Protocol Document

Dose-response Effect of Dietary Nitrate on Muscle Function in Older Individuals

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INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH

Dose-Response Effect of Dietary Nitrate on Muscle Function in Older Individuals

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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 the best dose of BRJ to improve muscle speed and power in older subjects. We will be comparing the effects of two doses of BRJ versus the effects of a placebo (BRJ without the nitrate that occurs naturally 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 the U.S. Food and Drug Administration has not approved BRJ 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 internal grants.

HOW MANY PEOPLE WILL TAKE PART?

If you agree to participate, you will be one of up to twenty (20) participants who will be taking part in this research.

WHAT WILL HAPPEN DURING THE STUDY?

The study will take a minimum of 19 days to complete. The study begins from the time you sign this informed consent document. This study consists of three visits separated by a 5-15 day wash-out. The order in which you receive the placebo or lower or higher doses of BRJ will be randomized using a computer program. This study is considered a double-blind study, which means neither you nor the investigators will know the order in which you receive the doses. The Study Calendar is shown below:

	Screening	Minimum 5 Days		**5-15 Day Wash-out**		**5-15 Day Wash-out**	
Visit Number	**One**		**Two**		**Three**		**Four**
Informed Consent	X						
Physical Exam	X						
Blood Samples[a]	X		X		X		X
Resting EKG	X						
Breath Samples			X		X		X
Exercise Test	X[b]		X		X		X

[a]Total amount of blood drawn will be about 16 teaspoons
[b]Neuromuscular function test will be practiced at screening

Study Visit One (Screening) 1-2 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 undergo a complete medical history and physical exam and a resting EKG. You will have your blood drawn (about 1.5 teaspoons). 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.

During 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 study 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 hour prior to each study visit.

Study Visit Two – Approximately 5 hours

At the beginning of your visit 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 have a breath test to check nitric oxide. You will then drink about 280 mL (about 1 cup) of BRJ containing either 0 (placebo), about 12 mmol (about 0.03 ounces), or about 24 mmol (about 0.06 ounces) of nitrate. The smaller dose is roughly equivalent to about 3-4 whole beets or about 2 cups of cooked spinach, whereas the larger dose is twice that.

Blood and breath samples will be obtained every hour. Your heart rate and blood pressure will be measured at the same times the blood and breath 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. One final blood and breath sample will then be obtained.

Washout

After visit two, you will undergo a 5-15 day washout period where you will not drink the BRJ (or placebo).

Study Visit Three

You will return to the research center and undergo the same procedures as you did in Study Visit Two.

Washout

After visit three, you will undergo a 5-15 day washout period where you will not drink the BRJ (or placebo).

Study Visit Four

You will then repeat Study Visits Two and Three again

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) 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.

C) Needle Stick: Slight pain, bruising or bleeding can occur. Rarely, infection can occur. To minimize the discomfort and risks associated with blood draw, only trained staff will collect blood samples.

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.

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), 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.

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?
No. After the blood 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 $450. You will receive the payment in the form of a check mailed to you. You will receive the checks after visits 2, 3 and 4, in the amount of $150 per visit. 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	$150
Visit 3 (after first washout period)	$150
Visit 4 (after second washout period)	$150

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 Rich Hoffman, study coordinator, 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**:_____