Washington University in St. Louis

INFORMED CONSENT DOCUMENT

Project Title: **The Inorganic Nitrate for Exercise in Heart Failure (iNIX-HF) Trial (Aim 1: Dose Response)**

Principal Investigators: Linda R. Peterson, MD

Research Team Contact: Dakkota Thies, RMA (314) 747-3839
Susan B. Racette, PhD (314) 286-1424

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form, you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you have a history of heart failure.

The purpose of this research study is to determine the optimum dose of inorganic nitrate to improve exercise performance in patients with heart failure. We believe that increasing the body's nitrate levels will improve exercise tolerance. We will compare two doses of **potassium nitrate (KNO_3)**, also known as **saltpeter,** on blood nitrate (NO^{3-}), blood nitrite (NO^{2-}), and breath nitric oxide (NO) levels and on exercise performance. You will receive 10 or 20 mmol of KNO_3 in gel capsules during 2 study visits. There will be a 7-day wash-out period (a time when you are not given KNO_3) in between these visits.

Heart failure is a condition in which the heart cannot pump enough blood throughout the body. Heart failure often limits a person's ability to exercise because he or she becomes short of breath with exertion.

We know relatively little about the effect of diet / nutrition on heart failure, but there is evidence that dietary nitrates may improve exercise capacity in patients with heart failure. Nitrates are naturally-occurring substances that have a nitrogen atom and are found in foods and water. Nitrates also can be administered in a capsule in the form of KNO_3.

Although KNO_3 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 it as a medical therapy.

WHAT WILL HAPPEN DURING THIS STUDY?

- For this study, you are asked to give permission for the research team to access your medical record so they may verify your medical history. If you have recently (within one year) had some of the physical exams or tests described in this project, the investigators may elect not to repeat these exams.
- For the duration of the study, you will be asked to refrain from using mouthwash, antacids, Viagra, Cialis, or medicines like them (i.e., phosphodiesterase inhibitors).
- The study includes 2 or 3 visits. There will be a screening visit and 2 KNO_3 dose visits, but we may combine the screening visit with the first KNO_3 dose visit. At the screening visit you will complete a series of screening tests, including a medical history, physical exam, blood draw, and resting echocardiogram. For both of the KNO_3 dose visits, you will be given a gelcap containing either 10 or 20 mmol of KNO_3 (in random order; you will not know which dose you are receiving at each visit), have blood drawn, and complete a series of exercise tests.

Screening Visit.

1) **Physical Exam and Echocardiogram**: You will be asked to undergo a brief physical examination, have a blood sample drawn for a metabolic panel, and have a resting echocardiogram. An echocardiogram uses sound waves to make pictures of your heart, which helps show how well your heart pumps blood. A contrast agent may be administered intravenously to provide a clearer picture of blood flow in your heart during the echocardiogram. If you had these screening blood tests or echocardiogram done recently, then we may not repeat them.
2) **Questionnaires**: You will be asked to fill out questionnaires about your health. This should take about 15 minutes. A member of the study team will be available to answer questions. You are free to skip any questions that you prefer not to answer.

KNO_3 Dose Visit 1.

1) **KNO_3 gelcap**: You will receive 10 or 20 mmol of KNO_3 in the form of a gelcap.
2) **Blood Samples**: You will have blood drawn (20mL or about 1.5 tbsp). An intravenous (IV) catheter (flexible tube) will be placed in your arm to facilitate blood sampling 5 times during your visit. The first blood sample will be obtained before you ingest the gelcap and the others will be obtained once each hour for 4 hours after you ingest the gelcap. The blood will be used to determine the levels of nitrate and nitrite in your blood, and to measure blood lipids. A small sample of blood also may be saved for genetic analyses *(this is optional)*.
3) **Blood Pressure and Heart Rate**: You will have your blood pressure and heart rate checked 5 times: once before you take the gelcap and once each hour for 4 hours after you take the gelcap.
4) **Breath Nitric Oxide**: You will be asked to exhale into a tube attached to a small machine 5 times: once before and 4 times after you take the gelcap. This machine will measure the amount of nitric oxide in your breath.
5) **Saliva Sample**: You will also be asked to provide a saliva sample to determine the different types of oral bacteria. Some types of bacteria can convert nitrate to nitrite. This will be done only once.
6) **Leg Muscle Power Test**: 2 hours after ingesting the gelcap, we will measure the power of your leg muscles using an isokinetic dynamometer (a machine that measures voluntary muscle force production while controlling the speed of movement).

7) **Aerobic Capacity Treadmill Test**: This is an endurance exercise test that will enable us to determine your peak oxygen consumption ($\dot{V}O_2$peak). You will walk on a treadmill and breathe into a mouthpiece while wearing a nose clip (to prevent you from breathing through your nose). You will be asked to give your maximal effort as the speed or grade of the treadmill increases. Your blood pressure and heart rhythm will be monitored.

Washout period 1. You will be asked to refrain from eating foods high in nitrates for the next 7 days. A dietitian will instruct you as to which foods are high in nitrates.

KNO_3 Dose Visit 2.
At least 7 days after Dose Visit 1, you will receive a different KNO_3 gelcap than you received during Visit 1 (i.e., 10 or 20 mmol KNO_3) and then complete all of the assessments under KNO_3 Dose Visit 1 (except the saliva sample).

Will you save my samples or research data to use in future research studies?
As part of this study, we are obtaining blood samples as well as research data from you, which will become the property of Washington University**.** We would like to use this blood and data for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding heart and vascular function, or other diseases or conditions, including research to develop investigational tests, treatment, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your blood samples and research data, you give up any property rights you may have in the blood samples and research data.

We also request permission to draw and store 1 tablespoon of your blood for a period of up to 10 years to be used in future studies for screening for differences in genes related to nitric oxide metabolism (including, but not limited to, genes known as eNOS Glu298Asp and ACTN3 R577X). Genes are a unique combination of molecules (called DNA) that we inherit from our parents. There are millions of tiny differences in our genes that determine things like our height or the color of our eyes. Some of these differences may make some people more or less likely to develop certain diseases or conditions or to have certain characteristics. This test would be solely for research purposes. You will not hear from us regarding these results. We may share your blood sample or results with other investigators doing research in similar fields.

We will share your blood and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories, only qualified researchers who have received prior approval from individuals that monitor the use of the data will be able to look at your information.

If you change your mind and do not want us to store and use your blood or data for future research you should contact the research team member identified at the top of this document. The blood and data will no longer be used for research purposes. However, if some research with your blood or data has already

been completed, the information from that research may still be used. Also, if the blood or data has been shared with other researchers, it might not be possible to withdraw the blood or data to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My blood and data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My blood and data may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 25 people will take part in this aim of the study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for approximately 3 weeks.
The total number of visits is 3. The screening visit will last about 2 hours; the KNO_3 dose visits will last approximately 4½ to 5 hours.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Likely / Common:

Mild:

- The insertion of an intravenous tube for blood drawing or administration of the echocardiography contrast agent is associated with a small amount of discomfort while it is being placed. This should be brief.
- You may feel short of breath at the end of the treadmill exercise tests.

Less Likely / Less Common:

Mild:

- You may experience muscle pain or joint pain during or after the exercise tests.
- You may experience emotional discomfort when answering some questions in the health questionnaires. If any question makes you uncomfortable, you may discuss its importance and the need to answer it with us. You may choose not to answer any question that makes you feel

uncomfortable.

- You may experience temporary discomfort during blood pressure readings due to the pressure of the cuff on your arm.

Rare:

Life Threatening:

- Very rarely, a treadmill exercise test may be associated with serious complications including, but not limited to: fainting, erratic heart beat (too fast or too slow, which may require hospitalization), heart attack, stroke, or death. We will take every precaution to minimize these rare risks by closely monitoring you and your vital signs during the exercise tests. Emergency equipment and trained personnel are available during these tests to deal with an emergency.

Serious:

- There is a potential risk of an allergic reaction to the echocardiogram contrast material.
- There is a theoretical increased risk of upper gastrointestinal cancers associated with a compound called "nitrosamine" that is made from nitrates by the body. However, in large studies of many people followed for many years, a diet rich in fruits and vegetables (and very high in dietary nitrates) was not associated with an 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.

Mild:

- You may experience abdominal pain, nausea, vomiting, headache, a decrease in blood pressure, or diarrhea after ingesting KNO_3. If you develop a headache, you will be offered Tylenol. If you experience a symptomatic decrease in blood pressure, you will be treated by the cardiologist/study team member in attendance, initially with IV fluids.
- The insertion of an intravenous tube for blood drawing or administration of the echocardiography contrast agent is associated with a small risk of bleeding or infection.
- Possible risks associated with the echocardiogram procedures include an allergic skin reaction to the electrode gel and mild discomfort due to the light pressure of the ultrasound probe.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans and employers with greater than 15 employees to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance or long term-care insurance.

Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that in the future other people might benefit from this study because if KNO_3

improves exercise tolerance in patients with heart failure, it may be used as a treatment even in places of the world where pharmaceutical agents for heart failure are difficult to obtain. Also, we will have an improved knowledge of what to tell patients with heart failure in regards to their nutritional needs. We will also improve our understanding of how KNO_3 may improve muscle energy and exercise tolerance.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
You will not have any costs for being in this research study.

You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?
You will be paid for being in this research study. You will be paid $180 for completing the 2 KNO_3 dose visits. You will need to provide your social security number (SSN) for us to compensate you with a check. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you. It should take about 2 weeks to receive the check. If you do not receive it by 2 weeks, please contact the research coordinator Dakkota Thies at 314-747-3839. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

Payment will be pro-rated, with $50 allocated for dose visit 1 and $130 for dose visit 2.

WHO IS FUNDING THIS STUDY?
The National Institute of Health (NIH) is funding this research study. This means that Washington University is receiving payments from NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the principal investigator Dr. Peterson 314-362-4577, her secretary Ava Ysaguirre 314-362-1297, or the Human Research Protection Office at 1-800-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University**.** If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?
Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections), to complete federal or state responsibilities.
- The U.S. Food and Drug Administration.
- The Washington University granting agencies: Mentors in Medicine and Center for Clinical Imaging

Research (CCIR).
- Your primary care physician if a medical condition that needs urgent attention is discovered.
- Hospital or University representatives to complete Hospital or University responsibilities.
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.
- A data safety monitoring board.

To help protect your confidentiality, we will enroll you in the study in a private setting. You will be able to ask questions of the study team member in a private setting.

Interventions will generally occur with only you and research study team members in the room. Some research rooms are semi-private, but curtains may be pulled to provide the privacy necessary for you to have their blood pressure checked, have an IV placed, or to have blood drawn in a manner respecting your privacy.

The information collected during the study is necessary to make sure you qualify for the study and so we can answer the scientific questions being posed. We will ask your permission to access your personal medical records. If you do not agree, you will not be enrolled in the study. Your PHI will not be made available to anyone outside the study team. All data collected will be stored on password-protected computers in locked rooms. You will be assigned unique identifiers that will be used to label blood tubes, other study samples, and study data. The key to the identifiers will only be available to the members of the study team and will be under double-lock.

All hardcopy charts will be stored in a locked cabinet in a locked room. Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others. Sharing this information will allow others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.
A description of this clinical trial will be available on http://www.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.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu/participants//withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- We may contact you to schedule your study visits or to send reminders of study visits.

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risks associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your health information via email?

_____ **Yes** _____ **No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu/participants/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because it would not be safe for you to continue, because your condition has become worse, because you are or became pregnant, or because funding for the research study has ended.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dakkota Thies, research coordinator at 314-747-3839 or Linda Peterson, MD at 314-362-4577.

If you experience a research-related injury, please contact: Dakkota Thies at 314-747-3839 or Linda Peterson, MD at 314-362-4577.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 09/26/18.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)