Assessing Response to Inhaled Prostacyclin with Hyperpolarized 129Xe MRI

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Protocol Title:

Assessing Response to Inhaled Prostacyclin with Hyperpolarized 129Xe MRI

Purpose of the Study:

To determine whether hyperpolarized 129Xenon MRI can detect improvements in pulmonary gas exchange in patients with PH treated with iTRE. We will associate this with changes in serum concentrations of treprostinil and levels of peripheral vasodilation.

Background & Significance:

Pulmonary hypertension (PAH) carries a significant economic burden, with average annual health care costs of ~ $100,000/yr. The diagnosis of PAH can be challenging, as it requires fulfillment of specific clinical and hemodynamic criteria. However, these are limited because they do not allow the diagnosis of PAH in the setting of concomitant left heart disease or lung disease. Patients with mild to moderate idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD), which are common in older patients, technically cannot be diagnosed with true PAH, but are diagnosed with Pulmonary Hypertension (PH). Similarly, hemodynamic criteria are limited by arbitrary cutoffs for mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PVR) obtained at right heart catheterization (RHC) (PH is defined as mPAP $\geq$ 25 mmHg; PAH is defined as mPAP $\geq$ 25-mmHg and a PCWP $\leq$ 15 mmHg, with some criteria recommending an additional cutoff of PVR $\geq$ 3 Woods units. Moreover, it is currently unclear what constitutes abnormal hemodynamics in the setting of in lung disease, which can increase the PVR. These hemodynamic criteria also frequently exclude patients who may have a borderline elevation in mPAP or abnormalities primarily associated with exercise that are not captured with a resting heart catheterization. As the majority of patients who are now evaluated for PAH are older with common cardiac and pulmonary comorbidities, the clinical and hemodynamic criteria are frequently inadequate for diagnosing patients who actually have PVD.

This work seeks to apply and test a novel non-invasive methodology, hyperpolarized (HP) 129Xenon (Xe) magnetic resonance imaging (MRI), for the diagnosis of PVD. Hyperpolarized 129Xe MRI has been under active development and used in clinical research at Duke for over 7 years. Over 250 patients and volunteers have undergone 129Xe MRI. The technology permits 3D quantitative imaging of both pulmonary ventilation and gas exchange during a breath-hold exam. It has been used at Duke and around the world to study COPD, asthma, and interstitial lung disease. However, until recently it has not been applied to PVD. In preliminary studies under an existing protocol, two patients in whom PVD was suspected, but who did not meet strict PAH criteria, underwent 129Xe-MRI research studies. These patients had no other evidence of significant lung disease, despite undergoing a thorough evaluation that included pulmonary function tests, CT scan, and RHC. In both patients, the 129Xe study demonstrated spectroscopic and imaging indices consistent with a barrier to diffusion of 129Xe to red blood cells (RBCs). These patients subsequently had lung tissue obtained (one at time of lung transplant, the other with a surgical lung biopsy). Strikingly, both biopsies demonstrated PVD. We believe that the abnormalities seen on 129Xe MRI scans in these patients represent areas of PVD that are associated with a barrier to gas diffusion. Moreover, these changes appear to be different to those seen in other lung diseases associated with barriers to gas diffusion, such as idiopathic fibrosis. Among the objectives of this proposal is to clarify and strengthen these distinguishing features.

If successful, 129Xe MRI could overcome the current limitations of PVD diagnosis while conferring a number of potential benefits. First, imaging the abnormalities in the lungs allows the diagnosis of PVD in the setting of concomitant heart or lung disease. With HP 129Xe MRI, abnormalities in gas exchange secondary to PVD can be directly visualized. Second, non-invasive diagnosis of PVD could remove the need for an invasive RHC. While RHC is a relatively safe procedure, there are a number of limitations to the interpretation of RHC, including arbitrary cutoffs for mPAP, PCWP, and PVR. Third, the abnormalities on HP 129Xe MRI could be used to non-invasively monitor response to therapy. If we are successful in demonstrating the applicability of HP 129Xe MRI, this technology holds the promise of greatly improving the diagnosis and management of PVD.

Design & Procedures:

This study will consent 15 patients (accrued 12 subjects total) with pulmonary hypertension (PH). Patients will be on inhaled treprostinil (iTRE) as standard of care for their PH. Inhaled treprostinil (iTRE) is an FDA approved medication under the brand name of Tyvaso. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. The medication is delivered noninvasively, directly to the lungs using the approved ultrasonic nebulizer delivery system. Patients will take the inhaled treatment four times a day, about every four hours.

Patients will be characterized by their ^{129}Xe MRI imaging, peripheral vasodilation and serum treprostinil concentration before and after treatment with iTRE. As iTRE has a plasma concentration half-life of ~ 45 minutes and time-to-peak concentration of 15 minutes, imaging will be conducted immediately before, 15 minutes after and 2-4 hours after drug treatment. This would potentially allow the visualization of changes in gas diffusion and peripheral vasodilation associated with iTRE. This is similar to changes seen in ventilation in asthma after treatment with bronchodilators. A follow-up scan at the 2-4hr time point would also allow us to test whether vasodilation persists in the lung vasculature compared to the peripheral circulation. This study seeks to deploy several forms of 129Xe MRI contrast. Specifically, the 129Xe MRI scans will provide 3D images of ventilation and gas exchange, and spectroscopic indices will be evaluated to test gas exchange dynamics with high temporal resolution. This will be augmented with several conventional 1H MRI scans to delineate the subject's thoracic cavity.

Once the subjects has signed consent, the study session will begin with a collection of relevant patient history and symptoms, measurement of hemoglobin levels (finger sensor), and urine pregnancy testing (if applicable). Study team will use the PFTs that are available from the medical record. Subjects will receive an IV catheter to be used for blood draws. The following activities will take place for the MRI procedure:

1. Patient receives first scan before scheduled dose of iTRE (trough study) Baseline timepoint: ^{129}Xe calibration and dissolved-phase spectroscopy - to obtain global RBC:barrier ratios, RBC oxygenation shifts, and spectral linewidths; Isotropic 3D ^{129}Xe gas exchange MRI – to detect focal defects in gas transfer from airspaces to RBCs in capillary bed; Other ^{1}H scans to obtain anatomic data on the lung.
2. Assessment of peripheral vasodilation in the arm and hands with noninvasive laser speckle imaging
3. Blood sample for serum treprostinil concentration
4. Subject takes iTRE treatment as with standard of care. Timepoint 1: Wait ~ 15 minutes to peak effect (peak study). Patient receives second scan: ^{129}Xe calibration and dissolved-phase spectroscopy - to obtain global RBC:barrier ratios, RBC oxygenation shifts, and spectral linewidths; Isotropic 3D ^{129}Xe gas exchange MRI – to detect focal defects in gas transfer from airspaces to RBCs in capillary bed; Other ^{1}H scans to obtain anatomic data on the lung.

5. Assessment of peripheral vasodilation in the arm and hands with noninvasive laser speckle imaging
6. Blood sample for serum treprostinil concentration
7. Timepoint 2: 2-4 hrs after initial treatment with iTRE; Patient receives third scan: ^{129}Xe calibration and dissolved-phase spectroscopy - to obtain global RBC:barrier ratios, RBC oxygenation shifts, and spectral linewidths; Isotropic 3D ^{129}Xe gas exchange MRI – to detect focal defects in gas transfer from airspaces to RBCs in capillary bed; Other ^{1}H scans to obtain anatomic data on the lung.
8. Assessment of peripheral vasodilation in the arm and hands with noninvasive laser speckle imaging
9. Blood sample for serum treprostinil concentration

With each time point (baseline/trough scan, timepoint 1 scan, timepoint 2 scan) the patient will undergo several scans after inhalation of HP 129Xe gas. Each dose will be limited to a volume less than 25% of subject lung capacity (TLC) as is the case for all protocols currently carried out under IND 109,490. After each 129Xe dose, the table will be moved out of the magnet bore and the subject queried for any symptoms. The next 129Xe dose and scan will be administered when the subject and study personnel are ready. Subjects will undergo a 129Xe MR spectroscopy calibration scan, 129Xe ventilation MRI, and 129Xe gas exchange MRI. Any given 129Xe MRI scan may be repeated, if necessary. There is no limit to the number of 129Xe scans allowed during the session, although current 129Xe production capabilities generally limit this to 5 129Xe doses.

Selection of Subjects:

We propose to recruit and consent 15 subjects (accrued 12 subjects total) with known PH on treatment with iTRE that are followed in the Duke Pulmonary Vascular Disease Clinic. Inclusion criteria includes: PH (mPAP $\geq$ 25 mmHg, PCWP $\leq$ 15 mmHg in the absence of significant concomitant left heart disease or lung disease), , maintenance on a stable, well-tolerated treatment dose of iTRE (ideally $\geq$ 8 breaths QID). Pregnant women will be excluded from this study. Women of childbearing potential must have a negative urine pregnancy test in order to participate on this study.

Definition of Women of CBP: The median age of menopause in the US, defined as 12 months of amenorrhea, is 51 years; by age 48, approximately 15% of women will be postmenopausal, while virtually 100% will be post-menopausal by age 55. Women are considered past the age of "child-bearing potential" if they are greater than 55 years of age, OR they are at least 50 years of age AND o have not menstruated for at least 12 months, OR have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL. they are at least 45 years of age AND o have not menstruated for at least 18 months, OR o have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL. For drugs classified, or likely to be classified, as FDA Category X, the duration of amenorrhea for women of all ages must be 24 months, consistent with FDA labeling of these drugs.

Subject Recruitment and Compensation:

Patients will be recruited based on predetermined inclusion criteria. They will be recruited in the Pulmonary Vascular disease clinics and inpatient services at Duke by their care providers. The patient's provider will initiate conversation with the subject about the research trial and assess their interest in participation. The screening of subjects will be conducted by the study coordinator and will include the informed consent process.

Before entry into the protocol, the nature and risks of the study will be reviewed with each subject. Each subject will be given the opportunity to read the consent form and ask questions. After all questions by the study subject are answered, and before any protocol specified procedures are initiated, each subject will sign and date the consent form. A copy of the signed consent will be provided to the subject.

Dr. Driehuys is founder and chief technology officer of Polarean, Inc. a start-up company that seeks to commercialize hyperpolarized 129Xe gas MRI technology. He is a shareholder in the company and provides it with technical consulting. In addition, Polarean has licensed from Duke, a patent on which Dr. Driehuys is an inventor, and is currently evaluating several others. For these reasons he has had a conflict management plan, administered by the Duke Office of Research Integrity. The study proposed here uses Polarean technology, but is not sponsored by the company nor is it being used for regulatory advancement with FDA. However, if the findings are positive, Polarean may have an interest in commercializing these aspects of the technology as well. Therefore, consistent with his management plan, Dr. Driehuys will not serve as principal investigator on this study, nor will he obtain consent from subjects. He will oversee the technical aspects of hyperpolarized gas production and MR image acquisition. However, data analysis will be overseen by Dr. Rajagopal, who also serves as overall principal investigator on this protocol. Duke is being paid to conduct the study by United Therapeutics. Subjects will take their standard of care iTRE medications during the necessary timepoints in the study. Subjects will receive $150 for their time and travel expenses.

Consent Process:

See Section 14 of the e-IRB submission form and complete the questions in that section.

Subject's Capacity to Give Legally Effective Consent:

Subjects without capacity to give consent will not be recruited into this study.

Risk/Benefit Assessment:

Potential Risks
The risks of participating in this study are considered greater than minimal risk. MRI is a non-invasive imaging modality that involves no ionizing radiation. All subjects will have already completed a standard questionnaire to screen for contraindications to MRI imaging since the parent trial also employs MR imaging.

Risks of Xenon Inhalation
Inhalation of hyperpolarized 129Xe may carry some minor risks. Xenon is a general anesthetic when breathed continuously at concentrations greater than 70% for extended periods of time. In the proposed study, xenon will be delivered in a single breath, with alveolar concentrations below 25%. At these concentrations, subjects may experience transient effects including dizziness, slight tingling or numbness of the extremities, nausea, smelling of flowers, or a feeling of well-being and euphoria. These effects will wane within 1-2 minutes of exhaling the xenon and are documented in the consent forms.

A second risk comes from administering HP 129Xe without oxygen. This is necessary to preserve good image quality, because O2 is paramagnetic and depolarizes the HP 129Xe. Administration of a single anoxic 1-liter breath has been well tolerated by subjects undergoing both 3He and 129Xe MRI because for a single breath, the residual oxygen in the subject's lungs is sufficient to maintain blood O2 saturation during the breath-hold. If a subject has an oxygen saturation below 90% at baseline, the attending medical professional may provide supplemental oxygen via nasal cannula as needed. Numerous studies have now been published demonstrating the safety and tolerability of hyperpolarized 129Xe MRI.

Hyperpolarized 129Xe is treated as a drug by the FDA and is covered by our existing Investigational New Drug Filing (IND# 109,490), which has been active for 7 years and has reported no SAEs, and no early withdrawals from the study. The proposed studies will use hyperpolarized 129Xe prepared in exact accordance with the Drug Master File that is part of the IND held by Polarean, Inc. Our center has been granted the rights by Polarean to cross-reference this IND for their own filings. We will continue to follow a 129Xe administration protocol that is well established in our hands.

Risks of Incidental Findings
Since the MRI methods being tested are experimental, the MRI images will not be formally reviewed for incidental findings. However, if there is something that is of concern to the PI, then the PI will approach the IRB for guidance on how to proceed on a case-by-case basis. The consent will clearly state that the MRI images will not be evaluated for incidental imaging findings.

Protection Against Risk: Study visits and informed consent will be performed in private rooms, to prevent potential loss of confidentiality. This individual will be present in the MRI suite during 129Xe administration and will monitor all aspects of the subject's wellbeing and record any transient CNS effects and adverse events should they occur. The subject will be monitored continuously by an MRI-compatible pulse oximeter, recording both heart rate and oxygen saturation. Subjects may discontinue the study at any time. The MRI suite is also equipped with a safe source of supplemental oxygen that can be provided if needed for patients with pulmonary disease to maintain O2 saturation. All subjects will receive a 24-hour follow-up phone call to check for any symptoms or adverse effects. Any symptoms or effects will be recorded, regardless of their suspected association with 129Xe MRI.

Extraordinary care will be taken to ensure that all patient data remains confidential and any information is deidentified prior to publication or presentation. All study personnel will have completed their institution's mandatory training in human subjects' research and protecting PHI.

Potential Benefits to Subjects:

We anticipate no direct benefit to subjects as a result of participating in the study, since our primary emphasis is to collect a range of MR images and develop interpretation of these results over time. However, it is conceivable that either the anatomical 1H scans or 129Xe MR scans may reveal an incidental pathology that requires medical attention. Such a finding could benefit the subject because it will be found earlier than would likely be the case during the subject's normal medical care. Any such findings will be immediately communicated to the subject and his/her physician and all associated records of the study will be made available to them for any further work-ups. The potential benefit of this research is in the noninvasive diagnosis of PAH, which would obviate the need for invasive RHC in these patients.

Costs to the Subject:

There are no additional costs to the subject for the MRI examination. Subjects will be compensated $150.00 for the study visit.

Data Analysis & Statistical Considerations:

We will perform pairwise comparisons for all endpoints before and after treatment with iTRE with correction for multiple comparisons. We will also compare the baseline and post-treatment values to a group of normal subjects so we can assess the degree of normalization of gas transfer associated with drug treatment.

Data & Safety Monitoring:

All of the protocols in this proposal trial will be approved by Institutional Review Boards and reviewed periodically (every 12 months). Any adverse event will be reported to the appropriate IRB, the NIH Office of Biotechnology Activities (OBA), and if deemed related to xenon, will also be reported to FDA. Per Institutional and FDA policy, any serious adverse events (SAEs) will be reported within 24 hours. An annual progress report (or more frequently, if requested) will be submitted to the IRB, OBA and FDA.

The clinical investigator(s) will terminate the study immediately if the occurrence of serious adverse events that suggests unacceptable risk to the health of the subjects. All observed or volunteered adverse events, regardless of suspected causal relationship to the study procedure(s), will be recorded on the adverse events page(s) of the CRFs or worksheets. Events involving adverse experiences occurring during the study procedure(s) will be recorded.

Subjects will be monitored before, during, and after each dose of xenon to assess for adverse events and changes in vital signs. The parameters monitored include the following: subject assessment of anesthetic/analgesic effects, heart rate, and SpO2. The subjective sense of analgesia is assessed by in inquiring about how the subject feels after administration of the Xenon dose. The subject will be asked to describe how they feel as well as about specific symptoms including: dizziness, light-headedness, numbness, euphoria, sleepiness, and tingling in extremities. SPO2 is measured at baseline and after each Xenon dose. A decrease of SpO2 by greater than 5% is considered significant. If the subject is to receive another dose, the next dose will not be administered until the SpO2 is within 5 % of its baseline value. If the subject has received their last dose, they will be observed until the SpO2 is within 5% of its baseline value or until the end of the observation period, whichever is longer. The subject will be monitored for the duration of the Xenon dose and post-procedural period, as well as the MRI with contrast by a qualified medical professional.

Privacy, Data Storage & Confidentiality:

All consent and case report forms will be stored in a locked filing cabinet in the office of the study coordinator or principal investigator. Any other digital data (images, image analysis) will be associated only with the subject identification number and the date and time of the MRI. Image data will be retrieved and analyzed only by study personnel. Data will be captured in a RedCap database. After all manuscripts have been published the key to the code will be destroyed.

Statistical Plan

We will perform pairwise comparisons for all endpoints before and after treatment with Tyvaso with correction for multiple comparisons. We will also compare the baseline and post-treatment values to a group of normal subjects so we can assess the degree of normalization of gas transfer associated with drug treatment.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Assessing Response to Inhaled Prostacyclin with Hyperpolarized 129Xe MRI

This is a research study to find out if magnetic resonance imaging (MRI) using inhaled hyperpolarized xenon gas can help visualize lung function in patients with pulmonary hypertension. The study will also find out if this MRI with xenon gas can detect lung and body changes after treatment with inhaled treprostinil (Tyvaso) that is taken as standard of care for pulmonary hypertension.

Participants will have three MRI scans on one day. The first MRI scan will be done right before you take an inhaled treprostinil (Tyvaso) treatment, the second scan right after the inhaled treprostinil treatment, and the third scan is done 2-4 hours after the inhaled treprostinil treatment. Each scan will take around 1 hour each from start to finish. The total time for three MRI scans and other study activities will take around 6 hours of your time. There is no direct medical benefit to you for taking part of this study. This information learned during the study may help others with pulmonary hypertension in the future. The MRI or Magnetic resonance imaging uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. Risks of the xenon gas are slight numbness in legs, nausea, a feeling of well-being, mild tingling in fingertips. Study team will use pulmonary function tests that are available from the medical record
The information presented in this section may be discussed in greater detail later in the consent form. If you are in interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you are a patient with pulmonary hypertension (PH) being treated with a medication called treprostinil. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Sudarshan Rajagopal will conduct the study and it is funded by United Therapeutics Corporation. United Therapeutics Corporation, will pay Duke University to perform this research, and these funds may reimburse part of Dr. Sudarshan Rajagopal salary. Dr. Rajagopal also receives personal compensation from United Therapeutics for serving on their advisory board.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, your doctors will be Drs. Sudarshan Rajagopal, M.D, Bastiaan Driehuys, Ph.D, and Jospeh Mammarappalil, M.D., Ph.D and they will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

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Please note that Dr. Driehuys holds several patents related to the technology used in this study. These patents are licensed to Polarean, Inc for commercial development. While Polarean, Inc. is not sponsoring the present study, Dr. Driehuys does have an ownership stake in this company. However, the findings from this study could lead to financial benefit for Polarean.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to determine whether magnetic resonance imaging (MRI) using inhaled hyperpolarized xenon gas can help visualize impaired lung function and detect changes over time in patients receiving treatment. Hyperpolarization is done by exposing the xenon gas to a special type of laser light, and does not change the chemical properties of the gas in any way. ^{129}Xe is a special type of xenon gas and when inhaled during MRI may be able to show areas of abnormal thickening of parts of the lungs. These images may provide a better way to look at lung structure and function in patients with pulmonary hypertension. We anticipate that the images acquired in this study will provide more specific information about lung disease than standard lung function tests. The use of ^{129}Xe MRI is investigational. "Investigational" means that these tests have not yet been approved by the US Food and Drug Administration and are being tested in research studies like this one.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 15 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible.

The study involves the following study visits:

- **Screening:** This will take place before your first MRI scan. You will be asked for your medical history, record of medications, and your vital signs will be measured. You will be asked to fill out a questionnaire to ensure that you are eligible to undergo an MRI scan. Also, the following procedures will be performed:
  - You may have a finger sensor portable machine placed on one of your fingers to check your oxygen carrying capacity in your blood (hemoglobin level),
  - If you are female of child-bearing potential, you will be required to undergo urine pregnancy test and it must be negative before you can continue to participate in this study.

- **Imaging Study Visit**. This visit may will occur at the same time as the screening visit or shortly after. This visit will take around 6 hours. The following will occur:

  1. An IV will be placed in your arm to allow us to draw your blood.

  2. **MRI**:. For each of the three MRI scans, you will lie on your back on a table, wearing a vest that transmits and receives signals for the MRI and a small sensor will be applied to

your finger to monitor your pulse rate and blood oxygen levels. The table will be slid into the bore of the MRI scanner (a tunnel about 6 feet long and 25 inches in diameter) and we will obtain one or more (up to a maximum of 5) MRI scans of your lungs. After this, you will be instructed to inhale a small calibration dose of hyperpolarized ^{129}Xe from a plastic bag through a mouthpiece. Following this, you will be asked to inhale additional doses of hyperpolarized ^{129}Xe to acquire different kinds of lung scans (up to a maximum of 5). For each ^{129}Xe dose you will be asked to hold your breath for approximately 15 seconds while the scan is obtained. During each scan, your heart rate and your oxygen saturation will be monitored. After each ^{129}Xe dose, the table will slide out of the MRI bore so that you can communicate with study personnel. When you are ready, the next xenon dose will be administered. After the MRI examination, you will remain with study personnel until you feel recovered from any study effects and your heart rate and oxygen saturation are within an acceptable range. You will then be free to go home. At any time after the exam, you may contact a member of the study team if you feel that you are having any symptoms or effects related to your participation in the study. Each scan will take around 1 hour each from start to finish.

- The first MRI scan will take place just prior to your treprostinil dose. After the first MRI scan, you will take your inhaled treprostinil treatment as prescribed by your PH care doctor. The second scan will be done after you have completed your treatment. The third MRI scan will be done around 3- 4 hours after this inhaled treprostinil treatment and right before the next dose. You will not take your inhaled treprostinil any differently than prescribed to you by your PH doctor as part of this study. You will be provided with space and time to complete your inhaled treprostinil treatment outside the MRI machine room.

3. **Blood Draw:** 3 blood samples (about 2 tablespoons each time) will be taken from your IV. The first samples will be taken prior to or right after the first MRI scan and before you take your inhaled treprostinil treatment. The second blood sample will be taken after you take the inhaled treprostinil treatment and are preparing for the second MRI scan or right after. The third blood sample will be taken 2-4 hours after the inhaled treprostinil treatment. The blood samples will be taken to determine the amount of treprostinil that is in your bloodstream at different time points.

4. **Imaging of the hands:** You will have 3 scans done of your hands at the same time point before your blood is taken. The scans are done to assess the how much blood flow there is to your hands. The scan involves 3 laser images of your hands. First scan will be of your right hand, second scan will be of your left hand and the third will be with your dominant hand while you have a blood pressure cuff on your upper arm. The blood pressure cuff be inflated and deflated once for a total of 15 seconds. These scans are not invasive. The scanner does not touch your skin.

5. **Pulmonary Function Tests:** Study team will use the PFTs that are available from the medical record

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The study doctor may stop your participation in this study at any time without your consent. Potential reasons for ending your participation may include safety concerns or general reasons related to the conduct of the research study itself. The total time for three MRI scans and other listed study activities will take around 6 hours of your time.

HOW LONG WILL I BE IN THIS STUDY?
Your study involvement will last approximately1-2 days for scanning and follow-up.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information but this cannot be guaranteed.

Risks associated with inserting an IV (intravenous) catheter into your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

MRI Risks:
Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, you will be excluded from participation in this research study.

The study involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. During MRI scanning you will hear loud machine-like noises. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire. The MRI scan can be stopped at any time if you request it.

You should be aware that the MRI images are for research purposes only and will not be reviewed for the purposes of your healthcare.

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Risks of Xenon Gas:
Inhalation of xenon gas may cause you to feel the following effects:

- Slight numbness in the legs
- Nausea
- A sensation similar to smelling flowers
- A feeling of well-being or elation
- Mild tingling in the fingertips

If you experience these effects they typically resolve within 1-2 minutes of exhaling the xenon gas. This breath of xenon will not contain any oxygen. This could briefly cause the oxygen levels in your blood to decrease. These oxygen levels will return to normal when you begin normal breathing again. The oxygen level in your blood will be monitored at all times by the study team.

Female
Being a part of this study (MRI with ^{129}Xe) while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. Females, who are of child bearing potential will have a urine pregnancy test on the day of the MRI, and a negative result is required to participate in the study.

***Risks of Drawing Blood*:** Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there will not be direct medical benefit to you. We hope that in the future the information learned from this study will benefit other people with your condition.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests and procedures may be reported to United Therapeutics and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration,

representatives and affiliates of United Therapeutics, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.
As part of this study, you will be asked to have certain tests, MRIs, and/or procedures performed. Some of these tests, x-rays and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the representatives and affiliates of United Therapeutics. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.
If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Sudarshan Rajagopal**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Assessing Response to Inhaled Prostacyclin with
Hyperpolarized 129Xe MRI

The study sponsor, United Therapeutics, has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

WHAT ABOUT COMPENSATION?
You will be paid $150 for your participation in the study.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., your Duke physicians, or the funding source for this study, United Therapeutics Corporation, to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Rajagopal at 919-684-6237 during regular business hours. After hours, weekends, and holidays please call the hospital to page Dr. Rajagopal at 919-684-8111.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Rajagopal in writing and let him know that you are withdrawing from the study. His mailing address is:
DUMC
Box 102351
Durham, NC 27710

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

DUKE UNIVERSITY HEALTH SYSTEM

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Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

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

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For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Person signing Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time

_____
Printed Name of Person Obtaining Consent

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Assessing Response to Inhaled Prostacyclin with Hyperpolarized 129Xe MRI

This is a research study to find out if magnetic resonance imaging (MRI) using inhaled hyperpolarized xenon gas can help visualize lung function in patients with pulmonary hypertension. The study will also find out if this MRI with xenon gas can detect lung and body changes after treatment with inhaled treprostinil (Tyvaso) that is taken as standard of care for pulmonary hypertension.

Participants will have three MRI scans on one day. The first MRI scan will be done right before you take an inhaled treprostinil (Tyvaso) treatment, the second scan right after the inhaled treprostinil treatment, and the third scan is done 2-4 hours after the inhaled treprostinil treatment. Each scan will take around 1 hour each from start to finish. The total time for three MRI scans and other study activities will take around 6 hours of your time. There is no direct medical benefit to you for taking part of this study. This information learned during the study may help others with pulmonary hypertension in the future. The MRI or Magnetic resonance imaging uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. Risks of the xenon gas are slight numbness in legs, nausea, a feeling of well-being, mild tingling in fingertips. Study team will use pulmonary function tests that are available from the medical record
The information presented in this section may be discussed in greater detail later in the consent form. If you are in interested in learning more about this study, please continue to read below.

You are being asked to take part in this research study because you are a patient with pulmonary hypertension (PH) being treated with a medication called treprostinil. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Sudarshan Rajagopal will conduct the study and it is funded by United Therapeutics Corporation. United Therapeutics Corporation, will pay Duke University to perform this research, and these funds may reimburse part of Dr. Sudarshan Rajagopal salary. Dr. Rajagopal also receives personal compensation from United Therapeutics for serving on their advisory board.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, your doctors will be Drs. Sudarshan Rajagopal, M.D, Bastiaan Driehuys, Ph.D, and Jospeh Mammarappalil, M.D., Ph.D and they will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

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Please note that Dr. Driehuys holds several patents related to the technology used in this study. These patents are licensed to Polarean, Inc for commercial development. While Polarean, Inc. is not sponsoring the present study, Dr. Driehuys does have an ownership stake in this company. However, the findings from this study could lead to financial benefit for Polarean.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to determine whether magnetic resonance imaging (MRI) using inhaled hyperpolarized xenon gas can help visualize impaired lung function and detect changes over time in patients receiving treatment. Hyperpolarization is done by exposing the xenon gas to a special type of laser light, and does not change the chemical properties of the gas in any way. ^{129}Xe is a special type of xenon gas and when inhaled during MRI may be able to show areas of abnormal thickening of parts of the lungs. These images may provide a better way to look at lung structure and function in patients with pulmonary hypertension. We anticipate that the images acquired in this study will provide more specific information about lung disease than standard lung function tests. The use of ^{129}Xe MRI is investigational. "Investigational" means that these tests have not yet been approved by the US Food and Drug Administration and are being tested in research studies like this one.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 15 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible.

The study involves the following study visits:

- **Screening:** This will take place before your first MRI scan. You will be asked for your medical history, record of medications, and your vital signs will be measured. You will be asked to fill out a questionnaire to ensure that you are eligible to undergo an MRI scan. Also, the following procedures will be performed:
  - You may have a finger sensor portable machine placed on one of your fingers to check your oxygen carrying capacity in your blood (hemoglobin level),
  - If you are female of child-bearing potential, you will be required to undergo urine pregnancy test and it must be negative before you can continue to participate in this study.

- **Imaging Study Visit**. This visit may will occur at the same time as the screening visit or shortly after. This visit will take around 6 hours. The following will occur:

  1. An IV will be placed in your arm to allow us to draw your blood.

  2. **MRI**:. For each of the three MRI scans, you will lie on your back on a table, wearing a vest that transmits and receives signals for the MRI and a small sensor will be applied to

your finger to monitor your pulse rate and blood oxygen levels. The table will be slid into the bore of the MRI scanner (a tunnel about 6 feet long and 25 inches in diameter) and we will obtain one or more (up to a maximum of 5) MRI scans of your lungs. After this, you will be instructed to inhale a small calibration dose of hyperpolarized ^{129}Xe from a plastic bag through a mouthpiece. Following this, you will be asked to inhale additional doses of hyperpolarized ^{129}Xe to acquire different kinds of lung scans (up to a maximum of 5). For each ^{129}Xe dose you will be asked to hold your breath for approximately 15 seconds while the scan is obtained. During each scan, your heart rate and your oxygen saturation will be monitored. After each ^{129}Xe dose, the table will slide out of the MRI bore so that you can communicate with study personnel. When you are ready, the next xenon dose will be administered. After the MRI examination, you will remain with study personnel until you feel recovered from any study effects and your heart rate and oxygen saturation are within an acceptable range. You will then be free to go home. At any time after the exam, you may contact a member of the study team if you feel that you are having any symptoms or effects related to your participation in the study. Each scan will take around 1 hour each from start to finish.

- The first MRI scan will take place just prior to your treprostinil dose. After the first MRI scan, you will take your inhaled treprostinil treatment as prescribed by your PH care doctor. The second scan will be done after you have completed your treatment. The third MRI scan will be done around 3- 4 hours after this inhaled treprostinil treatment and right before the next dose. You will not take your inhaled treprostinil any differently than prescribed to you by your PH doctor as part of this study. You will be provided with space and time to complete your inhaled treprostinil treatment outside the MRI machine room.

3. **Blood Draw:** 3 blood samples (about 2 tablespoons each time) will be taken from your IV. The first samples will be taken prior to or right after the first MRI scan and before you take your inhaled treprostinil treatment. The second blood sample will be taken after you take the inhaled treprostinil treatment and are preparing for the second MRI scan or right after. The third blood sample will be taken 2-4 hours after the inhaled treprostinil treatment. The blood samples will be taken to determine the amount of treprostinil that is in your bloodstream at different time points.

4. **Imaging of the hands:** You will have 3 scans done of your hands at the same time point before your blood is taken. The scans are done to assess the how much blood flow there is to your hands. The scan involves 3 laser images of your hands. First scan will be of your right hand, second scan will be of your left hand and the third will be with your dominant hand while you have a blood pressure cuff on your upper arm. The blood pressure cuff be inflated and deflated once for a total of 15 seconds. These scans are not invasive. The scanner does not touch your skin.

5. **Pulmonary Function Tests:** Study team will use the PFTs that are available from the medical record

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Consent to Participate in a Research Study
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The study doctor may stop your participation in this study at any time without your consent. Potential reasons for ending your participation may include safety concerns or general reasons related to the conduct of the research study itself. The total time for three MRI scans and other listed study activities will take around 6 hours of your time.

HOW LONG WILL I BE IN THIS STUDY?
Your study involvement will last approximately1-2 days for scanning and follow-up.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information but this cannot be guaranteed.

Risks associated with inserting an IV (intravenous) catheter into your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

MRI Risks:
Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, you will be excluded from participation in this research study.

The study involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. During MRI scanning you will hear loud machine-like noises. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire. The MRI scan can be stopped at any time if you request it.

You should be aware that the MRI images are for research purposes only and will not be reviewed for the purposes of your healthcare.***Risks of Xenon Gas:***
Inhalation of xenon gas may cause you to feel the following effects:

- Slight numbness in the legs
- Nausea
- A sensation similar to smelling flowers
- A feeling of well-being or elation
- Mild tingling in the fingertips

If you experience these effects they typically resolve within 1-2 minutes of exhaling the xenon gas. This breath of xenon will not contain any oxygen. This could briefly cause the oxygen levels in your blood to decrease. These oxygen levels will return to normal when you begin normal breathing again. The oxygen level in your blood will be monitored at all times by the study team.

Female
Being a part of this study (MRI with ^{129}Xe) while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. Females, who are of child bearing potential will have a urine pregnancy test on the day of the MRI, and a negative result is required to participate in the study.

***Risks of Drawing Blood*:** Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there will not be direct medical benefit to you. We hope that in the future the information learned from this study will benefit other people with your condition.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests and procedures may be reported to United Therapeutics and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of United Therapeutics, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

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Consent to Participate in a Research Study
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As part of this study, you will be asked to have certain tests, MRIs, and/or procedures performed. Some of these tests, x-rays and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the representatives and affiliates of United Therapeutics. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.
If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

An external investigator from the University of Virginia will be helping analyze the MRI images for this study. They will have access to your historical data for your right heart catheterizations, pulmonary function tests, laboratory results, echocardiograms as well as other pertinent data to help with analyzing. Minimal information about you will be shared with this external investigator. Identifiable data shared can include sex, ethnicity, birthdate and date of study procedures and/or labs. We will share only the minimum necessary information in order to conduct the research.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

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Durham, NC 27710

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

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_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Person signing Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time

_____
Printed Name of Person Obtaining Consent