CONSENT FORM TO PARTICIPATE IN ALLOPURINOL/PLACEBO 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 your blood uric acid level is slightly elevated and 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 lowering uric acid, with a diet low in fructose or a medication - allopurinol, will improve blood vessel stiffness.

- 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 8 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.

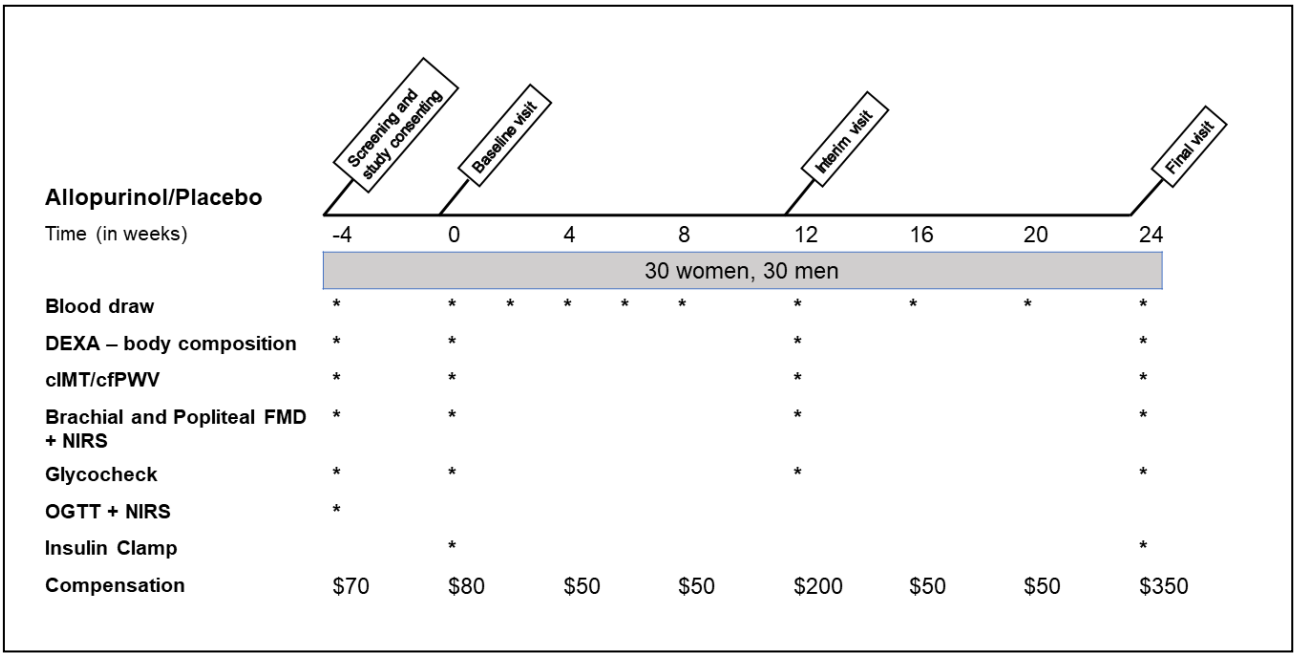

Figure 1.

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

The goal of this study is to determine if a drug, allopurinol, that reduces blood uric acid will improve blood vessel stiffness in patients with type 2 diabetes when compared to placebo. Our plan is to decrease uric acid in your blood for a period of 6 months by having you take the study medication and assess changes in the stiffness of your blood vessels. The tests performed are not

part of standard medical care. About 400 people will be screened and 60 people will complete this arm of the study at the University of Missouri.

WHAT IS INVOLVED IN THE STUDY?

In general, this research is measuring how plasma uric acid levels may impact cardiovascular health in the setting of type 2 diabetes. Based on your blood results and your medical history, you are eligible to participate. You have been assigned to the allopurinol/placebo group, which means you will be randomized to an active treatment (allopurinol) or to a placebo treatment. If you chose to participate, you will be enrolled into a research study. As described below, this research includes today's consenting visit followed by 9 study visits over a 6-month period.

STUDY PLAN

The following paragraphs describe the schedule and details of the procedures, study visits, and blood draws you will undergo while participating in this research study **(Figure 1**).

CONSENTING AND BASELINE VISIT

You have already been preliminarily screened to participate in this study. Based on your results, you qualify to take the next step to achieve entrance into the study. Today you will be told the treatment you will have 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 (safety visits, interim visit, and final visit) after the conclusion of your baseline visit.

The timing of the three main 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 the **Figure 2**.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor the researcher team will choose what group you will be in. You will have a one in two chance of being placed in any group.

Whether you receive Allopurinol (up to a dose of 300 mg) or placebo will be determined by chance. A placebo looks like the study drug but has no active medication.

PROCEDURES

The following paragraphs describe the schedule for the study visits (**Figure 2 and Figure 3**).

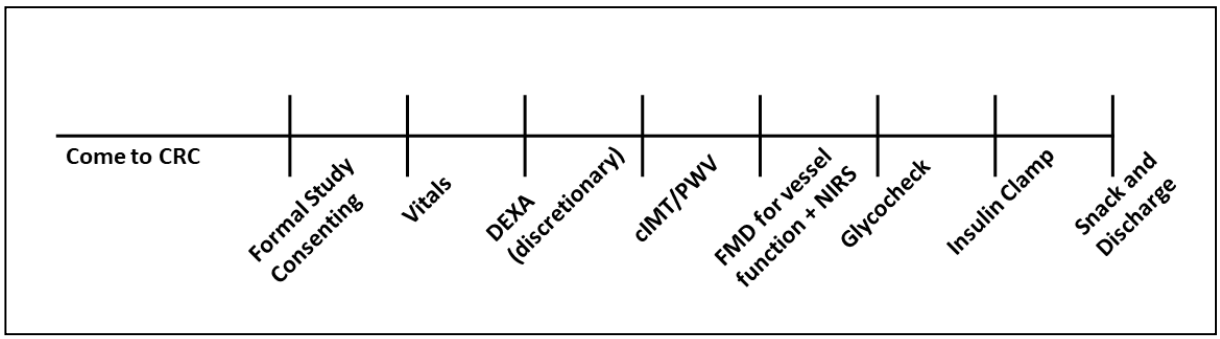

Figure 2.

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 up to 8 hours. This visit will include blood drawing, measurements of blood pressure, heart rate and waist circumference, cIMT, PWV, FMD with NIRS, Glycocheck, and 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 6-month drug treatment, overseen by the study physician, Dr. Celso Velázquez. You will receive a pill bottle of drug and Dr. Velázquez or Dr. Manrique will instruct you how many pills to take daily.

Interim visit

At 3 months, 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) (**Figure 3)**. This visit will take approximately 4 hours and you will have 3 tablespoons of blood drawn. Following this visit, you will continue to the medication for another 3 months.

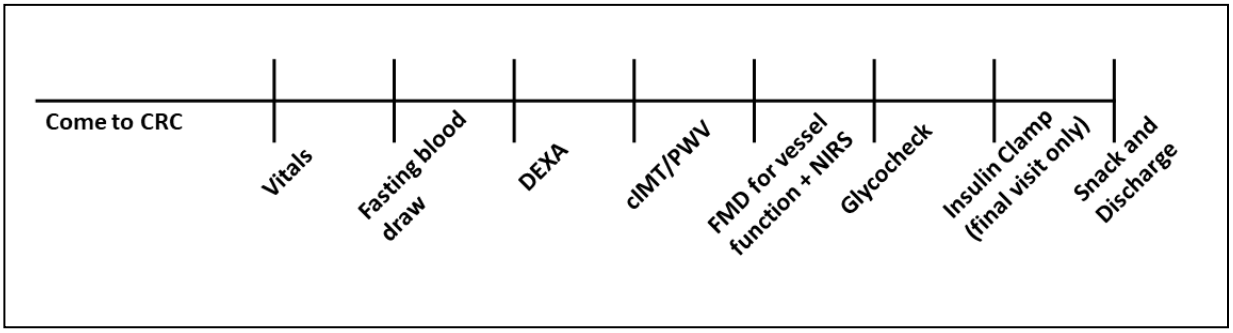

Figure 3

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, and DEXA and you will undergo an insulin clamp procedure with blood draws. **(Figure 3)** 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.

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 140 mL (~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.

Dose monitoring blood draws
After your baseline visit, for the first two months, you will be seen every 2 weeks for a blood draw (2 teaspoons) to monitor the uric acid levels in your blood. This blood draw will take place at the CRC. Because you do not have to fast for this blood draw, these visits can be scheduled any time at your convenience. Dr. Velázquez or Dr. Manrique will review your blood test results and contact you by phone with instructions on how many pills to take each day. After two months, you will come into the CRC for a blood draw once a month.

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 16 oz (or about 2 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 and/or flushing. These symptoms occur in about one in 200 subjects and are mild in intensity in 90% of those subject 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 screening, 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.

Study drug: Allopurinol
Allopurinol is a common prescription drug given to patients with gout and other diseases to lower uric acid in their blood. You will take allopurinol as prescribed by the study physician. Dr. Manrique or Dr. Velázquez will notify you to increase your dose according to study procedure by telephone or e-mail after safety lab results are reviewed. Risks: Common side effects of taking this drug can include pain in your ankles, knees, and big toes, stiffness or swelling in your joints, and skin rashes. Other side effects that are uncommon are nausea, gout, and liver and kidney irritation. Other side effects that are rare include hepatitis and hair loss. Notify study staff immediately if you experience any side effects. Watch for nausea or for a rash occurring on your skin. Allopurinol may have significant interactions with other medications so be sure to notify study staff of your current medications.

Being in the control/placebo group
The researchers have found that your blood uric acid level is elevated and that you have increased risks for future heart disease. There is currently no proof that not treating your level of uric acid has any risk. For this research to be successful, it is important for us to monitor your heart health over the next 6 months to determine if any changes occur naturally with aging.

Constant diet and activity
You have been assigned to a group that will treat your blood uric acid levels with a drug/placebo. For the researchers to determine the effect of that drug, we ask that you avoid making major changes to your diet and exercise regimens. After the study is completed, the researchers and study dietitian nutritionist can assist you in efforts to change your diet and exercise.

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 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 study, there may not be direct medical benefit to you. You may also 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 no compensation for travel to our facilities or for 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 for the participating in the tests in the final visit. You will also be compensated monthly for your participation in the study ($50/per month that does not include a full CRC visit). If you are required to come in for any additional, unscheduled safety visits, you will be compensated $25/additional visit. 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 will also 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 OF PARTICIPANT

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

*The presence and signature of an impartial witness is required during the entire informed consent discussion if the patient or patient's legally authorized representative is unable to read.

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