INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH

Dietary Nitrate and Muscle Power with Aging

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WHY IS THIS RESEARCH BEING DONE?

The purpose of this study is to see if drinking **beetroot juice (BRJ)** is beneficial for aging subjects. We hope to determine the effect of BRJ on exercise performance. BRJ may improve exercise performance in athletes and normal people. We are trying to determine if BRJ improves exercise performance in aging subjects. We will be comparing the effects of BRJ versus the effects of a placebo (BRJ without the nitrates that are naturally occurring in beets and other similar foods). It is thought that the benefits of BRJ may come from its natural nitrate content. Although BRJ is available for purchase in grocery stores, for the purposes of this study it is considered investigational, which means that it has not been approved as a medical therapy.

You were selected as a possible participant because you are a male or female, age 65 to 79, in good health.

The study is being conducted by Andrew Coggan, Ph.D. Associate Professor, Department of Kinesiology. It is funded by external grants.

HOW MANY PEOPLE WILL TAKE PART?

If you agree to participate, you will be one of up to one hundred (100) participants who will be taking part in this research.

WHAT WILL HAPPEN DURING THE STUDY?

The study will take a minimum of 50 days to complete. The study begins from the time you sign this informed consent document. This study consists of two parts of 3 weeks each separated by a minimum of a 2 week wash-out period where you will not drink BRJ. You will be randomly assigned to receive either the BRJ or placebo during the first part. During the second part you will receive the opposite of what you had during the first. Additionally, if you would like to participate in this study, you will be required to be in another research study entitled "Musculoskeletal Function, Imaging and Tissue (FIT) Resource Core" IRB study #1707550885. More information about the FIT Core study is provided below. This is considered a double-blind study, which means neither you nor the investigator will know what form (BRJ or placebo) you are receiving. The Study Calendar is shown below:

	Screening	**>5 Day Wait**		7 days later	7 days later	**>= 2 week Wash-Out**		7 days later	7 days later
Visit Number	**One**		**Two**	**Three**	**Four**		**Five**	**Six**	**Seven**
Informed Consent	X								
Physical Exam	X								
Resting EKG	X								
Blood Samples[a]	X		X	X	X		X	X	X
Urine test	X								
Exercise Test	X[b]		X		X		X		X
Fit Core[c]	X		X		X		X		X
Health Question-naires	X		X	X	X		X	X	X

[a]Total amount of blood drawn for the study will be 115mL or about 23 teaspoons

[b]Neuromuscular function test will be practiced at screening

[c] The specific procedures for the Fit Core study will be described in a separate consent form

Study Visit One (Screening) 5 hours

The purpose of the screening visit is to explain all aspects of the study. We will also determine if you can participate in the study. You will provide a complete medical history and undergo a physical exam by a study physician. You will complete a questionnaire asking about your levels of fatigue and how much physical activity you do. You will undergo an EKG, which is a painless test that detects and monitors the electrical activity of your heart. You will have your blood drawn (about 1.5 teaspoons) and you will provide an urine sample. You will also practice the entire neuromuscular

function exercise test. During this test, the strength of your muscles will be determined by having you kick, push and/or pull back as hard as you can while your leg is strapped to an exercise device.

After the exercise test, a snack/meal can be provided if you would like.

As stated above, if you would like to participate in this study, you will be required to be in another research study entitled "Musculoskeletal Function, Imaging and Tissue (FIT) Resource Core" IRB study #1707550885. If you don't want to participate in the FIT study, you cannot participate in this study. The reason you must participate in both is because certain information collected in the FIT study will also be used for this study. You would complete the FIT Core procedures 5 times during the study (see table above), during visits 1, 2, 4, 5 and 7.

You will receive a separate informed consent that details the study tests and associated risks for the FIT study. In brief, it includes drawing blood and measuring how well you perform about 30-45 minutes of tests of your physical abilities including: hand grip strength, how fast you can walk, and how quickly you stand up and down. Data collected in the FIT study will be used by other researchers to understand the causes and consequences of different physical function and activity levels across a large population. The main risks of participation in the FIT study are the risk of blood draw (pain, infection, bruising) and fatigue and falls from the testing. More information about the FIT study is in the separate Informed Consent you will receive. You should read the Informed Consent Statement for the FIT study before deciding whether you want to participate in this study.

As part of the FIT study you will also be asked to undergo special imaging tests of your muscle and bones called a DXA or bone density test, a special scan of your forearm called a peripheral quantitative computed tomography (pQCT) and another scan of your lower leg called a high resolution pQCT (HRpQCT). These tests image the bone and can tell the amount of bone and how it is arranged. These tests carry a very slight amount of radiation. More information about the radiation risks is included in the FIT study consent.

During the remainder of the study you will be instructed to consume your normal diet. However, you will be asked to avoid eating foods high in nitrate such as beets, spinach, and collard greens the evening before each visit. You will be asked to refrain from the use of antibacterial mouthwash, such as Listerine or Cepacol, during the study. Chewing gum, alcohol, and food and drinks containing caffeine (coffee, tea, chocolate, and soft drinks) should be avoided 24 hours prior to each visit. You will be asked to fast for 12 hours prior to each study visit.

Study Visit Two – Approximately 5 hours

Study visit 2 will occur 6-28 days after the screening visit. At the beginning of your visit you will have your vital signs assessed and you will complete a questionnaire asking about your levels of fatigue. Then a catheter (small, flexible, sterile plastic tube) will be placed through a vein in one of your arms. This is for collection of blood samples. Your blood will be drawn four times during this visit. Each draw

will be 6mL or about 1.2 teaspoons. Your first blood draw will check nitrate and nitrogen levels. You will then drink 140 mL (about 2/3 of a cup) of BRJ (or placebo). Blood samples will be obtained every hour. Your heart rate and blood pressure will be measured at the same times the blood samples are obtained. You will then rest quietly in a private room for about 2 hours after ingestion of BRJ (or placebo) then you will perform:

- The neuromuscular function test that was practiced during the screening visit.
- Complete the FIT Core study procedures
- One final blood sample will then be obtained.
- You will then be provided a 7 day supply of BRJ (or placebo) and will continue to drink two bottles (about 5oz) every morning.
- You will also be provided with an activity tracker. This will be worn at the hip during all waking hours except when bathing or swimming. This monitor will measure total activity time and sedentary time.
    - You will be given a paper log to record the times that you wear the activity monitor. You will be asked to return that log at the next visit.

Study Visit Three – 1 hour

Study visit 3 will occur 1 week after study visit 2. You will return to the research center with the empty BRJ bottles. At this visit your vital signs will be measured and a single blood (1.2 teaspoon) sample will be collected. You will then complete a questionnaire to rate how tired you felt during the previous week. You will be provided another 7 day supply of BRJ (or placebo) and will continue to drink two bottles every morning. You will be given a paper log to record the times that you wear the activity monitor. You will be asked to return that log at the next visit**,** as well as return the empty BRJ bottles

Study Visit Four – Approximately 5 hours

Study visit 4 will occur 1 week after study visit 3. You will return to the research center and undergo the same procedures as you did in Study Visit Two. You will also complete a questionnaire that will rate how tired you felt during the previous week. You will return the activity monitor and the paper log and the empty BRJ bottles.

Washout

After visit four you will undergo a minimum of a 14 day washout period where you will not drink the BRJ (or placebo). There are no dietary restrictions at this time; you may consume caffeine, alcohol, gum, mouthwash, etc. You will then repeat Study Visits Two, Three, and Four again. However, during this you will be given the opposite form of BRJ you had received before.

Study Visit Five

After the washout period of at least 14 days, you will repeat the procedures completed during Study Visit Two.

Study Visit Six

Study visit 6 will occur 1 week after study visit 5. You will repeat the procedures completed during Study Visit Three.

Study Visit Seven

Study visit 7 will occur 1 week after study visit 6. You will repeat the procedures completed during Study Visit Four.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

While participating in the study, the risks, side effects, and/or discomforts include:

A) Beetroot Juice: Beetroot juice consumption or the consumption of the BRJ placebo may cause stool and/or urine to appear pink. This does NOT indicate bleeding. You may experience mild gastrointestinal distress (cramps, bloating) or diarrhea following ingestion of the BRJ. In rare cases there is a theoretical increased risk of upper GI cancers if a compound called "nitrosamine" is made from nitrates by the body. However, in large studies of many people followed up for many years, a fruit and vegetable-rich diet (where the acceptable daily intake of nitrates was exceeded several-fold) was not associated with any increase in cancer or mortality. The 2003 Joint Food and Agricultural Organization/World Health Organization Expert committee concluded that there was no evidence that nitrates are carcinogenic to humans.

B) Needle Stick: Slight pain, bruising or bleeding can occur. Rarely, infection can occur. On rare occasions some people may feel faint. To minimize the discomfort and risks associated with blood draw, only trained staff will collect blood samples.

C) Questionnaires: You may experience emotional discomfort when answering some questions in the health questionnaires. If any particular question makes you uncomfortable, you may discuss its importance and the need to answer it with the specially trained interviewer. You may choose not to answer any question with which you still feel uncomfortable.

D) Exercise Test: Your muscles may feel tired during the exercise test. You may also develop soreness in your muscles or joints. Very rarely, an exercise test, such as the neuromuscular function test, may be associated with serious complications including, but not limited to:
    a. Fainting and disorders of the heart beat (too fast or too slow) which may require hospitalization; heart attack, stroke, or death; and muscle or joint pain. We will make every effort to minimize these rare risks by observing and monitoring during testing. However, no guarantees can be made. Emergency equipment and trained personnel are available to deal with any emergency.

E) EKG: you may experience a slight rash where the electrodes touch your skin. This usually goes away within a few days and does not require treatment.]

Another risk of this study is the possible loss of confidentiality, which is minimal. Even though the risk is small, a link exists between your protected health information and your sample. In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with participation in this study. You will be informed in a timely manner of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THE STUDY?

We don't know if you will benefit from being in this study. We are doing this research to see if BRJ will improve exercise tolerance in aging subjects. We hope that in the future other people might benefit from the results of this study.

WILL I RECEIVE MY RESULTS?

We may learn things about you from the study activities which could be important to your health or to your treatment. If this happens, you can decide whether you want this information to be provided to you. You may request a copy of laboratory results obtained during the study. If you decide that you want this information, you may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions. Please initial one of the following options:

_____ Yes, I want to be provided with this information.

_____ I do NOT want to be provided with this information.

HOW WILL MY INFORMATION BE PROTECTED?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. No information which could identify you will be shared in publications about this study. To minimize the risk of loss of confidentiality, the following steps will be implemented. All the personal and medical data will be considered confidential to the extent allowed by law. Only authorized personnel will have access to the samples, coded databases, or the results. The samples will be labeled with a code and not with a volunteer's name. All volunteer information will be stored in locked cabinets and on computers that are password protected. Only authorized persons will have access to the sample and patient information.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, the Indiana Clinical Research Center (ICRC) and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP), , and the National Institutes of Health (NIH), etc., who may need to access your medical and/or research records.

A description of this clinical trial will be available on **ClinicalTrials.gov**, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers may not disclose or use any information, documents, or specimens that could identify you in any civil, criminal, administrative, legislative, or other legal proceeding, unless you consent to it. Information, documents, or specimens protected by this Certificate may be disclosed to someone who is not connected with the research:

(1) If there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases);
(2) If you consent to the disclosure, including for your medical treatment;
(3) If it is used for other scientific research in a way that is allowed by the federal regulations that protect research subjects
(4) For the purpose of auditing or program evaluation by the government or funding agency

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?

No. After the blood and muscle samples have been completely tested, the labels and any identifiers will be removed the samples will be discarded.

WILL I BE PAID TO PARTICIPATE?

The total compensation for completing the study is $1000. You will receive the payment in the form of a check that will be sent to you. If you withdraw or are removed from the study you will be paid for the parts of the study you have completed. If you receive $600 or more in one calendar year from Indiana University, you will receive a 1099 tax form the following January. Indiana University reports the money you receive to the Internal Revenue Service. A breakdown of payments is shown in the table below.

Study Visit Completed	**Payment**
Visit 2	$250
Visit 4	$250
Visit 5 (after washout)	$250
Visit 7 (end of study)	$250

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. If you have a government insurer, your insurer will not be billed and you may be responsible for those costs. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher, Dr. Coggan, at 317 274-0656, or the research coordinator Rich Hoffman at 317-274-0648. If you cannot reach the researcher during regular business hours (i.e., 8 a.m. to 5 p.m.), please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu. After business hours, please call Dr. Coggan at 636-675-1692.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu.

WILL I BE CONTACTED ABOUT RESEARCH IN THE FUTURE?

If you agree, we may contact you after your participation is over to request additional information or biospecimens. Please initial one of the following options:

_____ Yes, I agree to be contacted for the purpose of collecting additional health information and/or possibly additional biospecimens.

_____ I do NOT agree to be contacted for the purpose of collecting additional health information and/or possibly additional biospecimens.

CAN I WITHDRAW FROM THE STUDY?

If you decide to participate in this study, you can change your mind and decide to leave the study at any time in the future. The study team will help you withdraw from the study safely. You may withdraw by telling the study team you are no longer interested in participating in the study or in writing to Dr. Coggan at the following address:

Dr. Andrew Coggan
Department of Kinesiology
901 W New York Street
Indianapolis, IN 46202

Your participation may be terminated by the investigator without regard to your consent if it is determined to be in your best interest to do so. Your participation may be terminated if you fail to follow the instructions given to you or if you are unable to adequately perform the study procedures.

You will be told about new information that may affect your health, welfare, or willingness to stay in the study.

PARTICIPANT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study. I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Participant's Printed Name:_____

Participant's Signature:_____ **Date**:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date**:_____