Pulmonary Hypertension and Anastrozole Trial
(PHANTOM)

Informed Consent

June 04, 2020

Version 3.0

NCT03229499

Steven M. Kawut, MD, MS
Perelman School of Medicine at the
University of Pennsylvania
Principal Investigator

Pulmonary Hypertension in Anastrozole Trial (PHANTOM)
ICF Cover Page

This is a one page description of the study. You should review the entire consent form before deciding whether to participate in this study.

This study is voluntary: you can decide not to participate or withdraw at any time. This will not change the care you receive from your PAH doctor.

Purpose of the study:

- To see if anastrozole can improve how far you can walk
- To assess how well patients tolerate anastrozole

Study Drug:

- 1 pill a day (anastrozole or placebo (sugar pill)) for approximately 1 year
- Vitamin D supplement for approximately 1 year

There are no right heart catheterizations ("cath") performed in this study.

This Study DOES require (and pays for) the following tests (2-4 times during the study):

- Blood draw and urine collection
- Ultrasound of the heart (echo)
- 6-minute walk test (done in clinic and/or where you live)
- Bone density scan
- Activity monitor (like a Fitbit) worn on the waist (like a pager) for 7 days at a time

Study visits:

- Each visit 1.5 – 2.5 hours
- 4-5 visits over one year; some study visits could be combined with usual visits to your PH doctor
- Some visits may be completed where you live due to COVID-19 restrictions

Risks:

- Risks of study drug: muscle aches, joint pain and stiffness, flushing, vaginal dryness, high blood pressure, mild weakening of the bones (which is reversible), and hot flashes
- Risks of tests
- Risks of sharing your information

Payment:

- Approximately $1000 over the year if all visits attended and activity monitoring equipment are returned

UNIVERSITY OF PENNSYLVANIA
RESEARCH PARTICIPANT
INFORMED CONSENT FORM & HIPAA AUTHORIZATION

Protocol Title: Pulmonary Hypertension and Anastrozole Trial (**PHANTOM**)

Principal Investigator: Steven M. Kawut, MD, MS
Penn Medicine at University City
Harron Lung Center, 10th Floor
3737 Market Street, Philadelphia PA, 19104
215-662-8585

Emergency Contact: 215-662-8000 (Ask for Pulmonary attending)

Sponsor: National Institutes of Health - NHLBI

Why am I being asked to volunteer?

You are being asked to participate in this study, because your doctor has diagnosed you with pulmonary arterial hypertension (PAH), a disease that involves high blood pressure in the lungs.

You are being asked to participate in a clinical research study in which anastrozole, a drug that reduces estrogen, is being evaluated to see what effect it has on PAH.

Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The main purpose of this clinical research study is to study the effects of anastrozole on the distance walked during a 6 minute walk test (6MWT) in adults diagnosed with PAH. Your daily physical activity will also be monitored a few times during the study using an activity monitor, a device that is worn on a belt for one week. The study will also see if anastrozole improves the function of the heart.

A description of this clinical trial will be available on http://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 when available. You can search this website at any time.

How long will I be in the study? How many other people will be in the study?

Your participation in the study will generally be approximately 13-14 months (which includes time before you start the study medicine and after you finish it). Participation in the study may extend longer if study visits cannot be performed in the clinic due to COVID-19 restrictions. There will be 84 total participants from seven medical centers in the United States in the study. Men aged 18 or older and post- menopausal women 18 years or older may be eligible to participate if they have PAH.

What treatment is used and which will I receive?

Anastrozole is an FDA-approved medication used for more than 20 years to treat breast cancer in women after menopause. Anastrozole will be given as an investigational drug in this clinical trial. It is investigational because it is not FDA-approved to treat PAH. Estrogen may cause PAH and anastrozole decreases estrogen production so it may be useful in treating PAH.

In this study, you will be asked to take the study pill for approximately 1 year. Half of the participants will receive tablets containing the investigational drug, anastrozole (1 milligram tablet taken each day), while the other half will receive placebo tablets (inactive substance, 1 taken each day). You will be randomly assigned (like by a "flip of the coin") to receive either anastrozole or placebo. Your chances of receiving anastrozole are approximately fifty percent while your chances for receiving placebo are approximately fifty percent. Neither you nor the research team will know which study medication you are receiving. If there are concerns about what the study medication is doing, it will be possible for your doctor to find out which study medication you are taking.

All participants will also take a vitamin D supplement in the study which helps protect the bones from weakening with anastrozole. You will be instructed to take 2 tablets (2000 IU) each day, once a day. Vitamin D is the usual supplement for patients taking anastrozole for breast cancer.

It is important for you to know that it is not necessary for you to change your current PAH treatment prescribed by your doctor. You will receive the study medication in addition to your current therapy. You can receive any additional PAH medications during the study, if needed.

What am I being asked to do?

During the study, you will be asked to come to the clinic for up to five visits and be available for two phone calls. Some of these visits can be combined with your regular visits to your PAH doctor. Certain results of the research tests can be shared with you if you wish.

Screening Visit (2 hours)

Before you can start the study, the study staff will talk to you about the study. If you agree to join the study, you will sign this form before the research staff can figure out if you are able to be in the study.

The study doctor or study staff will do the tests listed below. A description of each procedure is provided below the first time it appears.

- **Health and Medication Questions:** You will be asked about your general health, your medical history, and the medications you take.
- **Demographics**: You will be asked about your age, gender and race/ethnicity.
- **Vital Signs: Blood Pressure, Heart Rate and Pulse Oximetry:** Your blood pressure will be checked by putting a band around your arm. This will squeeze your arm for about a minute. How fast your heart is beating will be checked. Pulse oximetry measures how much oxygen is in your blood using something placed on your finger.

- **Physical Exam, Body Height and Weight:** The study doctor or nurse will complete a physical exam and measure your height and weight.
- **Bone Density Scan**: We will measure your bone density by a method called dual energy x-ray absorptiometry (DXA). This method uses a very low-powered x-ray beam to scan the lumbar spine and hip. The results are analyzed by computer which estimates the amount and density of your bones. The test is done while lying on the soft tabletop of the DXA machine. It does *not* involve being enclosed inside a tunnel. This test can take up to 30 minutes.
- **Laboratory Tests**: The research staff will collect a small amount of blood from your arm (about 2-3 tablespoons) for routine clinical laboratories (such as electrolyte, kidney function, liver function, clotting tests, and blood count tests), including a blood test for menopause (if you are a woman).

If you meet the study requirements, we will schedule your next study visit within 28 days.

Visit 1 – Baseline (2.5 hours)

A member of the study team will ask you to not eat or drink anything but water and to not exercise heavily or smoke in the 12 hours before the visit.

At this visit, we will do the following:

- **Urine Collection:** You will be asked to provide a urine sample upon arrival at the clinic. The study team will give you instructions on how to collect your urine.
- **Health and Medication Questions**
- **Vital Signs: Blood Pressure, Heart Rate and Pulse Oximetry**
- **Physical Exam, Body Weight**
- **Fasting Research Laboratory Tests:** You will be asked to provide approximately 3.3 tablespoons of blood at this visit for genetic tests, tests of blood proteins and hormones, and other future laboratory tests. Genetic testing may include studying genes involved with estrogen trying to understand why the study medication may work in some patients but not in others. Other lab tests may be discovered during or after the study or haven't been thought of yet and we may measure those as well.
- **Participant Questionnaires: SF-36 and emPHasis-10:** You will be asked to fill out two questionnaires. They contain questions about symptoms, activity and quality of life related to PAH.
- **Echocardiography:** You will be asked to complete an ultrasound of the heart.
- **6-minute walk test (6MWT):** You will be asked to complete a test that will measure how far you can walk in 6 minutes on flat ground.

If you meet the study requirements after these tests, you will be randomly assigned to receive either anastrozole or placebo. You will receive six months of study medication as well as a vitamin D supplement. You will be asked to take the first tablet of study medication and the vitamin D on study day 8 (one week after this visit). The research coordinator will call you to remind you the day before you should start the study medications.

You will be asked to bring all remaining study medication and Vitamin D and the bottles that they were dispensed in (even if they are empty) with you to your next research visit.

In addition to the study drug you will take the below items home with you:

- **Actigraph Equipment:** The actigraph is a device that looks like a pager that helps us measure your physical activity while you are awake. It is worn on your hip. You will put

the actigraph on yourself on the first study day and will wear it continuously (except while sleeping, swimming, showering, or performing a remote six minute walk test) until you go to bed for seven days. We will provide you with materials to return this equipment by mail.

- **Activity Diary:** You will be asked to complete an activity diary including what time you go to sleep and wake up in the morning, details of any exercise, and when you remove your actigraph device.

Note: In some instances, the screening and baseline visits may be combined into one visit. The study team will be able to tell you if this is a possibility for you.

A combination of the tests discussed above will be performed at the visits listed (shown in the table below).

Visit 2/Month 3 (1.5 hours)
Visit 3/Month 6 (2 hours)
Visit 4/Month 12 (2.5 hours)

At each visit:
Ten days before the visit, the study team will mail the **actigraph** and **activity diary** to your home with instructions for what day you should begin wearing the actigraph. You will be asked to wear the actigraph continuously (except while sleeping, swimming, showering, or performing a remote six minute walk test) for 7 days before coming to the next study visit. They will call you the day before you should start wearing the actigraph as a reminder and to answer questions.

A member of the study team will ask you to not eat or drink anything but water and to not exercise heavily or smoke in the 12 hours before the visits. In addition, you will not take any study medication until after all the procedures have been performed. We will call you 1-2 days before this visit to remind you about the visit and remind you to fast.

At these visits, your general health will be evaluated and we will also ask again about the medications you take. The members of the study team will ask you questions about how you have been feeling, to investigate whether you have had any side effects, and to evaluate your response to the treatment.

You must bring all of your study medication and bottles/packaging (even if they are empty) at every clinic visit. We will also collect the actigraph device and activity diary from you.

At Visit 3/Month 6:
You will be asked to provide a urine sample upon arrival at the clinic. The research coordinator will provide you with a sample container, antiseptic wipe, and instructions. You will also be asked to complete an echocardiogram at this visit. A member of the research team will give you a new supply of study medication bottles that contain 6 more months of study medication and vitamin D supplement.

At Visit 4/Month 12:
You will be asked to complete an echocardiogram and a DXA bone density scan. You will stop the study medication and the vitamin D supplement. The study will not provide you with the study drug after your participation ends. At this time, you can discuss your medical care with your PAH doctor.

Month 9 Phone Call (up to 20 minutes)

A member of the research team will call you on a scheduled day and time to ask you about your general health and if there are any changes in the medications you are taking. You will be given instructions on when to wear the actigraph (before Visit 4). Your next scheduled clinic visit will also be confirmed.

Week 54 Follow-up Phone Call (up to 20 minutes)

A member from the research team will call you on a scheduled day and time to ask you about your general health and to review any on-going side effects that may have occurred during your participation in the study.

Study Visit Schedule Table

	Consent	Screening	Baseline	Month 3	Month 6	Month 9	Month 12	Week 54
Visit #			1	2	3		4	
Telephone Call #						1		2
Day#		**within 60 days of consent**	**- 28- 0**	**90 ± 14**	**182 ± 14**	**272 ± 14**	**365 ± 14**	**380 + 7**
Informed consent	**X**							
Health and medication questions		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs/Physical Exam		**X**	**X**	**X**	**X**		**X**	
Blood draw (clinical laboratory tests* and fasting research labs)		**X***	**X**	**X**	**X**		**X**	
FSH (women only)		**X**						
DXA bone density scan		**X**					**X**	
Urine collection			**X**		**X**			
Actigraphy			**X**	**X**	**X**		**X**	
Participant questionnaires			**X**	**X**	**X**		**X**	
Six minute walk test			**X**	**X**	**X**		**X**	
Echocardiogram			**X**		**X**		**X**	
Symptom assessment/side effects			**X**	**X**	**X**	**X**	**X**	**X**
Dispense study drug/placebo			**X**		**X**			
Study drug compliance				**X**	**X**	**X**	**X**	

* Clinical laboratory tests are done at the screening visit. All other blood draws are for research laboratories.

Remote Study Visits

Study visits in the clinic may not be possible due to restrictions from the COVID-19 pandemic. In this case, we may perform “remote study visits”, which are study assessments completed while you are at home or where you are residing during times when “stay-at-home” restrictions are in place. You would not need to come to the clinic for research visits until COVID-19 restrictions are removed.

Remote study visits will be conducted by phone or web-meeting software at your convenience in a private space. The research staff will tell you when a remote study visit needs to be done. Prior to the remote study visits, the research staff will send you questionnaires on paper, the actigraph (device to monitor your activity), the activity diary, and six minute walk test materials. The six minute walk test materials might include a wearable device (“wristwatch”) that utilizes the Global Positioning System that works through an application you download to your phone.

You will be asked to wear the actigraph continuously (except while sleeping, swimming, showering, or performing a remote six minute walk test) for 7 days before the remote study visit. You will be called the day before you should start wearing the actigraph as a reminder and to answer questions.

The research study staff will evaluate if it is safe for you to perform a remote six minute walk test with the materials we will provide. If you are cleared to perform the walk test, the staff will explain to you how to conduct the walk test remotely. For your safety, it is important that another person be present when you do the six minute walk test.

At each remote study visit, the research staff will review the answers to your questionnaires, review your activity diary, and ask you to return the actigraph using material provided by the research staff. Certain measurements will be performed with equipment you have available at home (personal weight scale, pulse oximeter, blood pressure machine). There is no need for you to obtain or purchase this equipment if it is not already available or provided.

At each remote study visit, the research staff will ask you questions about how you have been feeling to investigate whether you have had any side effects. The research staff will review how many study drug doses you have taken. You will be contacted separately by either the study doctor or delegated nurse to evaluate you and perform a remote abbreviated physical exam, if possible.

Assessments such as the echocardiogram and DXA scan will be done at the study center when possible within a visit window. When you are able to return to the study center, you will also be asked to perform the six minute walk test in clinic. The research staff will inform you of that window and work with you to schedule the assessments. It may be possible to perform the research blood draw and urine collection at home through a visiting health service. If this is not available (or you prefer not to), then you can perform this testing at the study center, when possible.

Extension of Study Drug

In some cases, you may be asked to continue taking the study medication after the 1 year study period (up to 6 additional weeks). The study team will speak to you if this situation applies to you. The research staff will mail you the additional study drug supply.

What are the possible risks or discomforts?

Some possible risks that may be associated with participation in this study are provided below; however**,** there may be additional harmful consequences that are not discussed below or not yet known.

Risks of anastrozole: Anastrozole (study drug) was given to 1,920 post-menopausal women and placebo (inactive substance) was given to 1,944 women for five years, all without breast cancer. There was no increase in bone fractures, heart attacks, clots, or strokes with anastrozole in this study. Anastrozole did slightly increase the chance of muscle aches, joint pain and stiffness, flushing, vaginal dryness, and high blood pressure. Out of 100 women treated with anastrozole and 100 women with placebo, there were 2 to 8 more women in the anastrozole group compared to the placebo group with one of these side effects. Anastrozole decreased bone density (weakened the bones) in this study.

In older studies of women with breast cancer, the administration of anastrozole was associated with thinning of bones (weakening of bones), bone fractures, hot flashes, bone pain, physical weakness, high blood pressure, carpal tunnel, vaginal dryness, dry eyes, flu-like symptoms, and middle-ear pain (otitis media) compared to other medications for breast cancer. The rate of heart attack with long-term anastrozole use was approximately 1% in breast cancer. In other clinical trials, increased blood cholesterol and blood clots occurred in 1 to 3 of 100 women with breast cancer who used anastrozole. Other less common side effects, which happened in < 1 in 10,000 patients, include skin reactions (lesions (a growth or area of skin that does not resemble the area surrounding it), ulcers, blisters), angioedema (swelling below the surface of the skin,

usually around lips and eyes), and changes in liver function tests.

Other common side effects listed in the package insert from women with breast cancer are weakness, joint aches, joint pain (stiffness or swelling/arthritis), pain, sore throat, depression, nausea and vomiting, rash, back pain, sleep problems, headache, swelling of legs, ankles or feet, increased cough, shortness of breath, buildup of lymph fluid in the affected arm (lymphedema), and tickling, tingling or numbness of skin; however it is unclear how these relate to our study population.

We performed a study of post-menopausal women and men with PAH where twelve participants received anastrozole (study drug) and six received placebo (inactive substance) for three months. There were no risks associated with anastrozole in this study. It is important to note that we only included a few participants and it was a short period of time.

Vitamin D risks: The administration of vitamin D at the dose used in this study is well below the Institute of Medicine defined Safe Upper Limit. Excessive vitamin D can cause elevated calcium in the blood and urine and kidney stones, but this is more common when combined with calcium supplementation.

Blood draw risks: The risks of drawing blood include pain, bruising and in rare instances, infection. Some participants may experience nausea and dizziness after the blood draw. Standard care will be taken to avoid these complications.

Echocardiogram risks: The ultrasound probe used on your chest may lead to mild soreness in the area for about a day.

Six Minute Walk Test risks: This walk test may cause light-headedness, chest pain, or musculoskeletal discomfort; however, the risks of this study to participants are minimal. In order to ensure your safety during a remote Six Minute Walk Test, a second individual should observe the test.

DXA Scan risks: This research study involves exposure to radiation from DXA scans. Therefore, you will receive a radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the doses you will receive, it is very likely that you will see no effects at all.

Actigraph risks: Wearing the actigraph device may cause skin irritation.

Wearable Device ("wristwatch") with GPS for remote Six Minute Walk Test and phone application risks: Wearing the device may cause skin irritation, but this is unlikely for the short period of the testing.

Reproductive risks: Because women of child-bearing potential or breast-feeding mothers will not be enrolled in this study, there are no risks to unborn children or children who are being breast-fed.

Fasting risks: Prior to the four study visits, you are required to fast. This means refraining from food and drink (other than water) for 12 hours prior to each study visit. You may take your medications as usual. After you have completed the blood draw, you can eat a snack. There are some risks associated with fasting. If you experience any of the following symptoms, please contact researchers and discontinue your fast: shakiness, nervousness, sweating, dizziness or light-headedness, sleepiness, confusion, difficulty speaking, anxiety, or weakness. If you have

diabetes, the study doctor will instruct you about what to do with your diabetes medicines on the study day.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

This study will help us to determine whether we should perform further research on anastrozole for treating PAH. There is no guarantee that you will benefit directly from this research study. Information obtained during the course of this clinical research study may contribute to a better understanding or treatment of your disease. Regardless of any individual benefit, the knowledge gained from this study may contribute to information that would allow the use of this drug or similar drugs in later treatment for you and other patients with PAH.

What other choices do I have if I do not participate?

If you decide not to participate in this research study, there will be no issues with your further treatment for your PAH. There may also be other clinical research studies in which you may choose to participate. You should discuss these alternatives with your doctor and decide whether to participate in this study. Your study doctor will inform you should any new information about the investigational product, anastrozole, become available during the course of the study.

Will I be paid for being in this study?

You will be reimbursed for time/inconvenience of the study procedures and travel expenses necessary for your participation in the study. If you complete the screening visit you will receive $50. If you complete the baseline visit you will receive $150 and you will receive $50 dollars when you return the actigraph equipment/diary.

For in-person study visits (Visits 2, 3, and 4) you will receive $200 for study visits and $50 each time you bring back the actigraph equipment/diary.

For remote study visits, you will be reimbursed as follows:

- Visit 2 (Month 3) there will be no change in compensation: $200 for completion of visit regardless of whether or not you return to the center to complete the remainder of the Month 3 study assessments. You will receive $50 for returning the actigraph equipment/diary.
- Visit 3 (Month 6): $100 for completing the remote study visit, $100 for returning to the center to complete the remainder of the Month 6 study assessments. You will receive $50 when you return the actigraph equipment/diary.
- Visit 4 (Month 12): $100 for completing the remote study visit, $100 for returning to the center to complete the remainder of the Month 12 study assessments. You will receive $50 when you return the actigraph equipment/diary.

If you complete the study, your total reimbursement will be $1000.

Reimbursements for participation in the study will be administered using a Greenphire ClinCard, a reloadable prepaid card provided by the University of Pennsylvania. There are no fees for making online or in-store purchases, cashing out the card by presenting it to a teller at any major bank, calling the automated system for balance inquires, calling the customer service number and speaking to a live agent, or addition of funds to the card. The following activities will incur a fee to

the balance on your ClinCard: 1) not using the card or having funds added to it for more than 6 months will incur a monthly $3 fee. Every time the card is used or funds are added, this 6 month period is reset. 2) ATM withdrawals (fees vary based on location) 3) Requesting a paper statement (instead you can always check your available balance online or by calling Customer Service) 4) Requesting a replacement card through Customer Service will incur a $7.00 fee and take 7-10 days to receive by mail. Instead, if your card is lost, stolen or damaged, contact your study coordinator so that s/he can replace your card at no charge. 5) Requesting a check through Customer Service to remove funds from the card. Please read the ClinCard Cardholder FAQ given to you by the research team.

In order to be compensated for your participation in this study, you must provide your Social Security Number. The University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

The study drugs are provided free of charge. No other compensation is offered.

Will I have to pay for anything? Who is paying for this study?

There are no costs to you for taking part in this study. The National Institutes of Health is paying for this study. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study or if your insurance agrees in advance to pay.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed on the first page of the consent form. As always, you should seek emergency medical treatment for any emergencies.

You are encouraged to ask questions at any time during the study. In the event you experience a side effect or have further questions about the study, please contact **Dr. Kawut at 215-662-8585** during regular business hours, 8AM to 5PM, or a **Pulmonary Attending at 215-662-8000** after hours and on weekends and holidays. If the Pulmonary Attending is unable to assist you, he/she will contact **Dr. Kawut**.

When is the study over? Can I leave the study before it ends?

This study is expected to end after all participants have completed all visits and all information has been collected. You will not know the results of the study or whether you got the anastrozole or the placebo until ALL participants have completed this study. At that point, if you wish, the study team may tell you what pill you were receiving and inform you of the results of the study. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.

- The Sponsor, or the study Principal Investigator has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care. If you decide to stop taking the study medication or if this is necessary for your clinical care, we will ask you to still continue with the study visits and other procedures for the study, which will help us ensure your safety and the usefulness of the study. If you withdraw or are withdrawn completely from the study, you will be asked to come to the clinic for an early End of Study Visit. Participation will not affect your usual clinical care which you will continue during and after participation in this study.

What personal information about me may be collected, used, or shared with others?

If you choose to be in this study, the study doctor will get personal information from you. This may include information that might identify you. This information may include:

- Medical and Research Records
- Name, address, telephone number, medical record number, email address
- Date of birth, place of birth, city & country of birth (for GUID explained below)
- Social security number for tax purposes
- Records about study-related visits and phone calls
- Results from physical examinations, laboratory test, or other procedures
- Records about study drugs

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research and see if the research was done right
- to evaluate and manage research functions

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The principal investigator and other members of the study team
- Other Authorized Personnel at Penn including the finance department, billing personnel, the Penn Institutional Review Board and Office of Human Research
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of the School of Medicine, might receive my personal or de-identified information?

- The Office of Human Research Protections
- The study Data and Safety Monitoring Board
- The Data Coordinating Center at University of Pennsylvania
- Echo Core laboratory at the Mayo Clinic in Rochester
- The wearable device and phone application company (if used)
- The visiting health service (if used)
- All research centers participating in the center

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How will my personal information be protected?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Confidentiality of your records will be maintained to the extent possible. The Health Authorities, the Monitors and other study personnel representing the Sponsor, the Institutional Review Boards, Ethics Committees and regulatory authorities and your health insurance company may need and will be granted direct access to your medical records to verify either the clinical trial procedures or the data they contain. By signing this Informed Consent form you are giving your authorization to such access.

Certificate of Confidentiality

To help protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation for federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your Involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Exceptions: A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent in incidents such as child abuse, and intent to harm yourself or others.

Global Unique Identifier (GUID)

In order to share detailed medical and other information with researchers while protecting your privacy in the future, the Data Coordinating Center (DCC) will generate a unique ID number for you. Your privacy will be protected by removing your name, address and other “identifying” information at the end of the study and before providing data to researchers. This information is “de-identified” because it has had all personal identifiers removed including your name, address, or other information that identifies you or your family. Your information will be labeled with a code number (GUID) and stored on secured computers and servers and protected with encryption and passwords. Only authorized people will have access to the code and will be able to identify you if needed.

There are a small number of other researchers in the U.S. who have completed, are currently performing, or who may perform research in the future that may include you. You would have consented or will consent to participate in these other projects separately. In order to make the most of data collected for this project, we ask your permission to potentially share your information with researchers in charge of these other projects in order to link the data from this trial with other studies. The investigators would sign a Data Use Agreement before any data

were provided so that all uses would have to be in line with the guidelines of this study. The GUID would be used to link data with projects done by other researchers; the GUID does not contain any personal identifiers and no "protected health information" such as your name, birthdate, etc. would be related. The use of the GUID is necessary because it allows results about the same person in two separate studies to be linked together and used in a way that would not be possible without having the GUID. All studies using data from this study will have to undergo review and will have to comply with standard regulations regarding human research.

Other researchers may have new and different research questions which could be answered by the data from this study. These researchers can apply to use de-identified data from this study for research related to pulmonary hypertension or other conditions. Again, "de-identified data" means that the data will not contain identifying information such as names, birthdates, or addresses or other data which could be used to easily link you to the data. Researchers who would like to use information in this study must formally apply and they must sign a Data Use Agreement (which will put limits on how the data can be used). We will only release de-identified data to such researchers who want to perform studies with the data.

Future Research:

In the future, DNA obtained from your blood may undergo genome-wide analysis (GWAS) for PAH research. We may use this blood sample to look for genetic associations with PAH and related diseases. We may also look for genetic predictors of whether the drug works (if this study drug works better for individuals with certain genes). Results obtained from this testing will be shared for research purposes through the National Institutes of Health (NIH) GWAS data repository. Information about your genetic and physical characteristic information will be linked to a code number to protect privacy. There will be no identifying information about you with this genetic data.

This research includes genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.
A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

You may be concerned that your genetic information will be known by people not involved in this research. However, the likelihood that your participation in this genetic research will harm you is small. This is because procedures are in place to keep your participation and all of your genetic results as confidential as possible. Your genetic results will be protected by strictly controlled access to the files that hold your medical information and genetic results by using an

assigned code number in all research.

Sample Storage

Blood samples obtained will be stored in a secure laboratory with restricted access at the University of Vermont and the University of Pennsylvania. The samples will be identified by an identification number and will be kept confidential. Your name and all other identifying information will be removed. All other data will be stored in a password protected computerized database which will be maintained by the University of Pennsylvania's research staff. Testing of these samples will be performed at facilities at the University of Pennsylvania and the University of Vermont which serves as the core laboratory for all centers participating in this study.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record. If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g., health insurance company, disability provider, etc.). We will have a Certificate of Confidentiality in this study to help protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire. Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study. You will be given a copy of this Research Participant HIPAA Authorization describing your confidentiality and privacy rights for this study. By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research participant?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research participant, you should speak with

the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Participant's statement

This study has been explained to me. I volunteer to take part in this study. I have had a chance to ask questions. If I have questions later about the study, I can ask one of the researchers listed above. I have checked "Yes" or "No" to Question 8 below which asks if I would want to know about results which may affect my health and Question 9 below which asks if I want to be contacted for future studies.

1. I understand my participation in this study is voluntary and I can change my mind and withdraw at any time.
2. I understand that all attempts will be made to protect my privacy and my family's privacy. I understand that my personal information will be protected and saved in the study using a code and then erased at the end of the study.
3. I understand that by agreeing to participate, I may be contacted to update or correct my health information.
4. I am willing to allow my de-identified medical information (information without my name, address, birthdate, etc.) to be used for other medical studies related to my disease.
5. I am willing to allow my data to be shared with other researchers so that my information from this study can be linked to other studies in which I may participate.
6. I understand that I may not personally benefit from participating in this study or from the use of my de-identified medical information in any research study.
7. I understand that I can withdraw from this study at any time and remove my information.
8. If it is permitted, I would like to know of any findings or results that may affect my health.
   Yes ☐ No ☐
9. I would like to be contacted if I am eligible for future clinical trials or other studies.
   Yes ☐ No ☐
10. I understand the content of this form, I was given the background information, I had enough time to ask questions, all my questions were answered and I had enough time to decide that I want to participate in this clinical trial and I will be given a copy of this consent.

A copy of this signed consent form will be given to you.

Name of Participant (Print)	Signature of Participant	Time	Date

Legally Authorized Representative (Print)	Signature of Legally Authorized Representative	Time	Date

Name of Person Obtaining Consent (Print)	Signature	Time	Date