Informed Consent Form

Mechanism and Predictors of Cardiotoxicity after Prostate Cancer Treatment: A Parallel Cohort and Randomized Trial Comparing Radiation Alone, Radiation plus Leuprolide, and Radiation plus Relugolix

NCT Number: NCT05320406

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You Are Being Asked to Be in a Research Study

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study you will be one of 94 people who are being studied, at Emory.

Why is this study being done?
This study is being done to assess the impact of prostate cancer treatment, specifically hormone therapy, on the heart. Recently, the effect of hormone therapy that is routinely used for prostate cancer on the heart has emerged as a concern, yet studies to identify who is at risk and how damage to the heart may occur are lacking. Additionally, a new hormone therapy drug, relugolix, has recently been FDA-approved and may reduce toxicity to the heart. This study intends to further investigate the impact of standard hormone therapy and relugolix (compared with no hormone therapy) on the heart.

You are being asked to be in this research study because you have been diagnosed with prostate cancer and will be treated with radiation therapy with or without hormone therapy (determined by your doctor based on the aggressiveness of your cancer).

Do you have to be in the study?
It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. However, if you will be receiving radiation therapy with hormone therapy, you will not be eligible for the new hormone therapy drug, relugolix, if you choose not to be on study. You will receive standard hormone therapy (e.g. Lupron) in this scenario. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?
If you are eligible and want to be part of the study, you will participate for the duration of treatment and a follow-up period. Your visits will include your standard radiation treatment visits, PSA blood draw visits, and two additional two study visits (before and after treatment) where sophisticated imaging will be conducted on your heart. The total duration of study is 12 months; however, only 2 additional clinic visits on top of your standard appointments will be required (for the cardiac imaging tests, where sophisticated pictures of your heart will be taken).

The researchers will ask you to do the following: complete study cardiac imaging tests, complete standard radiation treatment and hormone therapy visits as prescribed by your doctor, and complete bloodwork studies, which will include standard PSA measurements as needed by your doctor, as well as additional blood tubes taken which will be used for research studies. All of these procedures will be paid for by the study or billed to your insurance.

How is this study going to help you?
If you are in the study, you will be helping the researchers answer the study question which will impact prostate cancer patients in the future. Additionally, you will be given the opportunity to undergo sophisticated cardiac imaging tests to evaluate your heart function at no cost to you. This study is not designed to benefit you directly.

What are the risks or discomforts I should know about before making a decision?
The study will take time with two additional clinical visits for cardiac imaging (which will be completed before you start treatment, and then again 6 to 12 months later). If you are prescribed hormone therapy by your physician, you will be randomly assigned to receive standard hormone therapy (e.g. Lupron) or relugolix. There is a 50% chance you will receive standard hormone therapy, and a 50% chance you will receive relugolix. The treatment is not expected to be any better or worse in terms of ability to kill the cancer, though side effects may be better with relugolix.

All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include rare risks associated with cardiac imaging test, specifically allergic reaction to contrast. More generally, there is risk of loss of privacy and breach of confidentiality, though very strict measures are taken to ensure privacy of all patients on study. A full list of expected risks are in the “What are the possible risks and discomforts?” section of this document.

Alternatives to Joining This Study
If you are not interested in participating in this study, you will still be offered standard of care treatment for your prostate cancer. If you require hormone therapy, you will be prescribed standard hormone therapy (e.g. Lupron). The cardiac imaging tests done in this study are not routinely done for patients with prostate cancer, but it could be ordered by your cardiologist.

Costs

The study will pay for certain items and services that you may receive if you take part in this study. The study will pay for the relugolix medication given in this study, but leuprolide (e.g. Lupron) injections is not covered by the study and will be billed to your insurance. Additionally, you or your insurance, however, will have to pay for the items or services for which the study does not pay, such as radiation therapy. The study will not pay for your regular medical care or clinic visits.

What Should I Do Next?

Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Make sure you understand which parts of the study are research and which are standard care that you would have even if you did not join the study. Take time to consider this, and talk about it with your family and friends.

Emory University and Saint Joseph's Hospital
Consent to be a Research Subject / HIPAA Authorization

Title: Mechanism and Predictors of Cardiotoxicity after Prostate Cancer Treatment: A Parallel Cohort and Randomized Trial Comparing Radiation Alone, Radiation plus Leuprolide, and Radiation plus Relugolix

IRB #: STUDY00003654

Principal Investigator: Sagar A. Patel, MD

Study Sponsor: Pfizer Inc, Myovant Sciences, Prostate Cancer Foundation

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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

What is the purpose of this study?
The purpose of this study is to investigate the impact of hormone therapy used for prostate cancer on the heart. This study will assess your heart function before and after treatment using sophisticated heart imaging (i.e. cardiac computed tomography [CT]) and blood biomarkers. This study will identify which of these tests may be useable in the future to identify which men may be at highest risk of damage to the heart from hormone therapy.

What will I be asked to do?
If you are receiving hormone therapy as part of your treatment, you will be randomly assigned to receive one of two hormone therapy options: 1) lupron, or 2) relugolix. Both drugs are FDA-approved hormone therapy options for prostate cancer, as discussed above. You will be assigned randomly by a computer to one of the drugs, and there is a 50% chance you will receive either drug.

If you are receiving radiation alone *without* hormone therapy, you will not be assigned to any hormone therapy drug.

This study asks you to do several things, but almost all of them would be done as standard of care if you were not on this study. Before starting your treatment, you will be asked to undergo your first cardiac imaging test, which is a 1-hour appointment where one of our cardiologists will take sophisticated pictures of your heart using a CT scanner. Additionally, you will also undergo standard pre-treatment blood work (which would happen regardless of whether you were on the study); however, additional tubes of blood will be drawn (approximately 2 tablespoons) and stored for the research studies (NOTE: there will **not** be additional needle sticks required for this).

Next, you will undergo standard-protocol radiation treatment visits (with or without hormone therapy, depending on your treatment plan with your doctor) and blood draw visits (to check PSA and testosterone levels in your body), all of which would happen regardless of whether you were on the study. At the time of the standard blood draws, three additional tubes of blood will be drawn and stored for research studies (NOTE: there will **not** be additional needle sticks required for this).

Finally, 6-12 months after your first cardiac imaging test, you will undergo another cardiac CT with one of our cardiologists, where sophisticated pictures of your heart using a CT scanner will be taken again.

Following completion of the second cardiac imaging test, you will continue standard of care follow-up for your prostate cancer with your doctor and clinical providers.

How will my medicine be provided?
If you are undergoing radiation therapy alone, this section does not apply to you. All your treatments will be coordinated by your treating doctor.

If you are undergoing radiation therapy with hormone therapy, you will be randomly assigned to receive standard hormone therapy (e.g. Lupron) or relugolix, both of which are FDA-approved hormone therapy agents for prostate cancer. Standard hormone therapy (e.g. Lupron) is administered as an injection, and this will be scheduled by your treating doctor. Relugolix is taken as a daily oral tablet; if assigned to receive relugolix, the medicine will be dispensed by the pharmacy and delivered to the principal investigator or study team member and provided directly to you at a clinic visit. If you have questions about the medicine, you should ask the study doctor or study research coordinator. You may also call the pharmacy at [redacted] if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

Who owns my study information and samples?
If you join this study, you will be donating your blood samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

What are the possible risks and discomforts?
The most common risks and discomforts in this study are related to known side effects of hormone therapy (similar for standard hormone therapy and relugolix), which typically resolve with time after completing hormone therapy:

- Common (10-25%) – fatigue, hot flashes, decreased libido, erectile dysfunction, weight gain, glucose increase, triglyceride increase
- Occasional (5-10%) – constipation or diarrhea, joint pains, muscle mass loss, hypertension, abnormal liver enzymes, decreased hemoglobin levels in blood
- Rare (<5%) – bone density loss

Additionally, the following common side effects are often observed during or after completion of radiation therapy (e.g. external beam radiation therapy, proton beam therapy, brachytherapy), which typically resolved with time after treatment:

- Common (20-50%) – urinary frequency, urinary urgency
- Occasional (5-20%) – loose bowel movements or diarrhea, weak urinary stream
- Rare (<5%) – burning with urination, rectal bleeding

Finally, you will undergo two CT imaging tests of your heart, called a cardiac CT before starting treatment and 12 months later. You will receive intravenous iodinated contrast (i.e. dye) for this imaging test. The dye makes it easier to see normal anatomy and abnormalities in your heart on the images. Occasional (5-10%) complications of contrast material include mild allergic reactions (e.g. itching, hives); rarely (<5%), you may have a severe allergic reaction (e.g. anaphylaxis). If you have a known allergy to iodinated contrast, it is very important for you to let your doctor know, as appropriate preventative steps can be taken, or the imaging test can be avoided altogether. You will be exposed to radiation from CT scans. These procedures are not necessary for your medical care and will occur because you participate in this study. The estimated radiation dose that you will receive is significantly less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, x-ray technologist, radiologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study, however, is minimal.

If you are a man: the effect of the treatments on sperm is poorly defined. To protect against possible side effects, if you are a man you should not get a sexual partner pregnant while undergoing the study procedure and six months after the last dose. You and the study doctor should agree on a method of birth control to use throughout the study.

If you will be receiving relugolix for hormone therapy (which will be taken at home in the form of daily tablets), keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

This study is not designed to benefit you directly. Your treatment to cure your cancer is expected to be no better or worse on this study. This study is designed to learn more about the effect of hormone therapy, especially between conventional hormone therapy (e.g. Lupron) versus relugolix, on the heart. The study results may be used to help other prostate cancer patients in the future.

Will I be compensated for my time and effort?

You will get $100 for each completed cardiac CT visit, to compensate you for your time and effort. If you do not finish the study, we will compensate you for the visit you have completed. You will get $200 total, if you complete all study visits. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options.

What are my other options?

If you decide not to enter this study, there is care available to you outside of this research study. You do not have to be in this study to be treated for prostate cancer. If you are undergoing radiation therapy alone, there is no change in your

treatment plan. If you are undergoing radiation therapy plus hormone therapy, you will receive standard hormone therapy (e.g. Lupron). The cardiac imaging tests done in this study are not routinely done for patients with prostate cancer, but it could be ordered by a cardiologist if you have one.

How will you protect my private information that you collect in this study?
Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will never appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

How is my Genetic Information Protected? What are the Risks?
The Genetic Information Nondiscrimination Act (GINA) is a federal law that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that GINA does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, and does not apply to employers with less than 15 employees.

In addition to GINA, the State of Georgia has laws that prohibit insurers from using genetic testing information for any non-treatment purpose. However, like GINA, this state law protection has exclusions: life insurance policies, disability income policies, accidental death or dismemberment policies, Medicare supplement policies, long-term care insurance policies, credit insurance policies, specified disease policies, hospital indemnity policies, blanket accident and sickness policies, franchise policies issued on an insurance policy written as a part of workers' compensation equivalent coverage, or other similar limited accident and sickness policies.

Privilege
In the State of Georgia, in some circumstances your genetic information may have special legal protections called "privilege." This means that the information cannot be used as evidence in a court. By allowing us to use and disclose your genetic information for this research study along with other information about you that genetic information used in the research may no longer have that legal protection. Other protections described in this form will still apply. There are also other confidentiality protections for research data in general under Georgia state law.

Storing and Sharing your Information
De-identified data from this study (data that has been stripped of all information that can identify you), may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. We will remove or code any personal information that could identify you before your information is shared. This will ensure that, by current scientific standards and known methods, it is extremely unlikely that anyone would be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Your data and blood specimens from this study may be useful for other research being done by investigators at Emory. To help further science, we may provide your deidentified data and/or specimens to other researchers. If we do, we will not include any information that could identify you. If your data or specimens are labeled with your study ID, we will not allow the other investigators to link that ID to your identifiable information. If any commercially available product is developed as a research of research from your blood specimens, you will not be eligible for any compensation related to that product.

Medical Record

If you have been an Emory and Saint Joseph's Hospital patient before, then you already have an Emory and Saint Joseph's Hospital medical record. If you have never been an Emory and Saint Joseph's Hospital patient, you do not have one. An Emory and Saint Joseph's Hospital medical record will be made for you if an Emory Atlanta and Saint Joseph's Hospital provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory and Saint Joseph's Hospital medical record you have now or any time during the study.

Emory and Saint Joseph's Hospital may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory and Saint Joseph's Hospital medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: cardiac CT imaging results, research blood studies.

Tests and procedures done at non-Emory and Saint Joseph's Hospital places may not become part of your Emory and Saint Joseph's Hospital medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you believe you have become ill or injured from this research, you should contact Dr. Sagar Patel at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory and Saint Joseph's Hospital will help you to get medical treatment. Neither Emory and Saint Joseph's Hospital nor the sponsor have set aside money to pay for this medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

For Emory and Saint Joseph's Hospital, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory and Saint Joseph's Hospital employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Cost

The study sponsor will pay for certain items and services that you may receive if you take part in this study.

You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will

not pay for your regular medical care. If you have insurance, Emory will submit claims to your insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Standard hormone therapy with leuprolide (e.g. Lupron) will not be covered by the study and will be billed to the participant/insurance.

Withdrawal from the Study
You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done early, specifically:

- final cardiac CT scan
- final blood draw that will be stored for research studies

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study.

PHI that Will be Used/Disclosed:
The PHI that we will use or share for the research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form. If you do not sign this form, you may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- Pfizer Inc, Myovant Sciences, and the Prostate Cancer Foundation are the Sponsors of this study. The sponsors may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight of the study.
- The research team may use and disclose your PHI, including disclosure to insurance carriers to administer payment for subject injury.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory and Saint Joseph's Hospital offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Georgia Center for Oncology Research and Education (CORE)
    - Government agencies that regulate the research including: Food and Drug Administration
    - Research monitors and reviewer.
    - Accreditation agencies.
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Sagar A. Patel, MD
Assistant Professor
Department of Radiation Oncology
Winship Cancer Institute
Emory University School of Medicine
615 Peachtree Street NE
Atlanta, GA 30308
Email: [redacted]

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information
Contact Dr. Sagar Patel at [redacted] :

- if you have any questions about this study or your part in it,
- if you have questions, or concerns about the research

Contact the Emory Institutional Review Board at [redacted]:

- if you have questions about your rights as a research participant.
- if you have complaints about the research or an issue you rather discuss with someone outside the research team.

You may also let the IRB know about your experience as a research participant through our Research Participant Survey at **https://tinyurl.com/ycewgkke.**

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in this research study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the form to keep.

_____
Name of Subject

_____ _____ ____:____**am / pm**
Signature of Subject (18 or older and able to consent) **Date** **Time (please circle)**

TO BE FILLED OUT BY STUDY TEAM ONLY

_____
Name of Person Conducting Informed Consent Discussion

_____ _____ ____:____**am / pm**
Signature of Person Conducting Informed Consent Discussion **Date** **Time (please circle)**