UF UNIVERSITY of FLORIDA

College of Medicine
Department of Molecular Genetics & Microbiology
Center for NeuroGenetics

PO Box 103610
Gainesville, FL 32610-0266
PH: 352-273-6177
FX: 352-273-8284

Study Title: Safety and Therapeutic Potential of the FDA-approved Drug Metformin for C9orf72 ALS/FTD

NCT04220021

Document approval date: 4/6/2023
Document signature date: 8/28/2023

UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw.

If you have questions about your rights as a research participant, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of study participant:

_____

2. Title of this research study:

A Single-Center, Open Label Study to Assess the Safety and Tolerability of Metformin in Subjects with C9orf72 Amyotrophic Lateral Sclerosis over 24 Weeks of Treatment

3. Who you can call if you have questions about this research study:

Principal Investigator: Dr. Laura Ranum, PhD	352-294-5209
Study Coordinator: Deborah Morrison, MA	352-273-5189
24-hour Neurologist on call:	352-265-0111
Co-investigators:	
Dr. Emily Plowman, PhD, CCC-SLP	352-273-9215
Dr. James Wymer, MD	352-273-5550

4. Who is paying for this research study?

The sponsors of this study include the Center for NeuroGenetics in the College of Medicine at the University of Florida, the Amyotrophic Lateral Sclerosis Association (ALSA), and The Department of Defense (USAMRAA). Additional grants and sponsors may be sought.

5. In general, what do you need to know about this research study?

You are being asked to participate in this research study because you have been diagnosed with, or are likely to have *C9orf72* amyotrophic lateral sclerosis (C9-ALS).

This study that you are being asked to participate in is to determine if Metformin is safe and tolerable for use in patients with C9-ALS. Metformin is an FDA approved drug used with diet and exercise to control high blood sugar in adults with type 2 diabetes. In a research laboratory setting, treatment of mice with Metformin shows signs that the drug, in an unknown way, may improve C9-ALS symptoms.

Any samples collected during the screening and drug study will be analyzed and the information obtained will be kept until the end of the study. At the end of the study any samples collected will be destroyed unless you agree to have your samples stored for future research in the Center for NeuroGenetics Bank. If you decide to allow your samples to be used for future research, please let the study team know and they will provide a separate consent to allow your samples to be placed in the Center for NeuroGenetics bank.

If you decide that your tissue/data can be kept for research, but you later change your mind, please call the PI or study coordinator in section 3. You do not need to provide us with an explanation as to why you would like to have your samples removed.

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

This Authorization to use and share your health information goes on indefinitely unless you revoke it (take it back) sooner.

A description of the results of this clinical trial will be made available on http://www.ClinicalTrials.gov, as required by U.S. Law. Study results will not include information that can identify you. At most, the website will include a summary of the results. You can search this web site at any time.

If you have any questions now or at any time during this research study, please contact one of the research team members listed in section 3 of this form.

a) In general, what is the purpose of the research and how long will you be involved?

The purpose of this research is to determine the safety and tolerability of the drug Metformin hydrochloride extended-release tablets (Metformin) in individuals with C9-ALS.

We will also be testing whether the drug can lower proteins that are found in spinal fluid and blood that are produced by the *C9orf72* gene mutation.

You will be in the study for approximately 52 weeks. There are two study components:

(1) In-person study visits: This includes five [5] visits to our clinics over a period of 24-weeks. Due to COVID, we may combine the recruitment/screening visit with visit 1 to be completed over a 3-day period (assuming you meet study criteria). These visits will be followed by three additional in-person study visits.

(2) Check-in telephone calls: You will be contacted by telephone for additional evaluations at ~18, ~36, and ~52 weeks as part of the drug trial and follow-up.

Study staff may also contact you after that period for any long-term follow-up information. Participants may be contacted six months after the conclusion of the trial for a follow-up safety evaluation, including possible blood draw for further study. You may at any point at the conclusion of the trial request that study staff no longer contact you.

b) What is involved with your participation, and what are the procedures to be followed in the research?

You will first attend a recruitment/screening visit as described here. If you wish to participate in the research study, you must give written consent before any study procedures are done.

At the recruitment/screening visit you will undergo a series of evaluations for approximately one to two hours including a blood draw to confirm you carry the *C9orf72* repeat expansion mutation and to test for other eligibility criteria. We will perform tests and procedures to see if you qualify to take part in this research study. Your past and current medical history will be taken, including any medications you take. The study doctor will review the results of these tests and procedures. If you don’t qualify, the study doctor will explain why.

If you meet the inclusion criteria and are selected for the trial, you will be asked to complete additional study visits and will take Metformin tablets by mouth.

Description of study procedures:

At the screening visit and each on-site follow-up visit to our clinic, you may have one or all of the following procedures completed:

- A blood draw consisting of approximately 4 tablespoons of blood for clinical safety measures (hematology, blood chemistry, liver function tests and urinalysis) and laboratory screening for the presence of the *C9orf72* ALS mutation and other molecular features of disease.

- Urinalysis for clinical safety purposes.

- COVID-19 nasal collection and testing will be completed to determine if you are COVID negative. We will provide you with the results of the testing.

- A comprehensive, non-invasive physical exam will be conducted and will include completion of vital signs (blood pressure, temperature, height, weight, and Body Mass Index), and review of physiological systems.

- A comprehensive neurological exam: A standard, painless 15- to 20-minute medical examination of your neurological capacity.

- Review of health status and current state of disease.

- Review of medications you currently take and those that you either begin or stop taking during the trial.

- Collection of past and current medical history and demographics.

- Urine pregnancy test (for females who can become pregnant).

- Lumbar puncture (spinal tap). An approved IRB co-investigator from the Neurology department will perform this procedure in a private clinic room at one of two locations: the Fixel neurology building or at the Clinical Research Center on the UF Campus. A local anesthetic (lidocaine 1%) is injected into your lower back to numb the puncture site. The local anesthetic may sting briefly as it is injected. After the anesthetic is administered, the clinician inserts a thin needle through the lower back into the fluid-filled space below the end of your spinal cord. Once the needle is inserted, up to 20cc's of spinal fluid will be collected for the purpose of laboratory evaluation of the molecular features of C9-ALS including measurements of C9 RAN proteins to see if they are being reduced by the drug.

- VFSS Penetration Scale (swallowing evaluation). During the swallowing portion of this examination, we will take an x-ray of your swallowing, this is called a videofluoroscopic swallow study (VFSS) and is like a movie X-ray of you swallowing foods and liquids.

- Forced Vital Capacity test. Determines the amount of air that you can forcibly exhale from your lungs after taking the deepest breath possible.

- Peak Cough Flow test. Measures air flow out or your lungs.

- Brain Imaging (MRI/DTI) an enclosed magnetic resonance imaging system may be used to view non-invasive measurements of brain activity in relation to specific tasks you will be asked to perform; you will hold a sensor in your hand (if possible) and will be asked to push a button during the MRI.

- Completion of questionnaires that measure functioning related to ALS:
  - **Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised** (ALSFRS-R). Assesses ALS symptoms and disease progression.
  - **Becks Depression Inventory-FastScreen** (BDI-FS). Assesses depression levels.
  - **Eating Assessment Tool-10** (EAT-10). A short questionnaire to determine how you feel about your eating and swallowing ability.
  - **Functional Oral Intake Scale** (FOIS). Documents your level of oral intake of foods and liquids.

- Metformin will be dispensed for you to take home at the end of Visits 1, 2, and 3. The Metformin dose will start at 500 mg, escalating over three weeks to a dose of 2000 mg per day. You will continue to take the Metformin at the indicated doses for 24 weeks with an interim evaluation at ~6 and ~12 weeks and a final evaluation at ~24 weeks to evaluate the safety and tolerability of Metformin.

During the three check-in telephone calls (18, 36, and 52-weeks), a study team member will schedule with you to complete the following:

- Review of current medications or change in medications,
- Review of medical history and changes since your last visit,
- Questionnaires including the ALSFRS-R, EAT-10, and FOIS, and
- Discussion and recording of any adverse events.

c) What are the likely risks or discomforts to you?

Blood Draw: The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; infection (in rare occurrences); and lightheadedness or fainting from the procedure (uncommon).

COVID-19 nasal collection: You may experience some discomfort from the swab being inserted to the back of the nasal passage and while it is being swirled around in the nasal cavity for about 15 seconds. This discomfort will go away

quickly once the swab is removed. You may experience some watering of the eyes and runny nose after it is completed, and these will stop shortly after the collection is complete.

Magnetic Resonance Imaging (MRI): An MRI is a procedure that allows doctors to look inside the body by using a scanner that sends out a strong magnetic field and radio waves. This procedure is used routinely for medical care and is very safe for most people, but you will be monitored during the entire MRI scan in case any problems occur.

The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valve or brain aneurysm clips. Someone will ask you questions about this before you have the MRI.

There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in closed spaces ("claustrophobia"). Many people who do experience claustrophobia feel the anxiety immediately after being put inside the scanner. If that is the case, study staff will stop the procedure before the data collection has begun and the test will be canceled. During the procedure, you will be able to talk with the MRI staff through a speaker system and in the event of an emergency, you can tell them to stop the scan and researchers will remove you from the scanner within 1-2 minutes.

The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before you can have the MRI, you must have a pregnancy test.

Lumbar Puncture (LP; spinal tap): Lumbar punctures involve the removal of up to 20 cc's (about 1.5 tablespoons) of spinal fluid which will be naturally replenished by the body. The lumbar puncture procedure will be performed by a medical professional specifically trained and experienced in the procedure.

Although very rare, it is possible that participants may have an allergic reaction to the local anesthetic (lidocaine 1%) used for the lumbar puncture. This reaction would cause swelling and a skin rash where the anesthetic was injected. Participants will be encouraged to inform study staff if they have had a reaction to local anesthetic before (such as at the dentist).

During the procedure, you may experience temporary pain and discomfort at the puncture site. Sometimes patients experience a headache after the procedure, likely due to leakage of spinal fluids. If this headache persists it may require additional treatment. Uncommonly, a blood patch (an injection of blood into the lumbar puncture site to patch the spinal fluid leak) may be required. This procedure often relieves the headache immediately.

Potential, but rare, risks of lumbar puncture may include infection, damage to nerves in the back, or bleeding that may affect the spinal cord or brain. The risk of these events is very small (one of every ten thousand people who undergo the procedure).

At the end of this procedure, you will be required to remain lying down for a minimum period of one hour before you will be asked to sit up, and every effort will be made to ensure your comfort.

Videofluoroscopy and Swallowing Study (VFSS): This assessment involves exposure to radiation from x-rays. The radiation exposure you will receive from each swallowing test (Videofluoroscopy) is about 50 millirem. This radiation exposure is equivalent to 60 days of natural background radiation to which people in the United States receive each year. The risk from this radiation exposure is considered to be minor when compared to everyday risks. However, the effects of radiation add up over your lifetime. Repeated exposures may increase your risk of injury or disease. When deciding to enter this study you should consider previous and future potential exposures. Examples would include x-rays taken for a broken bone or radiation therapy treatments for cancer. The investigator will provide you with a contact person if you would like more information about radiation exposure.

Barium will be the material used to help us see your swallow function and sometimes when testing is done the barium may enter your lungs during swallowing causing you to cough or feel some discomfort. While small amounts of barium ingested into the lungs does not pose a significant health risk, large amounts ingested over several days can lead to aspiration pneumonia, which is a bad respiratory infection. Therefore, we will stop the test if we see barium enter the airway on more than two swallows of liquid or food to prevent major health risk.

Exposure to radiation during pregnancy can cause birth defects in unborn fetuses. Pregnant women should not undergo barium swallow procedures.

Neurological evaluations: During these evaluations, you might experience some slight discomfort, you might become tired, and you may be unable to do some of the tests. You can decide to stop the tests at any time, for any reason.

Study questionnaires: The study questionnaires may ask sensitive questions and/or be lengthy to complete. You may get tired or bored when we are asking you questions or you are completing questionnaires. Some questions may cause you to feel sad or upset about how your disease has changed or how well you can perform daily activities, and how it has affected your quality of life. Although it is best for the study if you answer all of the questions, you may skip over any questions or entries that you do not wish to answer. All your answers will be kept confidential.

If the depression questionnaire reveals that you have feelings of self-harming related to depression, study staff may refer you to mental health services available at Shands at the University of Florida.

Genetic testing: Participants entering the study will have a known diagnosis of *C9orf72* ALS. Genetic test results can provide a sense of relief from uncertainty about whether or not you have or will develop a condition. Knowing that you have a certain gene may help you and your family make better healthcare decisions, and may help you and your family make more informed life-planning decisions in cases when the gene may be passed on to a future generation. The physical risk of genetic testing is usually minimal, typically not more than providing a hair sample, cheek swab, or blood sample. However, there are potentially emotional, social, and financial risks. You may have emotional reactions such as anger, depression, anxiety, and guilt when learning whether or not you have a gene that may cause a disease in the future. Sometimes a positive test result can affect family relationships. You may have to decide whether or not to tell other family members who might also be affected by the gene. A genetic test may also reveal unexpected family relationships, such as having a different biological parent.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Additional information can be obtained at: http://irb.ufl.edu/gina.html or call 1-800-669-3362. If you think this law has been violated, it will be up to you to pursue any compensation from the offending insurance company and/or employer.

Metformin:

- Taking Metformin with drugs that lower blood sugar, like profenid, beta-blockers, sulfa drugs, salicylates, monoamine oxidase inhibitors and certain nonsteroidal anti-inflammatory drugs (NSAIDs), can raise your risk of hypoglycemia (low blood sugar).

- It is strongly recommended that patients whose kidneys do not work normally not use Metformin because the drug can increase the risk of developing a serious and potentially deadly condition called lactic acidosis, in which too much lactic acid builds up in the blood. Your kidney function will be evaluated by the physician reviewing your lab results prior to including you in the study and prescribing the study drug.

- Alcohol can lower your blood sugar and increase the chances of developing lactic acidosis and should be used in moderation or not used at all while taking Metformin.

- Metformin may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.

- Around 25% of patients report side effects when taking Metformin. The most common are diarrhea, nausea/vomiting, flatulence, asthenia (weakness or lack of energy), indigestion, abdominal discomfort, and headache.

- In the event you are directed to withhold food or fluids in advance of a surgical or other procedure, you should temporarily discontinue use of Metformin due to the increased risk for volume depletions, hypotension, and renal impairment.

- About 3 out of every 100 people who take Metformin report an unpleasant metallic taste when they start taking the medicine. It lasts for a short time.

- In Metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B levels was observed in approximately 7% of patients.

Other possible risks to you may include:

PI, Co-Investigators, and study staff will take appropriate steps to protect any medical, genetic and private health information that they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. This consent form outlines the information that will be collected, used, protected, and shared.

This research study may also include risks that are unknown at this time.

Please note, participating in more than one research study or project (at the same time) may further increase risk to you. If you are already enrolled in a research study, please inform one of the study team members listed in section 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

It is possible that ALS patients may experience some fatigue during the data collection sessions required for the study. Participants will be reminded to report any fatigue or discomfort to the research team. Participants are free to discontinue participation or to withdraw from the study at any time.

d) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

There are two drugs currently approved by the FDA to treat ALS, Riluzole (also called Rilutek) and Edaravone (also called Radicava). Riluzole has been shown to increase life expectancy by ~3 months. Edaravone has the potential to slow disease progression. If you do not wish to participate in the drug trial section of the research study, you should discuss your treatment options and your diagnosis with your local health care team and regular physician(s).

If you are not comfortable with any of the tests outlined in Section 5b (Description of study procedures), please discuss your concerns and desire for alternative procedures with the study staff and/or principal investigators. Some tests are necessary and required in the study and have no substitute and you may need to withdraw from the study if you do not or cannot perform the test.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

This research study will not provide you with any normal medical or clinical care. You should continue to receive routine medical care for your medical condition from your regular physician(s) while you are in the study.

Please report any changes in your normal clinical care routine to the study staff and make sure your health care team and regular physician(s) know that you are participating in this research study.

7. What will be done only because you are in this research study?

If you agree to participate in the study, you will be asked to take the study drug (Metformin) and undergo clinical and safety evaluations, including blood draws and lumbar punctures (spinal taps) to evaluate the effects of the drug. You may withdraw from the study at any time, at which time you will stop receiving the drug and will no longer take part in the clinical and laboratory evaluations.

An overall schedule of the drug study visits is summarized in the Table on page 11, and full descriptions of procedures are described in section 5b.

Following the recruitment/screening visit you will attend four additional appointments in Gainesville: Visit 1 (occurs over two days, usually immediately following the screening visit and may require an overnight stay depending on where you live), Visit 2 (~6 weeks after Visit1), Visit 3 (~12 weeks after Visit 1) and Visit 4 (~24 weeks after Visit 1; occurs over two days and may require an overnight stay depending on where you live).

Due to the COVID-19 pandemic, and after the pandemic, the study team may schedule Visit 1, Day 1 and Visit 1, Day 2, during the same week as the recruitment/screening visit to lessen your travel. In this case, you will return to the study site in Gainesville for three (3) other visits.

At each of these visits, you may undergo one or all of the following procedures:

- Labs including blood draw and urine testing,
- COVID-19 nasal collection and testing,
- A brief physical and neurological exam,
- Review of your current medications/changes in medications,
- Recording of vital signs,
- Urine pregnancy test for females of childbearing potential,
- Lumbar puncture (spinal tap),
- Brain imaging (MRI/DTI),
- Swallowing evaluation (VFSS) Peak Cough Flow test,
- Completion of paper assessments: ALSFRS-R, EAT-10, BDI-FS, and FOIS,
- Metformin dispensed

Summary Table of procedures:

Procedure Name	**Frequency** (how many will take place during the Drug Study)
C9+ confirmation, RAN protein and molecular studies blood draw	4 times
Clinical Labs for safety (hematology, chemistry, liver function and urinalysis)	4 times
COVID-19 nasal collection and testing	3 times
Urine Pregnancy Test (females of childbearing potential)	4 times
Lumbar Puncture (for RAN proteins and biomarkers)	4 times
MRI/DTI imaging	2 times
Forced Vital Capacity	3 times
Peak Cough Flow	3 times
VFSS (Swallowing test)	3 times

Participants may be contacted 12 weeks and six months after the conclusion of the trial for follow-up safety evaluations, including possible blood draws for further study.

8. What identifiable health information will be collected about you and how is it used?

The research team will collect information during the screening and drug study administration visits that includes demographic information, neurological and physical exam results, blood test results, medical and disease history, medication use and history, vital signs, and results of study questionnaires. In addition, the research team will collect CSF (spinal fluid) to test levels of disease related proteins and other biological markers of disease, and results of swallowing and breathing tests, brain MRI imaging data, and adverse event information and documentation (if applicable).

The research team may collect information from other healthcare providers such as laboratories that are involved in this research, healthcare providers that are not part of this research (other doctors, hospitals or clinics), or other professionals at the University of Florida or Shands Hospital who provide study-related care. The University of Florida Institutional Review Board (IRB) may also view your health information.

9. With whom will your health information be shared?

Your private health information may be shared with:

- The study sponsors listed in Section 4 of this form are permitted access to review your research records as part of human subject's protection oversight activities,
- United States governmental agencies which are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections,
- Government agencies which are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments,
- The IRB that reviewed this research study and ensures that your rights as a study participant are protected.

Otherwise, your identifiable health information will not be shared without your permission unless required by law or a court order. Once your health information is shared with those listed above, it is possible that they could share it without your permission because it would no longer be protected by the federal privacy law.

10. How many people are expected to take part in this research study?

We anticipate enrolling fifty (50) people with ALS, to be able to have sixteen (16) people complete the entire Metformin drug study. The exact number of participants will depend upon the portion of C9orf72 ALS mutation carriers within our recruitment population.

11a. What are the potential benefits to you for taking part in this research study?

If you participate in this research study, you may or may not benefit by experiencing a slowing or alteration in the progression of your disease during the study period, and ***there is no guarantee that any effect will be observed***. Laboratory research conducted for this disease using mice showed some positive results with Metformin, but this ***may not be true in humans.***

This study includes a complete swallowing exam which may lead to the early identification of swallowing problems, and information or instruction may be provided to you that may minimize potential swallowing problems such as choking or pneumonia.

The study drug may be prescribed to you once the study has ended if beneficial effects are observed and you are under the care of a physician or health professional who will continue to monitor your health.

11b. How could others possibly benefit from this research study?

Participation in this study will help the investigators learn more about the usefulness and impact of Metformin on disease progression in individuals with C9-ALS. The clinical and laboratory evaluations may inform future monitoring and treatment of ALS and other neurodegenerative diseases. The proposed study may tell doctors and researchers how to monitor disease progression and how to identify patients with the disease for future treatment and clinical trials.

11c. How could the research team members benefit from this research study?

In general, presenting research results helps the career of a researcher. Therefore, the research team listed in section 3 of this form may benefit if the results of this research study are presented at scientific meetings or in scientific journals. Additionally, Dr. Ranum is an inventor on a patent that is pending for the use of Metformin to treat *C9orf72* ALS patients. Dr. Ranum and her husband, Robert Ranum, have founded a company, RanTran, Inc., that may be interested in licensing the patent and related technology from UF in the future. Dr. Ranum is a director at, and owns stock in, RanTran, Inc. If Metformin proves to be an effective treatment for *C9orf72* ALS and RanTran, Inc. obtains a license from UF, Dr. Ranum could benefit financially through her affiliation with RanTran and also as an inventor on the patent.

11d. Will you be allowed to see the research information collected about you for this research study?

During the study, you may not be allowed to see all the research information collected about you from the study, including the research information in your medical record. When the study is over, you will be allowed to see any research information collected and placed in your medical record.

12. What other choices do you have if you do not want to be in this study?

You can still receive care from the UF Department of Neurology or a local neurologist, at your discretion. As noted earlier in the Consent Form, there are two commercial medications which have produced some benefits in ALS patients.

You may also refuse to authorize the use of your health information but if you refuse, you will not be consented to participate in this research study or receive any research-related

treatment, which is only available to study participants. However, your decision not to sign this Authorization will not affect any other treatment you may be eligible to receive.

13a. Can you withdraw from this study?

Your decision whether or not to participate will not affect your current or future relations with the University, the Neurology clinic or any of your physicians. If you decide to participate, you are free to withdraw at any time without affecting these relationships.

You may withdraw your consent and stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. If you decide to withdraw your consent to participate in this research study for any reason, please contact the study team members listed in section 3 of this form. They will tell you how to safely stop your participation.

You can also change your mind and take back this Authorization at any time by sending a written notice to the study team members listed in section 3 of this form to let them know your decision. If you take back this Authorization, the study team members may only use and disclose your health information which has already been collected for this research study. No additional health information about you will be collected or disclosed to the research team. However, if you withdraw your Authorization, you will not be able to continue in this study. Please discuss this with a member of the study team listed in section 3.

13b. Can the Principal Investigator withdraw you from this research study?

You may be withdrawn from this research study without your consent for the following reasons:

- In the event the study team members believe participation is adversely affecting your health.
- If you fail to follow directions for participating in this study.
- If it is discovered that you do not meet study requirements.
- If the study is canceled.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

Study Drugs

Metformin will be provided at no cost to you while you are participating in this study.

Study Services

The Sponsor will pay for or provide all study services/activities required as part of your participation in this study. There will be no cost to you. If you receive a bill related to this study, please contact Laura Ranum, PhD at 352-294-5209 and/or the study coordinator at 352-273-5189.

Items/Services Not Paid for by the Sponsor

Any other medical services provided to you that are not directly required by this study will be billed to you or your insurance company in the usual manner.

15. Will you be paid for taking part in this research study?

Funding is available for certain specified costs expected to be incurred by you in relation to study participation on a reimbursement basis. The table below indicates the **maximum** reimbursement amount for each visit, and is dependent upon delivery by you to the study coordinator of applicable receipts for approved costs. Please be aware that we are unable to reimburse expenses over and above the amounts listed below. Reimbursable funds will be made available through a prepaid debit card that will be given to you during the screening visit.

Approved reimbursable costs include:

- Air travel (roundtrip, plus one piece of luggage),
- Rental car (and related expenses),
- Mileage reimbursement for ground travel (roundtrip, according to number of miles traveled from your home to Gainesville),
- Hotel stays during the study visit periods, and
- Food costs (capped at $56.00 per full day/per person).

Additionally, in appreciation of your participation and at the completion of all study visits, you will be compensated at Visit 4 in the amount of $500.00.

Table of maximum reimbursement according to Visit:

Study Visit number:	**Up to these amounts:**
Screening and Visit 1	$2,400.00
V2	$1,200.00
V3	$1,200.00
V4	$1,800.00
V4 Incentive	$ 500.00
Maximum total compensation	**$7,100.00**

16. What if you are injured while in this research study?

The Principal Investigator will determine whether your injury is related to your participation in this study.

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact one of the research team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

Consent to be Photographed, Video and/or Audio Recorded

With your permission, you will have the following done during this research (check all that apply):

☐ photographed ☐ video recorded ☐ audio recorded

Your name or personal information will not be identified on photographs, video or audio recordings, and confidentiality will be strictly maintained. However, when these photographs, video and/ or audio recordings are shown or heard, others may be able to identify you.

The PI and co-Investigators of this study, or their representatives, will keep the photographs, video and/or audio recordings in a locked cabinet, in a folder on a password protected computer server drive, or as an encrypted electronic file. These photographs, video and/or audio recordings may be shown under their direction to students, researchers, doctors, or other professionals and persons.

Please indicate under what conditions Study Investigators have your permission to use the photograph(s), video and/or audio recordings, and sign and date below.

☐ I choose to have the following **destroyed once the study is closed** (initial next to all that apply):

____ photographs _____ video recordings _____ audio recordings

☐ As described in this Informed Consent form, and for purposes of **education at the University of Florida Health Science Center**, the PI and Co-I's may keep the following for an indefinite period of time in a locked file, in a password protected computer server drive, or as an encrypted electronic file (initial next to all that apply):

____ photographs _____ video recordings _____ audio recordings

☐ As described in this Informed Consent form, and for the purposes of **education at the University of Florida Health Science Center and for presentations at scientific meetings outside the University,** the PI and Co-I's may keep the following for an indefinite period of time in a locked file, in a password protected computer server drive, or as an encrypted electronic file (initial next to all that apply):

____ photographs _____ video recordings _____ audio recordings

_____ _____

Signature Date

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant or to a person holding the Power of Attorney to sign on their behalf, the purpose, procedures, possible benefits, the risks of this research study, alternatives to participating in the study, and how the participant's protected health information will be collected, used, and shared with others:

Signature of Investigator or Investigator's Representative (*Person Obtaining Consent and Authorization*)	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study, and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described throughout this consent form. By signing this form, you are not waiving any of your legal rights.

Signature of Study Participant (*Person Consenting and Authorizing*)	Date

Signature of Witness for participant with physical limitations	Date

☐ I witnessed the participant's mark on this consent form, and attest that it was made by the person who has agreed to participate in this study.

☐ I witnessed the consent discussion and attest that the participant has indicated their agreement to participate in this study (witness should not be a member of the study staff or a family member).