VANDERBILT UNIVERSITY
MEDICAL CENTER

"TranspulmonarY Estrogen Gradient and Estrogen Receptor (TYEGER) in PAH"

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Study Title: **TranspulmonarY Estrogen Gradient and Estrogen Receptors (TYEGER) in PAH**
Version Date: 12/18/19
PI: Eric D. Austin, MD, MSCI

Name of participant:_____Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key information about this study:

You are being asked to take part in this research study because you are over 18 years of age with pulmonary arterial hypertension (PAH) or pulmonary venous hypertension (PVH). While there are multiple FDA-approved therapies for PAH no treatments are curative, and have additional limitations including high expense, multiple side effects, and inconveniences.

The strongest risk factor for pulmonary arterial hypertension (PAH) is female sex (~3:1 female:male ratio). Many researchers have found that estrogen is different in PAH patients as compared to healthy controls. Our evidence suggests that this different estrogen profile may increase the risk of developing PAH. New studies suggest that anti-estrogen therapy is effective for both prevention and treatment in a mouse model of PAH.

To help to determine which patients would benefit from anti-estrogen therapy, we propose a single-center study in which we would measure the amount of Estrogen Receptor Density within the lungs using a PET CT scan. About 40 subjects will take part in this study at Vanderbilt University Medical Center. All subjects will also be treated with background standard of care therapy at the discretion of their physician.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

ESR-specific PET study: Potential risks associated with being in this study include mental and physical risks, time lost, and loss of confidentiality. Mental risks may involve anxiety or distress from the study procedures. The level of anxiety from these studies is usually low. During the scans, some people may feel afraid of small spaces when they have to lay down without moving for as long as 30 minutes in the tube of the scanner.

Some people may be uncomfortable lying flat for a long time. Although there are no known side effects to 18-F fluoroestadriol ([^{18}F]FES) when given in an IV, there is a rare chance of an allergic reaction or other side effect to radioactively labeled drugs. Just like with any medication, you could have an allergic reaction to the medications you are receiving in this

study. This can range from a mild skin rash to a more severe reaction, such as throat tightness, difficulty breathing, lowered blood pressure and rarely, death.

This research study involves exposure to radiation from 1 ESR-specific PET/CT study. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive by participating in this study is equal to your body receiving 41.5 months (3.45 years) of radiation from your natural surroundings, or about 21% of the amount allowed in a year for people who are exposed to radiation as part of their work.

To protect your bladder from the effects of the injected radioactive substances, you should drink plenty of fluids and empty your bladder every two hours for at least the first six hours after the PET/CT scan.

Because PET/CT imaging may be harmful to an unborn child, adequate birth control measures (that is, oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. In addition, women must not breast feed while in this study. To rule out pregnancy, women of childbearing potential will have a pregnancy test.

Blood Collection: is very low risk, however you may feel pain from the needle stick. It is possible that you may get a bruise and have a small amount of pain. Very rarely an infection might develop

Urine Collection: no risk, but you may find it somewhat inconvenient.

Sample sharing: samples from this study will be stored in locked laboratory freezers. Sample remaining after study testing is complete may be used for other research or shared with other investigators. If the samples are shared, they will be "deidentified". Your name and any identifiable information will be removed from the sample. The samples will be given a coded label when processed for research use.

Confidentiality: One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. To protect your privacy, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only study personnel will have access to your name.

Risks that are not known:
Not applicable.

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Good effects that might result from this study:

The benefits to science and humankind that might result from this study: There is the possibility that being in this study may help investigators determine which patients would benefit from estrogen therapy. If applicable, this finding could potentially benefit you as a PAH therapy in the future.

Procedures to be followed:
This study will "piggy-back" with IRB 140983, in which you are already enrolled. Samples that you provided in that study will be tested for estrogen hormones

Screening Visit:

- Review of inclusion/exclusion criteria
- Review medical history
- Review current medications
- Determine World Health Organization (WHO) functional class based upon discussion with subject
- Provide instructions on participation in the study
- Instruct subjects to bring routine medications to baseline visit, do not eat or drink (except water) 12 hours before baseline visit, and to avoid heavy exercise for 12 hours before the baseline visit

Visit 1/Baseline (Week 0):

The research coordinator will call you 1-2 days before the visit as a reminder. The coordinator will instruct you to not eat or drink (except water) and to avoid heavy exercise for 12 hours before the study day assessment. You will be instructed to take your routine medications on the morning of the visit and to bring your medications and a snack or meal with you to the visit to take at the center after blood draw.

Baseline information will be used to characterize the participants and to compare the experimental groups with regards to demographics and other variables.

You will arrive at the study site outpatient clinic or clinical research center. The following procedures will be performed:

- Blood draw-1 tablespoon for a variety of hormone studies/1 Tablespoon for safety pregnancy test
- Urine collection- a sample collection kit will be mailed to your home. Please bring your sample with you to your appointment. Instructions will be included with the kit.

- Review of inclusion/exclusion criteria
- ESR-specific PET study

Urine sample and blood samples for study assays will be processed and banked.

ESR-specific PET/CT study will be conducted. You will receive one PET/CT scans on Visit 1. The PET/CT scan uses ^{18}F-Fluoroestraiol (FES) which is a radioactive form of the hormone estrogen. It will be used to study estrogen receptor numbers before and after treatment. The PET is done as a PET/CT with a low-dose CT performed for attenuation correction. Prior to the PET (usually on the same day) female patients of childbearing potential must have a negative serum pregnancy test. The agent is administered through a needle inserted in your arm (i.v.).

For the PET scan, we will have you lay on a table and then slide the table into the circle of the PET scanner, and then will give you by I.V., a radioactive tracer. We will check your blood pressure and heart rate several times. After this scan, you will be helped from the table. The procedure from tracer injection until image completion takes approximately 2 hours.

Payments for your time spent taking part in this study or expenses:
You will be reimbursed $200 for participating in this study.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Eric Austin, MD, MSCI at (615) 343-7396 or Jeff Cunningham, RN at (615) 322-2653. If you cannot reach the research staff, please page the study doctor at (615) 831-4378.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

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Reasons why the study doctor may take you out of this study:
Your doctor has the right to end your participation in this study at any time. Your physician may end your participation in this study if:

- PI determination that the subject should be withdrawn for safety

If you are taken out of the study, you will be given a reason why.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Your study records will be labeled with a study identification number so your name will not be identifiable. Research records will be kept in a locked room in an overhead bin or cabinet that will only be accessible too research personnel. Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Austin and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

Study Results:
Results will not be shared with participants.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

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If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____