The Children's Hospital of Philadelphia®

Informed Consent Form and HIPAA Authorization

Study Title: A Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia

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Consent Name: Main ICF

Principal Investigator:	Shana E. McCormack, M.D.	Telephone: (215) 590-3174
Emergency Contact:	Shana E. McCormack, M.D.	Telephone: (617) 596-9067

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of this research study, and the risks and possible benefits of participating.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

In the sections that follow, the word "we" means the study doctor and other research staff.

Study Overview

You are being asked to take part in this research study because you have a confirmed genetic diagnosis of Friedreich's Ataxia (FA), but you do not have significant cardiovascular disease.

The purpose of this research study is test the safety and tolerability of short-term therapy with a nicotinamide mononucleotide (NMN), a form of Vitamin B3, in adults with FA who do not have heart failure. We will also test the effect of NMN on how the heart muscle uses energy. In this form, NMN may also be referred to as the "study drug."

In animal models, NAD+ use has shown promise for treatment of cardiac disease. Specifically, NR or NMN supplementation improves function in several models of heart failure in mice.

NMN has been well tolerated when administered to humans and other drugs in this class have demonstrated safety in FA, particularly when used in modest doses, therefore we propose to evaluate NAD+ precursor supplementation in FA with a focus on feasibility and safety, and obtaining preliminary data on potential effects on cardiac bioenergetics. The use of the study drug is considered experimental, as it has not been approved by the FDA for any indication.

If you agree to take part, your participation will last for up to 15 weeks and will involve 2-4 in person study visits. You will need to take the study drug (NMN) for 14 days (+/- 2 days). The main study procedures are:

- Receive study drug, NMN

- Have 2-4 research visits;
- Have multiple research MRIs;
- Have research blood tests, and ECGs

The main risks of this study are from the study drug NMN. These include: GI distress.

There is no direct benefit for participation in the study.

If there is anything in this form you do not understand, please ask questions. Please take your time. You do not have to take part in this study if you do not want to. If you take part, you can leave the study at any time.

Please see below for additional details about the study.

How many people will take part?

Approximately 10 individuals will participate in this study at The Children's Hospital of Philadelphia.

What is the current standard of treatment for this disease?

Currently, there is no proven treatment for FA. Supportive clinical care is recommended for patients, including regular neurological examinations, physical therapy, and routine orthopedic care.

What is involved in the study?

What are the study procedures?

Some of the procedures in this study will be repeated several times. Tests that are part of your regular, routine medical care will continue to be performed. Additional tests may be performed if any of your initial test results are not normal. The study involves the following tests and procedures.

Experimental Procedures:

Study Drug (NMN): You will need to take the study drug, in the form of 2 tablets, by mouth once a day for 14 (+/- 2) days.

Routine Clinical Trial Procedures:

Medical Record Review: We will review your medical records throughout the study to collect information about your medical history, current health, diagnosis, treatments, medications, and results of clinical tests.

Medical Interviews/Questionnaires: A member of the study team will take your medical history, along with a listing of any medications you are taking. Throughout your participation you will be asked to report if you think that anything bad has happened as a result of the study.

In addition, you will complete study questionnaires and surveys- they will be related to your overall health and quality of life.

Vital Signs: Routine exams will be conducted at each study visit including measurements of blood pressure, heart rate and respiratory rate, etc.

Physical Examination: A routine physical exam will be conducted at the baseline and follow up visits (i.e., listening to your heart and lungs, evaluating brain and nerve functions, etc.) We will also measure vital signs, including measurements of blood pressure, heart rate and respiratory rate.

Anthropometrics: We will measure weight, height, and waist circumference at both the baseline visit and follow up visit.

Blood Draw: Blood samples will be collected to monitor your safety and check levels of NMN in your blood while on the study drug, We will draw approximately 16 mL (~3 teaspoons) at both the baseline visit and the follow up visit.

Fasting: You will need to not eat for at least 10 hours before the blood draw at the baseline visit and follow up visit. You will be reminded prior to those visits. You may have water during the fasting period.

Pregnancy Test: *For Female Participants:* If you are pregnant or nursing, you will not be allowed to participate in this study. All female participants will be asked to take a urine pregnancy test before starting this study and during the study. The results will be shared with you. If you are found to be pregnant, you will not be able to continue participation in the study.

Birth Control: *For Female Participants*: You will need to take safety measures to prevent pregnancy (such as not having sexual intercourse, or using a medically accepted form of contraception) for the duration of your participation. If you have questions about how to avoid pregnancy, talk to your doctor or the researcher and they will provide you with information on contraceptive choices. You should contact Dr. McCormack at once if you become pregnant during this research study.

For Male Participants: You should not father a baby for a minimum of 12 weeks after administration of NMN. You need to take safety measures to prevent pregnancy (such as not having sexual intercourse or using contraception) for a minimum of 12 weeks after administration of NMN. If you have questions about how to prevent pregnancy, talk to your doctor or the researcher and they will provide you with information on contraceptive choices.

Electrocardiogram (ECG): An ECG is a test that measures the electrical activity of the heart. It is used to examine the heart's rhythm to see if it is steady or irregular. It can also help tell how well the heart pumps blood. Several small pads will be attached to your chest, shoulders and legs. They are attached to a machine that traces your heart activity.

Echocardiogram (Echo) (If Needed): An Echo uses sound waves to create a moving picture of your heart. It can find problems with heart function. You will lie on a padded table or a bed. A technician will glide a special device called a transducer across your chest to take pictures of your heart. A small amount of clear gel will be applied to your chest to help the transducer work better. You will need to complete an Echo if you have not completed one within the last year.

Hand Grip Dynamometry: Muscle strength will be measured using a hand-grip strength dynamometer. You will squeeze the handle on the device with each hand and the strength of the "squeeze" will be measured. The measure will take approximately 5 minutes to complete and does not involve any radiation

MRI: An MRI scan takes picture of your heart and your leg muscles. MRI uses a combination of a large magnet, radio waves and a computer to produce pictures. The MRI scan will take about 2 hours.

Visit Schedule

The table below provides a brief description of the purpose and duration of each study visit. The Screening (Visit 0) and Baseline (Visit 1) procedures can be completed on the same day. If Screening and Baseline are combined study procedures will be completed once.

Visit	Purpose	Main Procedures	Duration
Visit 0	Screening	Informed Consent, Demographics, Review Eligibility, Medical History, Vital Signs, Urine Pregnancy Test, ECG, Echo (If Needed)	2 hours
Visit 1, Day 1 and 2	Baseline (Start Study Drug)	Review/Update Medical History, Questionnaires, Vital Signs, Urine Pregnancy Test, Anthropometrics, Physical Exam, Blood Tests, ECG, Hand Grip, MRI, Dispense Study Drug	6-8 hours
Visit 2, Day 14 and 15 (±2)	Follow-Up (End Study Drug)	Review/Update Medical History, Questionnaires, Vital Signs, Urine Pregnancy Test, Anthropometrics, Physical Exam, Blood Tests, ECG, Hand Grip, MRI, Collect Study Drug	6-8 hours

What will be done with my data and specimens during this study?

During the study, we will collect blood and urine samples from you. By agreeing to participate in the study, you agree to give these samples to CHOP for research purposes.

Will I receive any results from the tests done as part of this study?

Results that could be important for your clinical care will be shared with you. We will not share other results with you.

What are the risks of this study?

Participating in a research study involves inconveniences and risks. If you have any questions about any of the possible risks listed below, you should talk to your study doctor or your regular doctor.

Like all medications, the study drug may cause side effects in some people. NMN is a form of vitamin B3. Safety data includes known adverse effects from other forms of B3

(including niacin, nicotinamide, and nicotinamide riboside) While in this study, you may experience the following side effects:

The main risks of the nicotinamide mononucleotide (NMN), are listed below. In addition, we have included potential risks that have been described associated with a closely related compound, niacin.

Common: (between 1 out of 10 and 1 in 100 participants affected)	• GI Distress: Nausea, Heartburn, Diarrhea, Constipation, Bloating
Less Common: (between 1 in 100 and 1 in 1,000 people are affected)	• Rash, Itching • Vasodilatory Effect (Flushing) (niacin) • Changes in blood pressure • Muscle Pain/Soreness
Rare: (between 1 in 1,000 and 1 in 10,000 participant affected)	• Liver Function Abnormalities or Toxicity • Blurred Vision (niacin) • Swelling or fluid in the eye (niacin)

While very rare, serious or life threatening reactions known as anaphylaxis can occur while taking the study drug. These reactions may include swelling of the throat or other body parts, blood pressure drops, difficulty breathing or swallowing, loss of consciousness, or death. A study physician will be available to treat any reactions, if one should occur during your study visit.

In general, some side effects, including the risk of an allergic reaction/anaphylaxis, may be life-threatening

Some medications may cause unwanted effects when combined with the study drug or may make it difficult to tell whether or not the study drug is working. Please tell the study doctor about all of the medicines you are taking. This includes prescription and over-the-counter drugs, supplements (including potassium supplements or salt substitutes), homeopathic, alternative, or herbal medicines, and vitamins. You should also contact the study doctor before starting a new medicine or stopping or changing any of your current medicines. It is important to maintain stable doses of the medications you take. We will go over which medicines you are allowed and which you are not allowed to take during the study.

***Reproductive Risks*:**

For **female** participants, if you are pregnant or nursing, you cannot participate in the study due to the study drug and exposure to radiation due to the unknown effects of the study drug on the fetus or infant. All female participants, will be given a pregnancy test before starting this study and at each study visit (2-3 times) during your participation. The results will be shared with you.

You and your partner will need to practice safe methods (such as abstaining from sexual intercourse or using a medically accepted form of contraception) to prevent pregnancy

through the duration of the study. If you have questions about preventing pregnancy, the study doctor, Dr. Shana McCormack, will be able to discuss your choices and methods.

Because this drug is experimental there may be other side effects we do not know about yet.

Risks Associated with Study Procedures:

Interviews/Vital Signs: There are no physical risks, but in-person and telephone interviews and vital sign exams may cause temporary discomfort or embarrassment. You do not have to answer any questions that cause you to feel uncomfortable. These will be performed in private.

Blood Test: Arm pain, bruising, bleeding, blood clot formation, and in rare instances, an infection might occur at the site where blood is drawn. There is also the possibility of dizziness or fainting while your blood is drawn.

Fasting: Fasting may cause discomfort and hunger. We will schedule the study procedures so as to reduce the amount of fasting time. If you feel unwell fasting before the study, you can stop fasting at any time.

Physical Examination: Potential risks include fatigue, feelings of anxiety and frustration, and discomfort.

Urine Pregnancy Test: Potential risks include feelings of discomfort and anxiety.

ECG: There is a small risk that redness or swelling could develop from the ECG electrodes (pads) that will be placed on the skin.

Echo: Echos are very safe. The gel may feel cold when it is first placed. Some people with sensitive skin can develop a rash from the gel.

Hand-Grip Dynamometry: The hand-grip dynamometer test may result in mild, temporary hand or forearm discomfort.

MRI: There are no known physical risks associated with MRI scanning. However, MRI machines produce loud noises, which may cause discomfort and irritation. We will provide you with earplugs or earphones to quiet the noise. You may also feel uncomfortable lying inside the magnet due to claustrophobia or inability to lie still. If you become anxious, you can tell us and we will remove you from the machine.

The MRI magnet is always activated and attracts certain metal objects. Any metal object on or inside of your body may heat up, move, and/or improperly function within the scanning room. Metal objects in the room can fly through the air toward the machine (magnet) and hit those in the area. However, there are many safety measures to prevent or reduce these risks.

Are there any benefits to taking part in this study?

There will be no direct benefit by participating in this study. Information from this research may help doctors learn more about the use of this study drug in the FA population.

Do you need to give your consent in order to participate?

If you decide to participate in this study, you must sign this form. A copy will be given to you to keep as a record.

What are your responsibilities?

Please consider the study time commitments and responsibilities as a research participant when making your decision about participating in this study. You will need to follow the study doctor's instructions, keep all appointments and take the study drug as directed.

What happens if you decide not to take part in this study?

Participation in this study is voluntary. You do not have to take part in order to receive care at CHOP.

If you decide not to take part or if you change your mind later there will be no penalties or loss of any benefits to which you are otherwise entitled.

Can you stop your participation in the study early?

You can stop being in the study at any time. You do not have to give a reason.

Can the study doctor take you out of the study early?

The study doctor may remove you from the study if:

- Your condition worsens.
- The study is stopped.
- The study drug is no longer available.
- You cannot meet all the requirements of the study.
- New information suggests taking part in the study may not be in your best interests.

What choices do you have other than this study?

There are options for you other than this study including:

- Continuing to receive your usual clinical care.
- Not participating in this study.
- You may discuss other options available to you with your doctor.

What about privacy, authorization for use of Personal Health Information (PHI) and confidentiality?

As part of this research, health information about you will be collected. This will include information from past and present medical records, study procedures/tests, and interviews

that are part of this research. Information related to your medical care at CHOP will go in your medical record. This could include physical exams, imaging studies (MRI scans), ECGs or tests done in the clinical lab. Medical records are available to CHOP staff. Staff will view your records only when required as part of their job. Staff are required to keep your information private. Information that could identify you will not be shared with anyone - unless you provide your written consent, or it is required or allowed by law. Laboratory test results will appear in your medical record with the exception of non-CLIA approved test results which are performed only for this research study. We will do our best to keep your personal information private and confidential. However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The results of this study may be shown at meetings and published in journals to inform other doctors and health professionals. We will keep your identity private in any publication or presentation.

Several people and organizations may review or receive your identifiable information. They will need this information to conduct the research, to assure the quality of the data, or to analyze the data or samples. These groups include:

- Members of the research team and other authorized staff at CHOP and UPenn;
- People from agencies and organizations that perform independent accreditation and/or oversight of research; such as the Department of Health and Human Services, Office for Human Research Protections.
- The Food and Drug Administration
- Metro International Biotech
- Medical Monitor

By law, CHOP is required to protect your health information. The research staff will only allow access to your health information to the groups listed above. By signing this document, you are authorizing CHOP to use and/or release your health information for this research. Some of the organizations listed above may not be required to protect your information under Federal privacy laws. If permitted by law, they may be allowed to share it with others without your permission.

There is no set time for destroying the information that will be collected for this study.

Your permission to use and share the information and data from this study will continue until the research study ends and will not expire. Researchers continue to analyze data for many years and it is not possible to know when they will be completely done.

Can you change your mind about the use of personal information?

You may change your mind and withdraw your permission to use and disclose your health information at any time. To take back your permission, it is preferred that you inform the investigator in writing.

Shana E. McCormack, M.D.
The Children's Hospital of Philadelphia
The Division of Endocrinology and Diabetes

34th Street and Civic Center Blvd.
Philadelphia, PA 19104

In the letter, state that you changed your mind and do not want any more of your health information collected. The personal information that has been collected already will be used if necessary for the research. No new information will be collected. If you withdraw your permission to use your personal health information, you will be withdrawn from the study.

You will be informed if changes to the study are needed to protect your health. You will be told about any new information that could affect your willingness to stay in the study, such as new risks, benefits or alternative treatments.

Financial Information

While you are in this study, the cost of your usual medical care – procedures, medications and doctor visits – will continue to be billed to you or your insurance.

Will there be any additional costs?

There will be no additional costs to you by taking part in this study.

Friedrich's Ataxia Research Alliance (FARA) and Metro International Biotech are providing financial support for this study. The following research procedures, study drugs and study visits will be paid by study sponsor.

- Cost of study drug (Metro International Biotech);
- Cost of study procedures (FARA);
- Cost of travel, parking and meals (FARA, Metro International Biotech);

Will you be paid for taking part in this study?

The compensation provided at each visit is designed to cover the cost of travel, parking, and meals as well as your time and effort.

Participants will receive $150.00 after completion of the Screening/Baseline Visit and $300.00 after completion of the Follow-Up Visit. Total compensation will not exceed $450.00.

If you receive payment using a bankcard, the bank will have access to identifiable information. The bank will not have access to any medical information.

If your travel to CHOP (e.g. flight, hotel) is arranged and paid for by the study team, the agency making the reservations and their representatives will have access to identifiable information.

For non-local participants/families travelling from outside a 50 mile radius of CHOP, we will reimburse eligible travel expenses over the duration of participation in the study. Eligible expenses for reimbursement include mileage, tolls with receipts, and hotel/lodging with receipts according to reimbursement guidelines.

We may share your specimens and data with third parties (other researchers/institutions or for profit companies). If there are patents or products that result from the research, the

third parties may make money from the research. You will not receive any financial benefit from research done on your specimens or data.

Who is funding this research study?

The Friedreich's Ataxia Research Alliance (FARA) will provide funding to support this study.

Metro International Biotech will provide funding to support reimbursement of travel expenses for participants/families traveling from outside a 50 mile radius of CHOP.

Please contact Dr. McCormack if you have any questions about how this study is funded.

What if you have questions about the study?

If you have questions about the study, call the study doctor, Dr. McCormack at (215) 590-3174. You may also talk to your own doctor if you have questions or concerns.

The Institutional Review Board (IRB) at The Children's Hospital of Philadelphia has reviewed and approved this study. The IRB looks at research studies like these and makes sure research subjects' rights and welfare are protected. If you have questions about your rights or if you have a complaint, you can call the IRB Office at 215-590-2830.

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.

What happens if you are injured during the study?

If you are hurt or get sick from something that was done as part of this study, doctors at the clinic or hospital can arrange for emergency care. Treatment may be billed to you or your insurer. If your injury is caused by a research procedure or the experimental drug, MetroBiotech Inc. may pay for treating the injury. This does not mean that a mistake happened.

The Hospital does not offer financial compensation or payment if you are injured as a result of participating in this research.

If you think you have been injured from taking part in this study, call Dr. McCormack at (215) 590-3174. She can go over things with you, let you know of resources that may be available and give you information on what you need to do.

In case of injury resulting from this study, you will not lose any legal rights by signing this form.

What will be done with my data and specimens when this study is over?

As part of the study, we will collect data and samples from you (including an additional blood sample for future analysis related to bioenergetics in FA). These blood samples will be given a unique code and will not include information that can identify you. Other types of samples (e.g. urine) will not be retained. Information that can identify you may be kept permanently on a secured shared drive at CHOP. Only the study doctors and

authorized CHOP personnel working with them on this study will have access to see information that can identify you.

Results will not be disclosed to you, but they may contribute to knowledge for future research studies.

If you leave the study, you can ask to have the data collected about you removed or the samples destroyed. You can also ask us to remove information that identifies you from the data or samples.

OPTIONAL Future Use of Data and Specimens for Future Research

Please indicate whether you will allow your data and samples to be used for future research by putting your initials next to one of the following choices:

_____ (initials) I agree that the data and/or specimens collected may be stored and used for future research.

_____ (initials) I **DO NOT** agree that the data and/or specimens may be stored and used for future research.

OPTIONAL Consent for Disclosure of Participation and results to the Participant's Personal Physician for Clinical Use

Please indicate whether you grant permission to have the study team disclose your participation and results to your personal physician for clinical use by initialing next to one of the following choices:

_____ (Initials) I agree to the disclosure of my participation and results to my personal physician for clinical use.

_____ (initials) I **DO NOT** agree to the disclosure of my participation and results to my personal physician for clinical use.

OPTIONAL Consent for 7.0T MRI Scan

If you provide consent, you may participate in an additional OPTIONAL MRI scan at the Hospital of the University of Pennsylvania. This MRI scan will be completed on a 7.0T MRI scanner.

Risks Associated:

7.0T MRI Scanners

While the FDA has not approved the use of 7.0T MRI scanners for diagnostic use, it does consider magnetic field strengths up to 8.0T to pose no more than minimal risk. No persistent adverse effects have been reported by facilities with magnetic field strengths at 7.0T. However, some people have reported transient dizziness, nausea, or a metallic taste upon being moved into and out of the scanner. These effects typically last less than 10

minutes, and can be minimized by reducing the speed at which the person is moved inside the magnet.

Experimental Device Clause
Some of the pulse sequences and/or RF coils are not FDA approved but are considered to pose no more than minimal risk.

Magnetic Fields Health Risks
There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. You may experience transient nausea and dizziness and nausea. We shall provide you with protective earplugs as necessary and make every attempt to ensure your comfort with blankets, etc. during your time in the scanner. If you wish to stop at any time, you can do so at any time by telling the technician, so s/he can safely stop the scanning.

Please indicate whether you with to participant in the additional OPTIONAL MRI scan on the 7.0T MRI scanner at The Hospital of the University of Pennsylvania by signing next to one of the following choices:

_____ (initials) I agree to complete the additional optional MRI scan.

_____ (initials) I DO **NOT** agree to complete the additional optional MRI scan.

OPTIONAL Consent to be Contacted for Future Research Studies

Please indicate whether you grant permission to be contacted for future research studies by signing next to one of the following choices:

_____ (initials) I agree to be contacted for future research studies.

_____ (initials) I DO **NOT** agree to be contacted for future research studies.

Consent to Take Part in this Research Study and Authorization to Use and Disclose Health Information for the Research

The research study and consent form have been explained to you by:

Person Obtaining Consent	Signature of Person Obtaining Consent
	Date

By signing this form, you are indicating that you have had your questions answered and you agree to take part in this research study. You are also agreeing to let CHOP use and share your health information as explained above. If you don't agree to the collection, use and sharing of your health information, you cannot participate in this study.

Name of Subject	
Signature of Subject	Date