IRB Protocol # 2000022193
NCT03746535

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Title of Project: Cardiovascular disease risk in women with endometriosis: **Healthy Controls**

Principal Investigator (the person who is responsible for this research): Nina Stachenfeld, Ph.D.
Yale School of Medicine 333 Cedar St. New Haven, CT 06510
Phone Number: 203-562-9901 x219
24-Hour Phone Number: Dr. Hugh Taylor 203-785-4247 or 203-785-4708, Dr. Victoria Wesevich 203-785-4708

Subject's Printed Name: _____

We are asking you to be in a research study. This form gives you information about the research.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.

Please ask questions about anything that is unclear to you and take your time to make your choice.

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to look at the effect of estrogen suppression on skin blood flow.
- Study procedures will include:
    - Flow mediated vasodilation
    - Skin blood flow studies with microdialysis
    - Taking a drug "Elagolix", which will suppress estrogen.

All subjects will be screened and undergo microvascular skin blood flow analysis two times, time before (baseline) and one time while taking a GnRH antagonist Elagolix. Thus, the research will involve 3 research visits to the lab over approximately 45 days.

- Visit 1 will take about 1 hour, visits 2-3 will take about 6 hours.
- There are some risks from participating in this study. You may experience minor bruising and discomfort from needles, some symptoms associated with the Elagolix.
- The study may have no benefits to you. The results could benefit medical science, as we hope to gain an improved understanding of the effects of estrogen on cardiovascular regulation in women with endometriosis.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

1. Why is this research study being done?

Endometriosis, a disorder that occurs in women, is when tissue normally found inside the womb is also found outside of the womb. This disorder impairs the function of the endothelium, the cells that line the body's blood vessels (endothelium). The endothelium helps to control blood flow in healthy vessels.

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Women with this disorder not only have an increased risk for high blood pressure and high cholesterol, but they also have an increased risk for cardiovascular disease.

With this study, we will learn how endometriosis impairs the lining of blood vessels and increases the risk for disease.

Why is this study being offered to me?

We are asking you to be a part of this research study because you fit our criteria for being a subject. We are asking you to take part in a research study because you are a young (18-45 years old) woman who does not have endometriosis. We are looking for 12 healthy, control participants to be part of this research study.

2. What will happen in this research study?

You will visit the lab on three separate occasions. Please read the descriptions of the visits and procedures below.

We may ask you to repeat a trial, procedure, or test. This could happen for many reasons such as equipment failure, power outage, inconclusive test results, etc. You do not have to repeat a trial, procedure, and/or test if you do not wish to do so

What are you asking me to do and how long will it take?

If you agree to take part in this study, this is what will happen:

The research will involve 3 visits to the lab over approximately 45 days.

Visit 1: Screening, informed consent, orientation.
Visit 2: (before taking Elagolix): Physiological studies
Visit 3: (while taking Elagolix): Physiological studies

Note: This study involves the use of drugs that are not approved by the FDA to treat disease. All of the drugs have been used in humans by us or others. We dilute the drugs in Lactated Ringer's, a type of saline fluid like that found throughout your body. The drugs are:
Elagolix – an FDA approved drug that stops your brain from releasing the hormones that make your ovaries release an egg, therefore this drug suppresses your estrogens and progesterone.
Acetylcholine – like a substance made by your body; causes blood vessels to dilate.
Estradiol – a naturally occurring hormone in your body.
Sodium nitroprusside – supplies nitric oxide; causes blood vessels to dilate.
Nitroglycerin – supplies nitric oxide; causes blood vessels to dilate.

A. Screening Visit

Visit 1: We will describe the study to you in detail. You will fill out a medical history form so we can make sure it is safe for you to be in this study. You will be given a pregnancy test at no cost to you. If you are eligible for the study and decide to participate, we will tell you about taking Elagolix, a drug that will be used in this study. We will also show you the room where the research studies will be done and demonstrate the equipment and procedures that will be used for the study.

1. You are to not eat, and drink only water, for 8 hours before the screening.
2. The Principal Investigator and/or study staff will perform the screening. The staff measures your height and weight, blood pressure (BP), heart rate (HR) and waist circumference. The staff reviews

your medical history. Women of childbearing age must provide a urine sample for a pregnancy test. Endometriosis patients will take an Endometriosis Health Survey.

3. The staff will draw 15 ml (1 Tbsp) of blood from a vein in your arm. We will send some of the blood to a lab to see if the proteins, blood cells, electrolytes, etc. are within normal range. We may test the blood for other substances of interest.
4. The researchers do not perform genetic tests on the blood nor look for disease (e.g. HIV).

Dosing schedule: Before the second study, you will take Elagolix pills for 4-7 days. Elagolix will be the study drug.

Elagolix Dose

1. If you are menstruating regularly, you will start taking Elagolix at the same time each day within the first week of getting your period.
2. We will give you a pregnancy test to take at home that first day. If you are pregnant, you should not start the Elagolix.
3. We plan for you to take Elagolix for 4 days, but you may take Elagolix longer should scheduling deem it necessary. You will not take Elagolix longer than 7 days.
    a. The dose of this drug is an F.D.A. approved dosage of 400 mg/day oral, 2 X 200 mg tablets/day. You will take one tablet each morning, and one tablet each night.
    b. You will come to the lab to pick up the pills. During that time, you must provide a urine sample for a pregnancy test. If the test is positive, we will not give you the pills and you will be withdrawn from the study.
4. We will give you verbal instructions about the therapy, as well as written instructions and information sheets to take home with you.
5. If you are allergic to Elagolix you will be excluded from the study.
6. If you have side effects from the Elagolix, such as hot flashes, etc.
    a. Call:
        i. Dr. Hugh Taylor, (Work/Clinic203-785-4247)
        ii. Study head, Nina Stachenfeld, Ph.D. (W: 203-562-9901 x219)
    b. See Section 3 below for more information.

B. Preparation for MD and FMD experiments

Visit 2 Physiological studies: We will ask you to wear a t-shirt to the lab. Before you begin taking Elagolix but in the first 7 days of your menstrual cycle, you will come back to the lab. You will be given a pregnancy test at no cost to you. You will be asked to provide a urine sample and you will be weighed. This visit will last about 6 hours. You will have a **Flow mediated Vasodilation (FMD) and a microdialysis (MD) tests.**

1. Do not drink alcohol in the 12 hours leading up to the experiment.
2. Do not drink caffeine (ex. coffee, tea, Coca Cola, chocolate) in the 12 hours leading up to the experiment.
3. On the day of the experiment
    a. Refrain from hard exercise, physical labor, and other tasks in which you might exert yourself more than you would on an easy walk.
    b. We will measure your blood pressure, heart rate, and oral temperature.
    c. All women of childbearing age who must provide a urine sample for a pregnancy test.

d. We draw 15 ml (about 1 tablespoons) of blood to analyze for relevant substances of interest, including levels of hormones related to blood pressure and reproductive function and cytokines to determine your immune function.

C. Flow Mediated Dilation (FMD)**:**

a. First, a blood pressure cuff will be placed around your forearm.
b. We will then place ultrasound gel on your upper arm, just above the elbow. This facilitates the movement of sound waves from the ultrasound probe into your body, allowing us to measure the size of your blood vessels and the speed of your blood.
c. We will first take a "resting" measurement, then inflate the cuff for 5 minutes to stop blood flow to and from the forearm.
d. After 5 minutes, we will deflate the cuff and obtain a second measurement for 3 minutes.
e. We will then repeat steps 1-6, but this time you will also be performing a hand grip exercise at 20% of your maximal handgrip strength for 2 or 3 minutes while the cuff is inflated.

D. Microdiaylsis (MD):

a. We will insert the microdialysis (MD) probes:
    i. After you wash the skin on your forearm, we will place a tight band around the forearm to ensure your veins are easily visible.
    ii. For each MD site, we make pairs of pen-marks on the arm 2.5 cm (1 inch) apart and away from any veins. The marks serve as entry and exit points for the MD tubing. We then remove the tight band.
    iii. We will clean the arm with alcohol, after which an ice bag will be placed on the site for 5 minutes to numb the skin.
    iv. We will then insert a thin needle into the skin near each entry mark. The needle's tip travels between the layers of skin for 2.5 cm (1 inch). The needle exits the skin near the matching exit-mark.
    v. We will thread the MD tubing through the needle and then withdraw the needle leaving the tubing in the skin.
    vi. We will prepare 3 MD sites.
    vii. Any skin redness caused by the insertion fades in about 60 minutes. During this time, Lactated Ringer's, a saline fluid similar to that found throughout your body, flows through the MD-tubing.
b. Skin Blood Flow (SkBF):
    i. We tape a thin fiber optic laser Doppler flowmeter probe and its holder over each MD site.
    ii. The thin probe measures skin blood flow with a weak laser light. We measure skin blood flow throughout the experiment.
    iii. We control the temperature of the holders. The holders start at 34°C (93°F).
    iv. We will also use one laser Doppler flowmeter probe and its holder with no MD probe and heat the probe to 40°C (104°F) for approximately 40 minutes. At the end of the heating, we will place a nitroglycerin patch under the probe and measure your skin blood for about 15 more minutes. This will happen during the MD studies.
c. Heart Rate: We place 3 ECG tabs on your chest and connect them to an ECG machine.

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d. Blood pressure: We may use two methods to measure blood pressure. Both methods use a cuff that inflates on your upper arm. In one, we listen with a stethoscope at the inside of your elbow. Another method, a Finometer, makes the measure from a cuff on your finger. The Finometer also measures heart rate. During the experiment, we record blood pressure and heart rate from your finger continuously.

e. If you are a participant with endometriosis, you will take the Endometriosis Symptoms Survey: we will ask you to fill out a questionnaire to ask you about your quality of life (QoL). This survey includes questions about feeling both physical and emotional pain associated with your endometriosis. If you are a Control subject, you will not take this survey.

E. MD Experiment

Probe 1. Lactated Ringer's only (control)
Probe 2. Lactated Ringer's + estradiol
Probe 3. Lactated Ringer's + Acetylcholine
Probe 4. Local Heating at 40°C (104°F)

Probes 1 – 3. MD Sites

1. First, we will add the Lactated Ringer's to the MD sites as stated above.
2. After 30 minutes we will add estradiol to probe 2 and Acetylcholine to probe 3.
3. Then every 10--15 minutes we will increase the dose of estradiol until the probe 2 site receives 5 total doses; at the same time, we will increase the dosage of Acetylcholine every 5 minutes until the probe 2 site receives 10 total doses.
4. Once the final dose of estradiol and Acetylcholine have been delivered, all test substances will be removed from all sites, with the exception of Lactated Ringer's. This leaves only Lactated Ringer's flowing through the tubing.
5. With Lactated Ringer's continuing to flow, we will then warm the probe holders at all sites to 43°C (108°F).
6. Once the probes reach 43°C (108°F), we will wait 30 minutes and then add Sodium Nitroprusside to all sites. While ensuring the temperature remains at 43°C (109°F), adding Sodium Nitroprusside will cause the blood vessels at those sites to dilate as much possible.
7. 10 minutes after receiving Sodium Nitroprusside, we will remove the MD tubing from your skin. Sterile bandages will be placed over the sites, and we can provide an ice bag to reduce the chance the chance of bruising, if you wish.
8. Lastly, we will measure blood pressure and heart rate before you depart.

Probe 4. Local Heating (no MD probe)

1. When estradiol is added to probe 2 and Acetylcholine is added to probe 3, the probe holder on site 4 will be warmed to 40°C (104°F) for approximately 40 minutes.
2. Then, the probe will be heated to 43°C (108°F).
3. Once the probe reaches 43°C (109°F), we will wait approximately 30 minutes and then place a nitroglycerin patch under the probe. While ensuring the temperature remains at 43°C (109°F), adding nitroglycerin will cause the blood vessels at this site to dilate as much as possible.
4. 15 minutes after placing the nitroglycerin patch, we will remove it and clean the skin.

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Visit 3. Physiological studies**:** This is the same as Visit 2. It will happen at least 4 days after you begin taking Elagolix.

Taking other medications while in this study:

1) While you are in this study, if you are sexually active, you must use a barrier method of birth control such as condoms or a diaphragm. You cannot use hormone methods like the pill or patch. You cannot count on Elagolix to prevent pregnancy. You cannot take other forms of hormones including estrogens, progestins or androgens.

2) You can take Tylenol but should not take Advil (ibuprofen).

3) If you find you need to take medication in case of an emergency or change in your health status, please call Dr. Taylor for guidance (203-785-4247 or 203-785-4708).

3. What are the risks and possible discomforts from being in this research study?

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Elagolix may stop your normal menstrual cycle. There is a risk that you may begin to have "hot flashes" after using the drug for about a week. You may also feel some mood changes during the first 24 hours you are on it. You may have headaches or bloating. The month you are on Elagolix, your period may come earlier or later than you expect and the flow may be heavier or lighter than usual. As far as we know, there are no long-term side effects of Elagolix.

IV placement can cause discomfort, bruising, and rarely, infection or formation of a clot.

Microdialysis (MD): The risks are less than that for a blood draw because microdialysis uses only a small, local area of skin. In contrast, a blood draw involves not only skin, but also large blood vessels and blood. In an effort to lessen any small amount of pain and bruising you might experience, similar to a blood draw, ice will be used to numb your arm when we insert the tubing. In addition, the small needle reduces any pain when we insert the tubing. You are not likely to have pain after the tubing is in place. You may feel a little pain when we remove the tubing from your skin. Needles make some people feel lightheaded or cause them to faint. Although rare, should the tubing break as we remove it from the skin, the remaining tubing will be removed by pulling on the other end. This presents no added risk for you. While even more rare, there is a possibility the tubing may break, leaving a piece under your skin; should this happen, we will remove it similar to how you would a splinter. We stop any bleeding with mild pressure and sterile gauze. Though infection is possible, the risk is very small because we use sterile techniques and supplies, like those used with blood draws. We apply a sterile bandage to the site after the experiment. You will be given instructions on how to care for the site.

Fluid flowing through the tubing: The substances flowing through the tubing only go to a 2.5 cm^2 (0.4 $inch^2$) area of skin at each tubing site. The amount that enters the skin is very small; however, there is a chance of having a bad reaction to the substances. A mild reaction might produce redness, itching, rash, and/or swelling, while a worse reaction could cause fever, breathing problems, changes in pulse,

convulsions, and/or fainting. Although rare, you could feel lightheaded. You could feel sick to your stomach or vomit, and you may become flushed or feel like your heart is pounding. We end the MD procedure if you have any of these signs and symptoms. We and other researchers have used these substances with microdialysis in skin, and there have been no reports of lasting, bad reactions. If a bad reaction should occur, we summon medical help.

Nitroglycerin is a substance used to prevent chest pain in people who have this. Nitroglycerin can cause low blood pressure (hypotension), and a potential allergic reaction to the nitroglycerin and patch adhesive**.** Although rare, you could feel lightheaded, or you could feel sick to your stomach or vomit. If this happens, we will end the procedure. We and other researchers have used nitroglycerin in skin, and there have been no reports of lasting, bad reactions. If a bad reaction should occur, we summon medical help. Headaches are the most common side effect of nitroglycerin treatment; however this side effect has been reported with daily treatment for 12-14 hours. You will only have 15 minutes of nitroglycerin treatment for each experiment. If you develop a headache, we will end the procedure. Additionally, this patch uses adhesives to stick to the skin. You must inform us if you are allergic to adhesives and decline to participate in the study.

Lactated Ringer's Solution: This fluid, containing salt, potassium, lactate and chloride, is similar to the natural fluids in your skin. The acid content is like that of your body's natural fluids. A bad reaction to this fluid is highly unlikely.

Acetylcholine, estradiol, Sodium Nitroprusside: These substances stop or mimic the action of your body's natural chemicals upon the blood vessels in the skin. A small amount of these substances enter the skin around the tubing. This only affects the blood flow in the vessels in a nickel-sized area of skin. The effect of these substances is gone within an hour after the experiment. The doses of the drugs in this study are very low, so the risk of the rest of your body reacting to sodium nitroprusside, estrogen and Acetylcholine is very small.

Laser Doppler Flowmetry: Weak lasers can hurt your eye if you stare into the light for a long time. We do not turn on the laser until the probes are taped to a surface. The tape may irritate your skin.

Local heating: We measure the temperature of your skin under the holders. During heating, the skin feels very warm but will not hurt. The heating makes the skin under the holder red like when you take a hot bath. The redness goes away within several hours. Some people may be more sensitive to heating. If your arm feels too hot, tell us, and we reduce or stop the heating.

Blood drawing: Over the course of the study you will have about 3 Tablespoons (45 ml) of blood drawn. Blood draws can cause mild pain, bruising, swelling, or bleeding. There is also a slight chance of infection or a small clot. If you are nervous about needles, your blood pressure and heart rate may increase for a little while. You may also feel lightheaded, sick to your stomach, or may faint. By using the same techniques employed in hospitals, we keep the chance of infection minimal. Do not exercise hard for 24 hours before a blood draw.

The Flow Mediated Vasodilation testing requires the inflation of a blood pressure cuff, which may result in some temporary mild discomfort similar to that experienced if your arm went numb if you fell asleep on it. There is a small chance the probe could irritate the skin. Although temporary, minor redness may occur where the researchers place the probe against the arm. The gel is the same as that used with medical ultrasound tests, and may feel cool or cold on the skin. A bad reaction to the gel is highly unlikely.

Blood Pressure (manual, Finometer): The researchers measure blood pressure with the method used in a doctor's office and/or they can use a machine. The cuff will first inflate on your upper arm, then as the cuff slowly deflates, the researchers listen with a stethoscope at the bend in the elbow. During the short time the researchers inflate the cuff, your arm may feel numb or tingly. The cuff could cause mild bruising. The Finometer works by slowly inflating and deflating on one of your fingers. This can make your finger feel number after it has been working for a long time. We try to reduce this by turning off the Finometer when we are not making measurements. If your finger becomes uncomfortable, let us know and we can move the cuff to a different finger or turn the machine off briefly.

Povidone Iodine: Researchers and hospitals use this orange-colored fluid to clean the skin. You should inform us if you are allergic to iodine, as this could cause you to have a bad reaction to this fluid. In this case, we use only alcohol instead. A bad reaction could cause redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse, convulsions, and/or fainting.

Latex: Some gloves and medical materials are made of latex rubber. You must inform us if you are allergic to latex and decline to participate in the study**.**

Tape and sticky disks: The tape or sticky disks could cause a rash. During screening, you tell us if you are sensitive to tape. If a disk sticks very strongly, removing the disk could cause an abrasion, like a rug-burn on your skin. An abrasion can feel tender or slightly painful, and can increase risk of infection. If you are sensitive to tape, you may have an increased chance for abrasion. An abrasion has occurred only twice during the years that the disks have been used in similar studies in our lab. We may use an adhesive remover like that used in a doctor's office to remove the disks. If you get an abrasion antibiotic ointment and a sterile bandage are applied. We tell you how to take care of the site. You could have an allergic reaction to the adhesive remover which could include rash, itching, fever, or breathing problems. Also, it could include changes in pulse, and/or blood pressure, convulsions, shock, and/or fainting. If a bad reaction should occur, we summon medical help right away.

Medical Screening: You may feel shy about giving health information. We will take your height and weight, and a small blood sample. We will measure your blood pressure and take your heart rate. Dr. Taylor will also discuss your general medical history and experiences you have and review medical records. We will also ask about any medications you take, and any special dietary and activity habits you have. We also discuss your menstrual history and whether you have regular menstrual cycles. The staff collects the information in a private and professional manner. You may feel shy about being measured. You may request someone of the same sex to conduct the screening.

Our studies may involve risks to you (or to the embryo or fetus, if you are (or become pregnant) that are currently unforeseeable.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to you?

You will receive a medical screening that could inform you about your health. You will learn the cholesterol level in your blood and your blood pressure. This knowledge is important because high blood pressure and blood cholesterol can lead to many serious health problems. If you have high blood pressure or blood cholesterol, we suggest that you to follow-up with a health care provider. You will also feel good knowing you are helping to identify the reasons for the increased risk for CVD in women with endometriosis.

4b. What are the possible benefits to others?

Endometriosis causes chronic pelvic pain and pain during intercourse. It also can reduce or end a woman's ability to bear children. This disorder affects 6% - 10% of women of childbearing age, and can occur in as many as 35-50% of women who have pain or cannot bear children. Despite these statistics, little research has been devoted to this disorder. This research can help to draw attention to the importance of this malady to women's health.

In addition, endometriosis impairs the function of the "endothelium" or the lining of blood vessels. Impaired endothelium increases the risk for getting high blood pressure and high blood cholesterol, and is a hallmark of cardiovascular disease (CVD). CVD is the leading cause of death in women. Women with endometriosis have an increased risk for these diseases. This study will expand the knowledge base regarding the mechanisms by which endometriosis increases risk for these diseases in women. The data from this study serve as a foundation for further investigation.

5. What other options are available instead of being in this research study?

Instead of participating in this study, you have some other choices.

If you do not wish to participate in this study, you will continue to be treated by your clinician and your care will not be jeopardized in any way. If you don't want to be a part of this study, you have some other choices.

- You can choose not to participate.
- Take part in another study.

6. How long will you take part in this research study?

Screening (1 Visit)	less than 1.5 hour/visit
Pill Pick up (2 Visits)	less than 0.25 hour/visit
MD/FMD Experiments (2 Visits)	6 hours/visit
Total: ~14-14.50 Hours	

7. How will your privacy and confidentiality be protected if you decide to take part in this research study?

We make efforts to limit the use and sharing of your personal research information to people who have a need to review this information.

- We keep the list that matches your name with your code number in a locked file. Only authorized members of the lab have access to these files.
- We label your research records with your code number and keep them in a locked file or password protected computer in a room that is locked when unoccupied.
- We label your research samples with your code number. We keep some samples in a dedicated ultralow freezer at the Yale School of Medicine until analysis.
- In the event of any publication or presentation resulting from the research, we do not share your personally identifiable information.

7a. What happens to the information collected for the research?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person. De-identified research data is shared with Penn State University.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research but we will not use your name or other ways that you could be identified (identifiers). We will not ask you for any additional permission. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. You will be identified within the laboratory with code names and numbers. We will keep files for 25 years after the study is completed.

Yale Human Investigation Committee (the committee that reviews, approves and monitors research on humans) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and social security number. This information will be "de-identified" at the earliest reasonable time after we receive it. That means we will replace your identifying information with code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. We store your personal information in locked cabinets, and do not use your name on our computers relating to the study. You are identified with code numbers or initials on password-protected computers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for no more than 25 years after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form for 25 years until it is destroyed.

7b. What will happen to my research information and/or samples after the study is completed?
The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

7c. How will my identifiable health information be used?
Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by The Yale School of Medicine created from: 2021 to: 2046

Including:

- Records about phone calls made as part of this research
- Records about your study visits
- Records about any study drug you received

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at The Yale School of Medicine who are responsible for the financial oversight of research including billings and payments
- The study sponsors
- The Principal Investigator, Dr. Nina Stachenfeld and the research team.
- Co-Investigators and other investigators
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan
- Your providers who are participants in the Electronic Medical Record (EMR) system
- Food and Drug Administration
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

Identifiers might be removed from your identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Your biospecimens (with identifiers removed) may be used for commercial profit and you will not share in this commercial profit.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital, and Yale Medical Group are required to comply with HIPAA and to ensure the confidentiality of your information.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission. We will also share information about

you with other researchers for future research but we will not use your name or other identifiers. We will not ask you for any additional permission.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

What will happen with my data if I stop participating?
When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used for analysis and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

8. What are the costs of taking part in this research study?
8a. What will you have to pay for if you take part in this research study?
If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits.

8b. What happens if you are injured as a result of taking part in this research study?
If you are injured while on the study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine does not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment.

You will be responsible for any co-payments required by your insurance.

No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form.

9. <u>Will I be paid for participation?</u>

Screening/orientation	$ 40.00	Review and sign consent form, experimental shown procedures
MD Experiment:	$ 120.00	($ 20.00 / MD probe inserted) (3 MD probes/experiment; 2 total experiments)
FMD Experiment:	$ 100.00	($50.00 each: 2 total experiments)
Elagolix	$ 20.00	($ 5/day)
Finishing Bonus	$ 100.00	(for completing all experiments)
Total	$ 380.00	

If you do not complete all parts of the study, you will be paid for the parts you completed. You will be paid by pre-paid debit card at the end of the study. We will have to share your name, address, and telephone number with the banking institution issuing the debit card for ePayments. You will need to

activate the card over the phone. You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments. If you need transportation the laboratory will reimburse you up to $20 each visit.

10. Who is paying for the study?

The National Institutes of Health

11. What are your rights if you take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.
- *If you choose to withdraw from the study, all data collected up to the point of withdrawal will remain part of the study and may not be removed.*

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include adverse reaction to the Elagolix. Other possible reasons for removal from the study include if the researcher deems that your health or behavior adversely affects the study or increases risks to you beyond those approved by the Institutional Review Board and agreed upon by you in this document. You may decline to answer certain questions. You may decide not to comply with certain procedures. However, your being in the study may be contingent upon answering these questions or complying with the procedures.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If you have questions or concerns about this research study, whom should you call?

Please feel free to ask about anything you don't understand.

Please call:

- Study head, Nina S. Stachenfeld, Ph.D. (W: 203-562-9901)
- The Study Doctor, Hugh Taylor 203-785-4247 or 203-785-4708

if you:

- Have questions, complaints or concerns about the research
- Believe you may have been harmed by being in the research study
- If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or contact the Office for Research Protections at (814) 865-1775, OR Protections@psu.edu

13. Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

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The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to *Nina Stachenfeld, 333 Cedar Street, New Haven, CT 06510* at the Yale School of Medicine, New Haven, CT 06510.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

What if I want to refuse or end participation before the study is over?
Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at 203-562-9901**.**

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Research Protection Program at (203) 785-4688 or email hrpp@yale.edu.

Certificate of Confidentiality
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

AUTHORIZATION AND INFORMED CONSENT TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

_____	_____	_____
Signature of person who explained this research	Date	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

_____	_____	_____
Signature of Subject	Date	Printed Name

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