CONSENT FORM TO PARTICIPATE IN A DIET RESEARCH STUDY

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PROJECT # 2012106

STUDY TITLE: SEX-RELATED DIFFERENCES IN ARTERIAL STIFFNESS IN TYPE 2 DIABETICS: ROLE OF URIC ACID

INTRODUCTION

This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision.

The Principal Investigator (also called the study doctor) is Dr. Camila Manrique. The people working with Dr. Manrique on this study are called the study team. Research studies include only people who choose to participate.

As a study participant you have the right to know about the procedures that will be used in this research so that you can make the decision whether or not to participate. The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision.

You are being asked to take part in this study because you have type 2 diabetes which gives you increased risk of arterial stiffening.

This study is being sponsored by the National Institutes of Health. In order to participate in this study, it will be necessary to give your written consent.

WHAT SHOULD I KNOW BEFORE I DECIDE WHETHER TO TAKE PART IN THIS STUDY?

- Research studies help us to learn new things and test new ideas about treating certain conditions/diseases.
- Taking part in a research study is voluntary. You decide if you want to take part, and you can stop taking part at any time. Your regular medical care at the University of Missouri Hospitals and Clinics will not be affected now or in the future if you decide you do not want to be in this study.
- We are doing this study because we want to learn if consuming a hypocaloric, low fructose interventional diet for 6 months will improve blood vessel stiffness.

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- You are being asked to take part in this study because you may have characteristics of increased vascular disease risk.
- About 140 people will take part in this study at the University of Missouri.
- If you take part in this study, you will come to the Clinical Research Center (CRC) for 10 scheduled visits. The CRC, located on the 5th floor of the University Hospital and has clinic rooms specially designed for research. You will have blood test, DEXA scans, ultrasounds, questionnaires and physical exams completed during this study. We will explain these procedures in this form.
- If you join this study, you will not have to stop your diabetes treatment for as long as you are in the study.
- The total amount of time you could be in this study is about 6 months.
- Taking part in this study may or may not make your health better. We hope that the information we learn from this study will help in the future treatment of people with type 2 diabetes and increased cardiovascular disease risk. There is no guarantee that taking part in this research will result in any improvement in your condition.
- As with any research study, there are risks that we know about and there may be some we don't know about. We will explain these risks in this form.
- We will only include you in this study if you give us your permission first by signing this consent form.

WHY IS THIS STUDY BEING DONE AND HOW MANY PEOPLE WILL TAKE PART?

The goal of this study is to determine if a reduced calorie diet low in fructose, that reduces uric acid level will improve blood vessel stiffness. Our plan is to decrease calorie and fructose intake in the diet for a period of 6 months and assess changes in the stiffness of the heart and blood vessels. The tests performed are not part of standard medical care. About 400 people will be screened and 40 people will complete this arm of the study at the University of Missouri.

WHAT IS INVOLVED IN THE STUDY?

As described in Error! Reference source not found., this research includes 3 clinical research center (CRC) visits, 3 food pick-ups, and meetings with a dietitian nutritionist over a 6-month

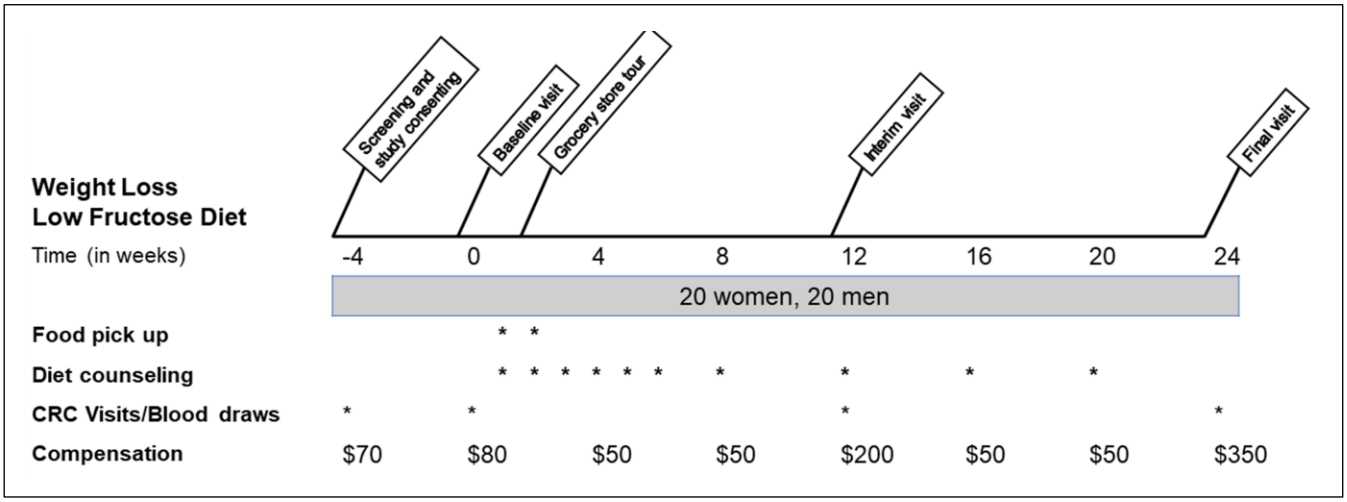

Figure 1. Depicts visits to the clinical research center (CRC), food pick-ups, and meetings with the registered dietitian nutritionist.

period.

STUDY PLAN

The following paragraphs describe the schedule and details of the procedures, 3 study visits, and diet counseling you will undergo while participating in this research study **(**Error! Reference source not found.**)**.

CONSENTING AND BASELINE VISIT

You have already been preliminarily screened to participate in this diet study. Based on your results, you qualify to take the next step to achieve entrance into the diet study. Today you will be told about the treatment you will receive and review the consent form. If you want to continue in the diet study after reviewing and signing the consent, you will complete blood draws, vascular measurements, and an insulin clamp as part of your baseline visit. You will be scheduled for consequent visits (dietary counseling visits, interim visit, and final visit) after the conclusion of your baseline visit. You will also be given a form to record your food intake for 3 days for the study dietitian nutritionist to review.

The timing of the three visits will occur at baseline (a mutually-convenient time for you and the staff), after 3 months and at 6 months on treatment. This consent form will explain your responsibilities during the study and the details of the procedures you will undergo. For this and the other visits, you will come to the CRC at the hospital. Details of the baseline visit are outlined in **(**Error! Reference source not found.**),** below.

The following paragraphs describe the schedule for the study visits **(**Error! Reference source not found. **and** Error! Reference source not found. **)**

Baseline visit
For 10 or more hours before the visit, do not use caffeine, alcohol, and vitamin supplements. You will come in after fasting overnight for 10 or more hours - no food, drink (except water), or glucose lowering AM medications after 10 PM. Please do not exercise the morning of this visit. This visit will take about 8 hours. This visit will include blood drawing, measurements of blood pressure, heart rate and waist circumference, cIMT, PWV, FMD with NIRS, Glycocheck, and

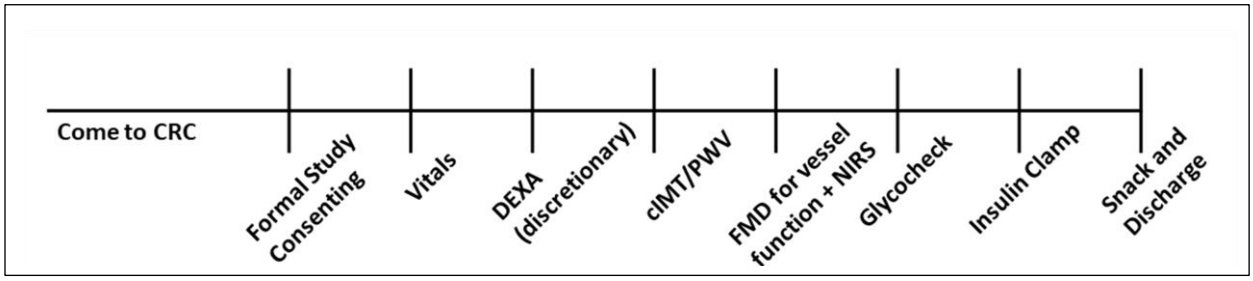

Figure 2. Order of events at the baseline visit.

DEXA and you will undergo an insulin clamp procedure with blood draws. Total amount of blood during this visit is about 10 tablespoons. After this you will be offered lunch and you will be asked to fill out some questionnaires to assess your physical activity level. If all baseline procedures are successful, you will begin your 5-month hypocaloric low fructose diet intervention, overseen by Dr. Manrique and the study dietitian nutritionist.

Diet counseling visits
Once a week, for the first 6 weeks of the study, you will meet with the study dietitian nutritionist at the CRC (or via tele-counseling per the discretion of the primary investigator.) Then, for the remainder of the study you will meet with the dietitian nutritionist at weeks 8, 12, 16, and 20. The dietitian nutritionist will guide you on how to eat a diet that matches the study criteria. The dietitian nutritionist will also be available to you by phone and email to answer any questions you may have while following the diet.

Interim visit
At 12 weeks, this visit will occur at the CRC. For 10 or more hours before the visit, do not use caffeine, alcohol, and vitamin supplements. You will come in after fasting overnight for 10 or more hours - no food, drink (except water), or glucose lowering AM medications after 10 PM. Please do not exercise the morning of this visit. This visit will include blood drawing, measurements of blood pressure, heart rate and waist circumference, cIMT, PWV, FMD with NIRS, Glycocheck, and DEXA (no clamp) Error! Reference source not found.. This visit will

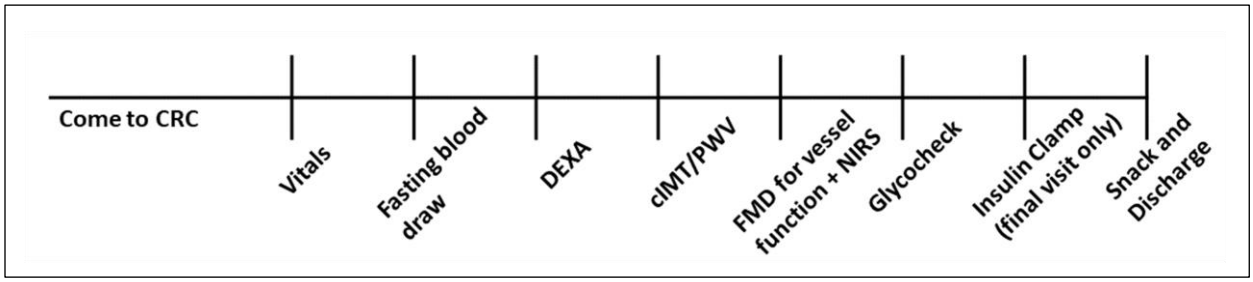

Figure 3. Order of events at the interim and final visits. No insulin clamp is administered at the interim visit.

take approximately 4 hours and you will have 2-3 tablespoons of blood drawn. Following this visit, you will continue to the diet for another 12 weeks.

Final visit
As you did with the baseline and interim visits for 10 or more hours before the visit, do not use caffeine, alcohol, and vitamin supplements. You will come in after fasting overnight for 10 or more hours - no food, drink (except water), or glucose lowering AM medications after 10 PM. Please do not exercise the morning of this visit. This visit will include blood drawing, measurements of blood pressure, heart rate and waist circumference, cIMT, PWV, FMD with NIRS, Glycocheck, DEXA, and an insulin clamp (Error! Reference source not found.). This visit will take up to 8 hours and you will have about 11-12 tablespoons of blood drawn. Following this visit, your participation in the study is completed. You may be asked to complete an exit survey upon completion of the study. Exit surveys will be administered via Qualtrics email link or in person depending upon your preference.

DETAILS ON PROCEDURES

Body composition
A DEXA scan will be performed to determine how much of your body is composed of fat, bone and muscle. This scan will expose you to a small amount of radiation. The amount of radiation received during the DEXA scan is less than that of an airline flight from California to New York and back.

Vascular function measures
A small video microscope probe will be placed under your tongue for a brief period of time (5 minutes approximately) to evaluate the blood vessels, this is what we referred as Glycocheck. A blood pressure cuff will be placed around the forearm or leg. This cuff will be inflated (up to 250mmHg), as is done when your blood pressure is being measured, but instead of deflating the cuff immediately it will remain inflated for 5 minutes. We will measure the blood flow to your arm by placing an ultrasound probe over the brachial artery (upper arm artery) and to your leg placing the probe over the popliteal (lower leg artery) before, during and after inflating the cuff. The probe will provide a measure of the speed at which your blood is traveling through your artery and the extent to which your artery dilates (i.e., expands). We will also measure the blood flow to your leg during the OGTT. In addition, during the vascular measurements another set of probes will be placed on the muscle of the leg and arm; the probe will be secured via an elastic band loosely wrapped around the site. These probes will stay in place for the duration of testing (these probes are the ones that will be used for NIRS).A pressure sensor (tonometer, the size of a pencil) will be placed over the skin of the neck region to obtain the pressure wave form in the carotid artery. Also a probe will be placed over your neck arteries to take an image of them. Additionally, in order to further characterize blood flow, we will be using an ultrasound to image the muscle of your leg during the administration of an ultrasound contrast agent that will be given through the IV. This agent, called Definity, is composed of tiny microbubbles smaller than the size of a red blood cell. These bubbles stay inside the blood vessels and go where the red blood cells go. This contrast agent allows us to evaluate blood flow in your leg muscle. Definity has been FDA approved for use in humans during ultrasound of the heart cavity and has been shown to be safe.

Oral glucose tolerance test (OGTT) with leg blood flow + NIRS
After an overnight fast, you will have a catheter (tube) placed into a vein in one arm to collect blood samples. Blood samples will be collected every 15-30 minutes over the next 2 hours after consuming the glucose beverage (75 grams of dextrose). The total volume of blood drawn during the OGTT will be less than 40 mL (~3 tablespoons). Before and during the OGTT, we will be using an ultrasound to measure blood flow in your leg.

Insulin clamp
The insulin clamp test helps to determine how well your body disposes of blood sugar (glucose) in response to insulin. You will have a small catheter (tube) placed into a vein in both of your arms. The insulin clamp requires that insulin and glucose be slowly infused into the arm vein and then multiple small blood samples will be taken during a 3 hour period allowing us to accurately assess your insulin sensitivity. During the entire test you will lay comfortably in a bed. The total volume of blood drawn per insulin clamp will be less than 140mL (~1/2 cup). During this time, we will perform repeated measures of blood flow in both legs and leg muscle blood flow using the ultrasound probe, measures of blood pressure, and measures of heart rate via ECG.

After this you will be offered lunch and you will be asked to fill out some questionnaires to assess your physical activity level. If all baseline procedures are successful, you will be provided with two weeks of complete meals, including all food and beverages. Following these two weeks, you will begin the diet on your own and you will be responsible for all foods eaten for the rest of the study. In order to help you with the diet, you will be taken on a grocery store tour with the study dietitian nutritionist, who will be able to show you what foods to avoid and what foods are acceptable. As shown in Error! Reference source not found., you will schedule appointments to meet several times with the dietitian nutritionist to make sure you eating the right kinds of foods and in the appropriate amounts.

WHAT ARE THE PROCEDURES AND RISKS OF BEING IN THIS STUDY?

Blood drawing and its risks
During this study you will have blood drawn through a needle. Risks: Drawing blood from your arm can cause minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely. As a result of your participation in this study you will have given blood. If you wish to perform other research after you finish this project, you should let the investigator know that you have donated up to 14 ounces (or about 1.7 cups). Your blood volume will be checked during screening to make sure that your volume is in safe limits.

Insertion of venous catheters
The potential risks of venous catheterization include infection, swelling and discomfort at the catheter insertion sites. Some bleeding may occur during the insertion of the catheters as well after the catheters have been removed. There is also the possibility of fainting, dizziness, and possible pain and bruising as a result of catheter insertion. These risks will be greatly minimized by using sterile procedures and having an experienced registered nurse placing the venous catheters.

Oral glucose tolerance test
There are no risks associated with this test. At screening, you will have an oral glucose tolerance test performed. You will be asked to drink a solution with 75 grams of glucose (sugar) which is similar to a 20-24 ounce soda in sugar content. This might cause your blood sugar levels to be elevated following the completion of the test.

Glycocheck
There are no risks associated with this test.

Near-infrared spectroscopy (NIRS)
There are no risks associated with this test.

Insulin clamp
The potential risks during the clamp include mild nausea or light-headedness, and mild to moderately high or low blood glucose levels. However, blood glucose will be continually monitored throughout the test. Also, drinks and snacks will be available at the completion of testing should you have low blood sugar or feel nauseous.

Perfluten (Definity)
A potential side effect from the Perflutren ultrasound contrast agents is temporary back pain, joint pain, headache, shortness of breath, or flushing. These symptoms occur in about one in 200 subjects and are mild in intensity in 90% of those who experience this reaction. If this happens then let us know and infusion of the agent will be stopped. The back and joint pain will go away in a few minutes. A serious allergic reaction to ultrasound contrast agents is unlikely (1 in 10,000), but possible. Symptoms of an allergic reaction include: Rash, itching, swelling, severe dizziness, chest pain and trouble breathing. We are using this contrast agent to measure blood flow in your leg muscles using a dose approved by the FDA.

Heart rate measurements via ECG
Some people may have a skin irritation from the patches that connect the wires on your chest to the computer. Skin and hair are pulled slightly when the patches are removed after the test. Research personnel will attach and remove the patches as carefully as possible.

Blood pressure cuff inflation and vascular function measures
The blood pressure cuff will squeeze your arm or leg tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released.

Measurement of body composition by DEXA
At baseline, interim and final visits, you will have a DEXA (Dual Energy X-ray Absorptiometry), which is a procedure to measure your body composition - how much fat and muscle your body has. It is a type of x-ray machine with a moving arm. This procedure involves lying on a table for 15 minutes while the DEXA machine passes over your body. Although you will need to remain very still and quiet, you will feel nothing and should have no discomfort.

Risks: If you have participated in any other research study involving ionizing radiation exposure in the past 12 months, discuss this with the Investigator to determine if you are eligible to participate in this study. You will be exposed to a small radiation dose which is about 2% of the

average radiation dose from all sources (natural background radiation, consumer appliances, radon gas, medical tests, etc.) that a person receives in the United States receives each year. However, radiation effects are cumulative. You should always inform future doctors of your participation in this study. For female participant, a urine pregnancy test will be performed before the scan.

Indirect calorimetry
Calorimetry carries no risk, however, this test may cause discomfort in those who are fearful of confined spaces or claustrophobic. Before the procedure is performed, subjects are allowed to become familiarized with the hood used to collect expired gas.

Test diets and physical activity
Foods: All foods given to you are commercially available and sold in supermarkets. All your food is provided for two weeks. This diet is designed to help you lose weight and to teach you how to reduce the added sugars and fructose that you normally eat. The amount of food given to you is calculated based upon the dietitian nutritionist's caloric recommendations; we ask that you eat all of the food and do not eat any extra food so that the hypocaloric, low fructose diet intervention can be evaluated accurately.

Study Diet: The study diet is designed to reduce calories and fructose in your diet while keeping your baseline fat and protein intake the same. In other words, the interventional diet will decrease the calories in your diet and will also replace foods that have sugars in them with foods that have starches in them. You will be given an example of the diet for 2 weeks, and then you will be responsible for following the diet for the remainder of the study. The study dietitian nutritionist will teach you how to eat the diet, ensure that you are following it, and will be available to answer any questions that you may have.

Beverages: You may consume non-sugar containing beverages including diet soda, regular coffee or tea without nondairy creamer added. You may add non-caloric sweeteners, and/or a maximum of 2 ounces of cream per day to the coffee or tea. Regular sodas and fruit juices that are high in fructose and/or added sugar are to be eliminated during the dietary intervention. Habitual alcohol consumption may be continued but we ask that you avoid alcoholic drinks containing fructose and/or added sugars (e.g., margaritas, fruit-containing drinks). Consumption of milk and milk products will be limited due to their sugar content.

Activity: You should not consciously change your physical activity while you are in the study. In other words, if you would like to join a gym or begin exercising more, we ask that you wait until the 6-month diet is over before you do this.

We anticipate no medical risks from consuming this diet for 2 weeks and no risk of eating the hypocaloric low fructose diet for 6 months. For the first 2 weeks, you will be consuming only the prescribed foods given to you and no other foods, then, you will be cooking and preparing the study diet at home.

Study exit survey
Surveys will be optional for subjects that complete study treatment. This poses no risks.

WHAT WILL BE MY RESPONSIBILITIES DURING THE STUDY AND ARE THERE BENEFITS?

While you are part of this diet study, the researchers will follow you closely to determine whether there are problems. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem, or purchased over the counter.
- Report to the researchers any injuries or illnesses while you are on the study, even if you do not think they are related.

If you agree to take part in this diet study, there may not be direct medical benefit to you. You may however expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. We hope the information learned will benefit people at risk of heart disease in the future.

WHAT ARE THE COSTS?

You will not be charged for any procedures that are part of this research study. Parking will be provided but there is not childcare during this study.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

You will be compensated a total of $900 for completing this study: $70 will be given for the screening visit, $80 will be given for the baseline visit, $150 will be given for the interim visit, and $300 or the participating in the tests in the final visit. In addition, you will also be compensated monthly for your participation in the study ($50/per month). In addition, if you leave more than 25 miles away from the CRC you will receive a travel stipend of $7 per 25 miles traveled (starting at a distance of 25 miles) for each visit. Checks are sent to you through the mail and usually take 1-2 weeks to arrive.

WHAT OTHER OPTIONS ARE THERE?

You do not have to participate in this study

WHAT ABOUT CONFIDENTIALITY?

Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. It is possible that your medical and/or research record, including identifying information, may be inspected and/or copied by the study sponsor (and/or its agent),

the Food and Drug Administration (FDA), federal or state government agencies, MU Health Sciences IRB, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri will use reasonable efforts to protect your privacy and the confidentiality of your medical information. The results of this study may be published in a medical journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

We will keep the information and/or samples we collect from you for this study to use in future research without asking for your consent again. Information that could identify you will be removed from your research data/samples so no one will know that it/they belong to you.

WHAT IF I AM INJURED?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff.

The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate. If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care at the University of Missouri. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end your participation in this study at any time after she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed. You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

A description of this clinical trial will be available on 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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

If you want to talk privately about your rights or any issues related to your participation in this study, you can contact University of Missouri Research Participant Advocacy by calling 888-280-5002 (a free call), or emailing MUResearchRPA@missouri.edu.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Dr. Camila Manrique at MUEndoManriqueLab@health.missouri.edu. A copy of this consent form will be given to you to keep.

SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

Subject	Date
Witness (if required)	Date

SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

Study Representative	Date

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