CONSENT FORM TO PARTICIPATE IN A 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 is designed to give you a brief overview of the projects that are being conducted in this research study. The form 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 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.

Today, you are deciding whether you would like to take the next step to participate in research. After today, if you are preliminarily eligible, and if you are interested participating in the study you will sign the formal consent to participate in the research. This study is being sponsored by the National Institutes of Health. In order to participate in this screening today, 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 various diets 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 10-12 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 lowering uric acid, with various diets low in fructose or a medication - will improve blood vessel stiffness. Our plan is to decrease fructose intake with or without caloric restriction or administer the medication for a period of 6 months and to assess changes in the stiffness of the blood vessels. The tests performed are not part of standard medical care. About 400 people will be screened and 140 people will choose to complete the study.

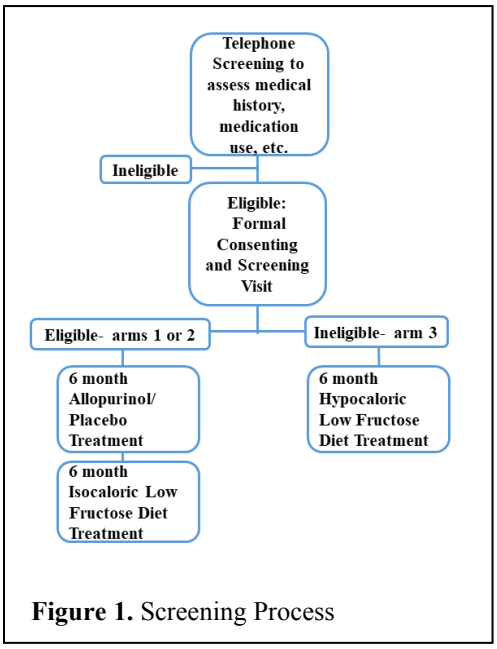

Figure 1. Screening Process

WHAT IS INVOLVED IN THE STUDY?

Today, we will describe the study in general. We will answer any questions you may have. Overall, the research project consists of 3 parts outlined below. If you are eligible and wish to continue, you will only participate in one part of the research study. Overall, this research includes one screening visit, a formal consenting visit/ baseline visit, and one of the following:

1) A 6-month low-fructose, weight stable diet;
2) A 6-month daily dose of the allopurinol or placebo; or
3) A 6-month low-fructose, weight loss diet

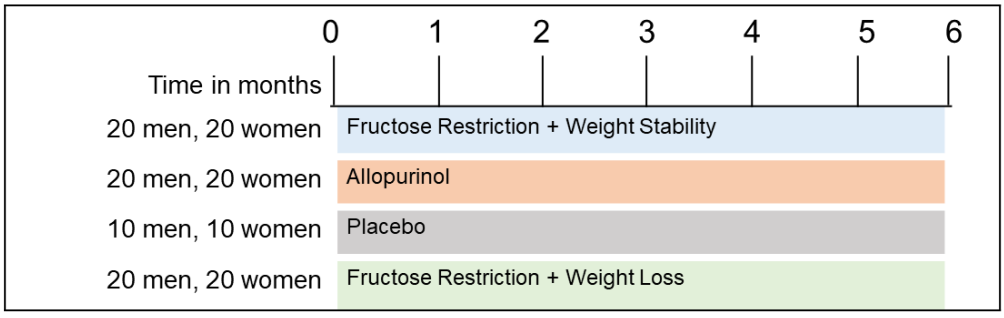

Figure 2. Overall design for study

STUDY PLAN

The following paragraphs describe the schedule for the screening visits and the three different parts of this study.

Screening visit

Today, to help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgeries you have had.

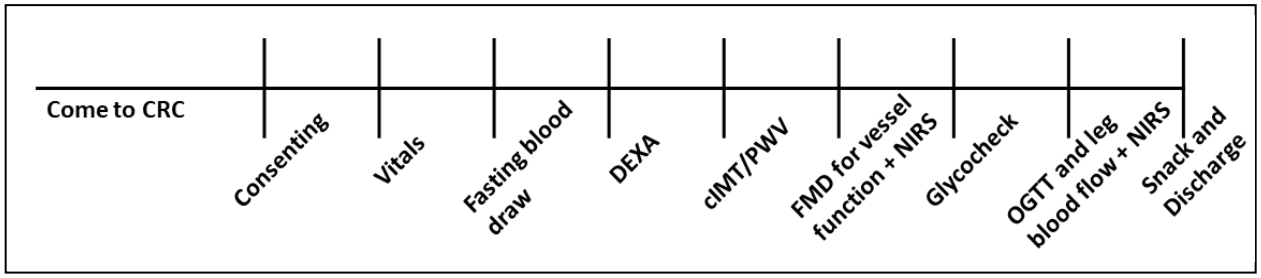

Figure 3. Order of events at the screening visit.

This visit is located at the Clinical Research Center (CRC). The CRC, located on the 5th floor of the University Hospital, has clinic rooms specially designed for research. You will come to the CRC after fasting overnight for 10+ hours (no food or drink, except water) and holding any glucose lowering AM medications (you can resume regular medications after visit). This visit will take approximately 6 hours. Research staff will meet with you at the CRC to review the study procedures, answer questions, sign this consent form and review your medical history. Some blood will be drawn (about 4 tablespoons) to check your general health and during the oral glucose tolerance test. Your height, weight, and blood pressure will be measured and you will complete cIMT, PWV, FMD with NIRS, Glycocheck, DEXA, and an OGTT with blood draws. Within a week after this visit, you will receive the results of all screening tests and someone on the study team will go over the results with you and describe the next steps. You will be given a copy of the test results, which you can share with your primary physician. **Figure 3** shows the order of events at the screening visit.

Consenting and baseline visit

If your first screening qualifies you to be in the study and if you are interested in proceeding you will be scheduled for a baseline visit. Before the baseline visit, the primary

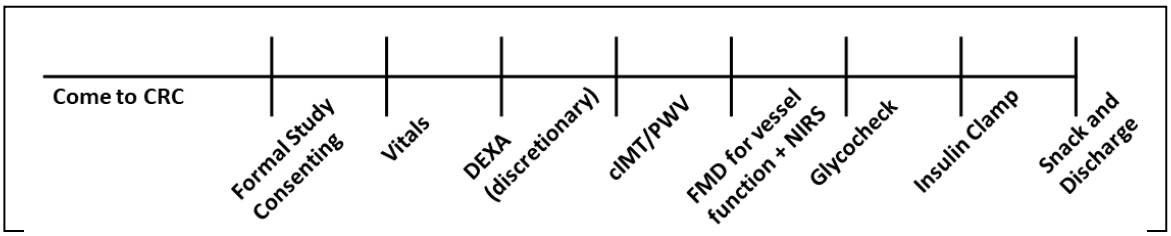

Figure 4. Order of events at the baseline visit.

investigator will review the consent form with you and inform you in what part of the study you have been assigned to participate. If you want to continue in the study, you will complete the baseline visit and be given a form to record your food intake for 3 days. Additional study appointments will be scheduled: safety visits, an interim visit, and a final visit. Consequent visits will include blood work and repeats of vascular measurements. **Figure 4** shows the order of events at the second visit (consenting and baseline visit).

PART 1, DIET THERAPY (LOW FRUCTOSE, WEIGHT STABLE)

If you are enrolled into this part of the research, you will consume a low-fructose diet for a 6-month period. For the first two weeks, all of your food will be provided while you learn how to limit your intake of fructose and simple sugars. After that, to better help you learn to eat the diet, you will have several meetings with a dietitian nutritionist over 6 months. You will come into the CRC for a baseline visit, again after 3 months for an interim visit, and one more time after six months for a final visit. Upon completing this phase of the study, you will be offered a free counseling session with the study dietitian nutritionist.

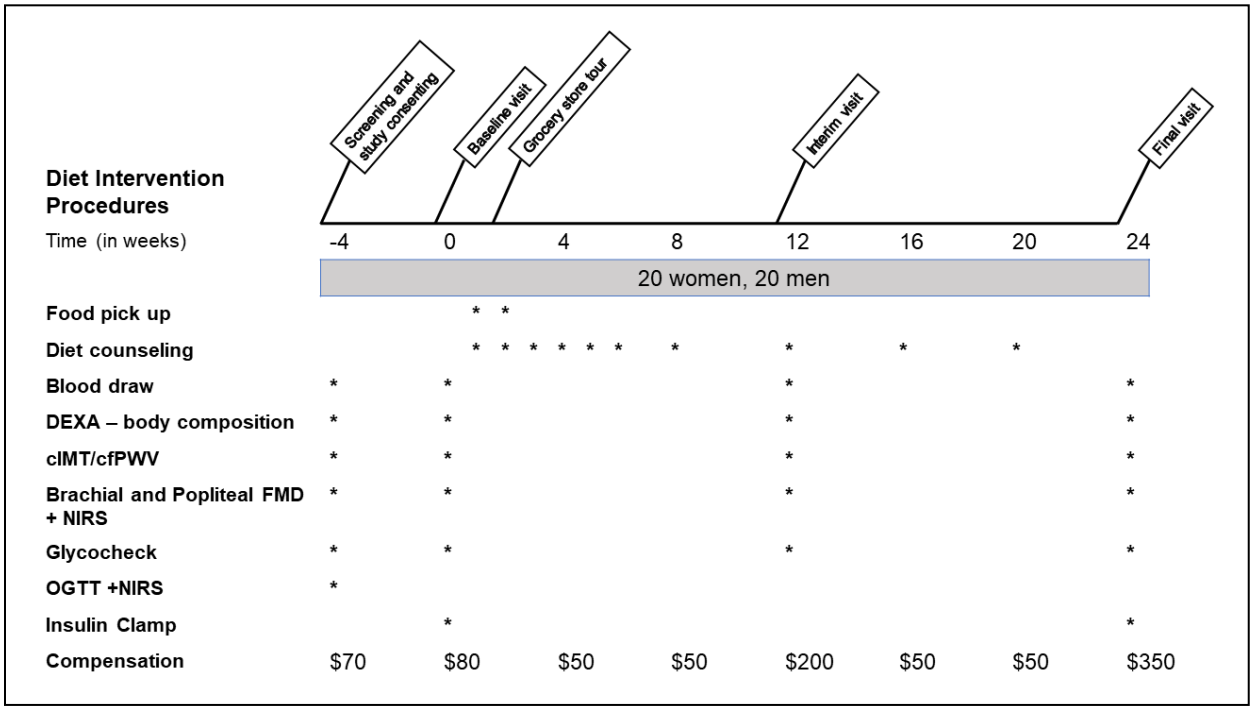

Figure 5. Study procedures and compensation for the diet interventions.

PART 2, DRUG THERAPY

If you are enrolled into this part of the research, you will take the drug allopurinol or placebo every day for 6 months. The allopurinol drug slows production of uric acid in your body and is commonly given to individuals with gout, which is a complication of high uric acid. Although you do not have gout, the study physicians Dr. Camila Manrique and Dr. Celso Velazquez, will work with you to take the drug to limit side effects that could occur like nausea or pain in your joints, and skin rashes. The complete risks of the drug will be discussed with you if you are randomized to that arm. This part of the study will not

involve any changes in your diet. You will come into the CRC for a baseline visit, and then every two weeks for 8 weeks to monitor and adjust your drug dose as needed. At 3 months, you will come in to the CRC for an interim visit, and then after 6 months you will come back one more time for a final visit. Between the interim visit and the final visit, you will come every 4 weeks for blood draw. Once you are assigned to a treatment, you will participate in three visits at the CRC. Each visit will take up to 8 hours. As shown in **Figure 6**, you will have a number of tests performed to measure your vessel function.

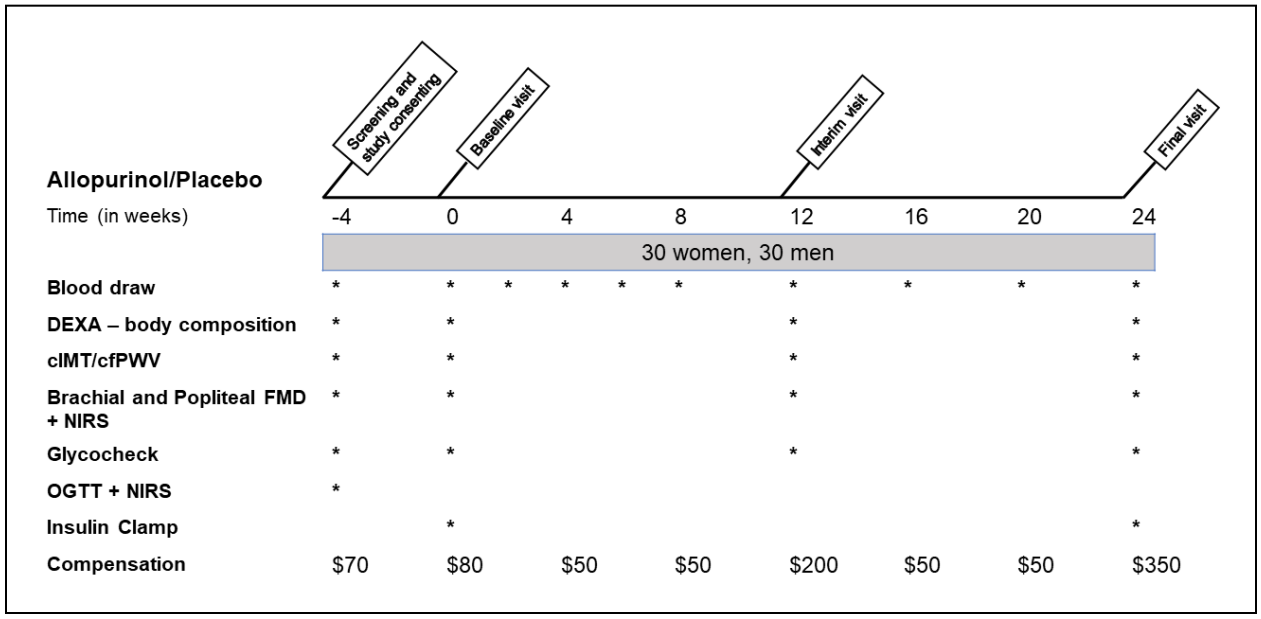

Figure 6. Study Procedures and compensation for medication/placebo intervention.

PART 3, DIET THERAPY (LOW FRUCTOSE, WEIGHT LOSS)

If you are enrolled into this part of the research, you will consume a low-fructose, reduce calorie diet for a 6-month period. For the first two weeks, all of your food will be provided while you learn how to limit your intake of fructose and simple sugars. After that, to better help you learn to eat the diet, you will have several meetings with a dietitian nutritionist over 6 months. You will come into the CRC for a baseline visit, again after 3 months for an interim visit, and one more time after 6 months for a final visit.

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.

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.

Perflutren (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 subjects 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.

Pulse wave velocity (PWV)
The blood pressure cuff will squeeze the arm and leg tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released.

Carotid intima-media thickness (cIMT)
There are no risks associated with this procedure

Oral glucose tolerance test (OGTT)
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. Ingestion of glutol (glucose drink) can cause nausea in some individuals.

Glycocheck
There are no risks associated with this test.

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

Flow-mediated dilation via doppler ultrasound (FMD)
There is a tightness felt when the cuff is inflated

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.

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 childcare during this study.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

As seen in Error! Reference source not found. **and** Error! Reference source not found.**,** 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, you will also be compensated monthly for your participation in the study ($50/per month that does not include a full CRC 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 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*	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