIAL BENEFITS FROM THE STUDY?

You will not benefit directly from taking part in this research. However, the knowledge gained from this study may contribute to our understanding of how a form of Vitamin B3 called nicotinamide riboside (Niagen®) can impact brain health in older adults with MCI. Possible benefits include the laboratory test results that you will receive.

NEW FINDINGS THAT COULD AFFECT YOUR PARTICIPATION

During the course of this study, we may learn new important information. This may include information that could cause you to change your mind about participating in the study. If any new important information becomes available while you are a participant we will let you know.

CONFIDENTIALITY: WHO MAY KNOW THAT YOU PARTICIPATED IN THIS RESEARCH?

Your study data will be handled as confidentially as possible. To minimize the risks to confidentiality, we will store your data under a unique participant number known only to the investigators. All data stored in a locked cabinet or on a password protected computer or server indefinitely. If results of this study are published or presented, individual names and other personally identifiable information will not be used. We may obtain recordings of your voice during cognitive testing sessions; however, these recordings will not be linked to your name and will be deleted as soon as we have scored the test. We will keep your study data confidential and only those with permission in the research team will have access to information that identifies you. We may have to report certain information for legal or ethical reasons, such as child abuse, or intent to hurt yourself or others. If required, your records may be inspected by authorized personnel from the University of Delaware Institutional Review Board, the National Institute on Aging (NIA) and the US Food and Drug Administration (FDA). A separate Data and Safety Monitoring Committee that is not affiliated with the study team will convene every 6 months to review data that may pertain to the safety of the study. Your data may be discussed; however your name and other personal information will not be shared with the committee.

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.

USE OF DATA COLLECTED FROM YOU IN FUTURE RESEARCH:

Identifiers about you will be removed from the identifiable private information and biospecimens, and after such removal, the information and biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

Future research might include whole genome sequencing (i.e., research about your DNA and complete genetic information); however, this will only be performed using de-identified specimens that cannot be traced back to you in any way.

COSTS AND COMPENSATION

There are no specific costs associated with participating in this study.

If you agree to take part in this research study, we will pay you up to $210 for your time and effort in the form of a check that will be mailed to you up to 8 weeks after completing or withdrawing from the study. You will not be paid for Visit 1 because you will receive health information free of charge. Compensation is based on completion of study visits, not individual procedures. You will be compensated for every visit that you attempt to complete. If you do not complete one of the visits at baseline (e.g.. MRI testing), you will not be scheduled for that visit at follow-up, and won't receive compensation for that visit. If you choose to leave or are withdrawn from the study for any reason before completing all of the study visits, you will be paid for each completed visit. Compensation does not cover costs of transportation; however, if you wish to be reimbursed for travel to and from study visits, we will reimburse you at the current IRS-approved mileage rate. A table outlining the total compensation for each visit is presented on the next page.

Compensation Schedule

	Visit #	Purpose	Duration	Total
Screening	Visit 1	Informed Consent & Screening Measures	1.5 hr	No compensation Subjects receive free health information
Baseline Testing	Visit 2	Vascular Function	3 hr	$30
	Visit 3	Cognitive Function	1.5 hr	$22.50
	Visit 4	Neural function/ Start Intervention	2 hr	$30
Intervention Period	No visit	Phone Check-In	10 min	$9.00
	Visit 5	Zoom Check-In Visit	0.5 hr	$9.00
	No visit	Phone Check-In	10 min	$9.00
	Visit 6	Zoom Check-In Visit	0.5 hr	$9.00
	No visit	Phone Check-In	10 min	$9.00
Follow-Up Testing	Visit 7	Vascular Function	3 hr	$30
	Visit 8	Cognitive Function	1.5 hr	$22.50
	Visits 9	Neural function (MRI)	2 hr	$30
	Total Compensation			**$210**

WHAT IF YOU ARE INJURED DURING PARTICIPATION IN THE STUDY?

If you need medical care because of taking part in this research study, seek medical attention immediately (if it is a medical emergency, first call 911). If you are injured during research procedures, you will be offered first aid at no cost to you. If you need additional medical treatment, the cost of this treatment will be your responsibility or that of your third-party payer (for example, your health insurance). By signing this document, you are not waiving any rights that you may have if injury was the result of negligence of the university or its investigators.

If you have a medical complaint or experience a side-effect to the study capsules that requires medical attention, you should see your primary healthcare provider. If the event occurs after business hours and requires immediate attention, please visit the nearest urgent care or emergency department. You may report side effects or complaints that do not require medical attention at any time by contacting the Neurovascular Aging Laboratory at 302-831-8137.

At the beginning of the study, you will be provided with a wallet-sized card containing general information about the study, including the name and dose of the nutritional supplement being studied. We recommend that you keep this card with you during your involvement in the study and present it to your healthcare professional if seeking treatment for a side-effect that you believe may be related to the study capsules. The name and contact information of the Principal Investigator is included on this card.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is your decision. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide later not to participate, or if you decide to stop taking part in the research, there will be no penalty or loss of benefits to which you are otherwise entitled. Your decision to stop participation, or not to participate, will not influence current or future relationships with the University of Delaware.

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include findings related to safety, progression to dementia, or if you do not comply with study procedures

If, at any time, you decide to end your participation in this research study, please inform our research by contacting the study coordinator. If you choose to leave or are withdrawn from the study for any reason before completing all of the study visits, you will be paid for each completed visit.

INSTITUTIONAL REVIEW BOARD

This research study has been reviewed and approved by the University of Delaware Institutional Review Board (UD IRB), which is a committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans. If you have any questions or concerns about your rights as a research participant, you may contact the UD IRB at hsrb-research@udel.edu or (302) 831-2137.

CONTACT INFORMATION

If you have any questions about the purpose, procedures, or any other issues related to this research study please contact the Principal Investigator, Christopher Martens at (302) 831-7270 or cmartens@udel.edu.

If you have any questions or concerns about your rights as a research participant, you may contact the University of Delaware Institutional Review Board at hrsb-research@udel.edu or (302) 831-2137.

CONSENT TO PARTICIPATE IN THE RESEARCH STUDY:

I have read and understood the information in this form and I agree to participate in the study. I am 18 years of age or older. I have been given the opportunity to ask any questions I had and those questions have been answered to my satisfaction. I understand that I will be given a copy of this form for my records.

_____	_____	_____
Printed Name of Participant (PRINTED NAME)	Signature of Participant (SIGNATURE)	Date
_____	_____	_____
Person Obtaining Consent (PRINTED NAME)	Person Obtaining Consent (SIGNATURE)	Date

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<u>OPTIONAL</u> CONSENT TO BE CONTACTED FOR FUTURE STUDIES:

Do we have your permission to contact you regarding participation in future studies? If you agree to being contacted in the future, we will keep your contact information. Please write your initials next to your preferred choice.

_____ YES _____ NO