Official Title: Xenon MRI in Pulmonary Hypertension

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Duke University Health System

Consent to Participate in a Research Study
Xenon MRI in Pulmonary Hypertension (Jupiter PH) Cohort 1

Version 2

CONCISE SUMMARY
You are being asked to take part in this research study because you have pulmonary hypertension (PH) and are being evaluated for lung transplant. PH can occur in advanced lung disease and can occur in diseases such as pulmonary arterial hypertension (PAH), chronic obstructive pulmonary disease (COPD), interstitial pulmonary fibrosis (IPF), and interstitial lung disease (ILD). 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.

The purpose of this study is to evaluate the ability of a new technology, called hyperpolarized xenon (^{129}Xe) Magnetic Resonance Imaging (MRI), to monitor changes in lung tissue and to determine how these changes may impact lung function in PH. ^{129}Xe is a non-toxic gas that when inhaled is expected to enhance the quality of images and data obtained by MRI. The FDA has recently approved Polarean's XENOVIEW™ (Xe 129 hyperpolarized) for use with MRI for the Evaluation of Lung Ventilation.
If you give written consent to be in the study, research procedures performed will include assessment of vital signs, MRI with ^{129}Xe (once), and collection of tissue from the lung removed during your transplant surgery. Additional tests, exams, and non-research procedures will be performed that are part of your standard care for PH.

There are no direct benefits to being in this study. Potential risks of the ^{129}Xe MRI include nausea and a mild tingling sensation in fingers. There also a risk of loss of confidentiality resulting from your involvement in this study.

Your study involvement will last approximately 6-8 weeks, depending on scheduling of study events and your lung transplant surgery. If you are 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 have pulmonary arterial hypertension (PH) and are being evaluated for lung transplant and are awaiting lung transplant or are anticipated to be listed for lung transplant. 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 them 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.

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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 a grant from the National Institutes of Health (NIH). Portions of Dr. Rajagopal's and his research team's salaries will be paid by this grant. The Xenon MRI was developed by a Duke start-up company called Polarean, Inc. Dr. Rajagopal has intellectual property that has been licensed to Polarean, and another member of the study team, Dr. Bastiaan Driehuys, founded the company. While Polarean, Inc. is not sponsoring the present study, if the study is successful, it is possible that Duke, Dr. Driehuys, and Dr. Rajagopal could benefit financially.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, ***Dr. Sudarshan Rajagopal, MD, PhD*** will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to evaluate the ability of a new technology, called xenon (^{129}Xe) Magnetic Resonance Imaging (MRI), to monitor changes in lung tissue and to determine how these changes may impact lung function in PH. The FDA has recently approved Polarean's XENOVIEW™ (Xe 129 hyperpolarized) for use with MRI for the Evaluation of Lung Ventilation.

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:

Screening/Baseline (V0)
After obtaining informed consent, the following data/will be collected and documented:

- Relevant disease history and symptoms
- Medical history (including WHO Functional class, comorbid conditions)
- Assess vital signs (temperature, heart rate, blood pressure, respiratory rate, and pulse oximetry) including weight and height
- Survey of other medications you may be taking
- If Pulmonary Function Test's (PFT) are not available from your medical record, these will also be collected. These are non-invasive tests of how well your lungs are working
- 6 Minute Walk Tests (6MWTs
- Echocardiogram (ECHO) – a standard of care ultrasound scan of your heart
- Ventilation/Perfusion (V/Q) S scan - standard of care imaging scan of your lungs
- Pre-and Postoperative Labs

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- EMPHASIS-10 Patient Reported Outcome. This will be administered by a clinical research coordinator.
- Patient Global Impression of Change of Symptoms Survey
- Patient Global Impression of Change of Functions Survey
- Patient Global Impression of Severity of Symptoms Survey
- Patient Global Impression of Severity of Functions Survey

Study Visit (V1)
The following data/will be collected and documented:

- Completion of MRI screening form.
- Urine pregnancy test for a female of childbearing potential
- Research MRI Session with inhalation of ^{129}Xe (^{129}Xe MRI)
    - MRI (Magnetic Resonance Imaging) is a way for us to see inside your body. MRI uses a powerful magnet, radio waves and a computer to produce detailed pictures of organs, bones and other internal body structures. For the MRI, you will lie on a table inside a scanner tube for about 30 minutes, while the scanner moves the reading unit over the areas of your body to be scanned.
- Assess vital signs (temperature, heart rate, blood pressure, respiratory rate, and pulse oximetry) including optional noninvasive, optical Hemoglobin measurement
- Discuss changes in your history or other medications
- Adverse event reporting after receiving the ^{129}Xe gas
- ~20 ml of research blood samples for plasma, DNA, and RNA

Follow-up/Release
The following data/will be collected and documented:

- Vital signs (temperature, heart rate, blood pressure, respiratory rate, and pulse oximetry) including optional noninvasive, optical Hemoglobin measurement
- Adverse event reporting

Lung transplant and Completion of the Study
When you are called in for a lung transplant procedure, tissue will be collected from the removed lungs for research use and you will have completed your involvement in the study.

HOW LONG WILL I BE IN THIS STUDY?
Your study involvement will last approximately 6-8 weeks, depending on the scheduling of study events and your surgery.

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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?

Risks of MRI

You may have an MRI study as part of this research. 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, including medical implants, devices such as pacemakers and internal defibrillators, or certain dyes found in in tattoos. We will also keep the MRI room locked so that no one carrying metal objects enters the room while you are in the scanner.

If there is any question about potentially hazardous metal within the body, you will not undergo the MRI. This may exclude you from participation in this research study. The MRI 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. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the MRI. During the MRI, you can have voice contact and physical contact with someone in attendance if you desire. Let the study doctor know if you have a fear of enclosed spaces.

Risks of Xenon Gas (^{129}Xe):

Inhalation of **^{129}Xe** 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.

Risk of Incidental Findings for MRI

Since the MRI methods being tested are experimental, the MRI images will not be formally reviewed for incidental findings not related to the research. However, if there is something of concern to the PI, then the PI will approach the IRB for guidance on how to proceed on a case-by-case basis.

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Reproductive Risks
For women: Pregnancy in women with pulmonary hypertension is associated with an increased risk of complications for mother and babies; over half of pregnant women with advanced pulmonary arterial hypertension die during or shortly after pregnancy. Because the ^{129}Xe may have other effects on a developing pregnancy, a urine pregnancy test will be done on the day of the MRI. If it is positive, the MRI will not be done and additional testing will be performed, and, if pregnancy is confirmed, you will be referred to a specialist in managing high-risk pregnancy.

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

Drug and Food Interactions:
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

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

Definition of DNA

Your genes are made up of DNA. DNA is short for deoxyribonucleic acid. DNA contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child.

Definitions of RNA and Protein

RNA is made from DNA. RNA is short for ribonucleic acid. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs.

a. Participation in genetic studies: The genetic studies described are for research purposes only. Therefore, you will receive no results from this study (except as described below). It is not the purpose of this study to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness. The research tests are not being used as diagnostic tests for any disease or illness. Your participation in this study is not a substitute for your regular medical care or check-ups.

b. Research Results: Through this research, we may find that you have an abnormal gene or gene product (DNA, RNA, or protein) which indicates a risk for developing a disease at some time in the future. It is also possible that the research results may indirectly provide unexpected personal information about you or your family (such as ethnic/racial background or an unknown genetic

relationship between family members). Please talk with the study doctor if you have any questions or concerns about the genetic testing being done in this research study.

c. Incidental Findings: It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician unless the information indicates that you may be at risk for a serious illness known at the time of testing to be treatable. In that case, we will attempt to notify you using the contact information you have provided, so that you can speak with Dr. Rajagopal at Duke University Health System (DUHS). DUHS staff will not provide this information in a voice mail, email, or otherwise prior to contacting you. Please notify us of any change in your contact information.

If you do not want to be notified of any incidental findings, please initial below.

_____ Please do not notify me of any incidental findings obtained from this research.

If you prefer, we can ask you at the time of notification whether or not you want to receive incidental findings information. In this case, please initial below.

_____ Please ask me at the time of notification whether or not I want to receive incidental findings information.

If at any time during or after the study you change your mind about whether or not you would like to be notified, you can contact us during regular business hours at 919-684-6237.

Analysis of The Sample

The sample may be analyzed to find out about variations in certain genes. Your samples will be used only for the purpose of this study, and for absolutely no other purpose. The information resulting from the analysis will be assigned a de-identified code number; your identity will never be revealed; your sample will only be known by this code number. These samples will be stored at the clinical site.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there will be no 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, the study team will record the results of your study-related laboratory tests including imaging results. These could include pulmonary function tests and imaging scans (e.g ^{129}xe

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MRI scans of the lungs with gas or VQ scans). In addition, the study team may obtain information from your DUHS medical record and use this to analyze the MRI scans obtained for this research study. The date and time included in your MRI scans will be stored indefinitely.

Your data and MRI will be labeled with a study number to protect your privacy., The study team will use initials, your year of birth, dates of study-related tests, and dates of study visits in your research information.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to National Institutes of Health (NIH), 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 National Institutes of Health (NIH), 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, x-rays, 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 Duke Pulmonary Vascular Disease Center and representatives and affiliates of National Research Health (NIH). 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.

Your data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. This de-identified data may be shared with other researchers, here, around the world, and with companies. The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

Databases and Repositories of Genetic Information for Future Research:
Even without your name or other identifiers, your genetic information is unique to you. There is a potential risk that someone will identify you from your genetic information or learn something about you by looking at your genetic information; this risk may increase in the future as technologies advance and as more researchers study your genetic information. These risks may also affect members of your family. You should discuss your participation in this study with your family and ask the study doctor about any questions or concerns you may have.

Your samples and genetic information may be used for research for many years in the future.
We will protect your privacy and confidential information by labeling your samples and genetic information only with a code number. Researchers outside of Duke University will not be given a link between the code number and your name or any other identifying information. While we hope this will prevent any potential loss of privacy or confidentiality, we cannot make any guarantees.

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Potential Risks and the Genetic Information Non-Discrimination Act (GINA):
There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.
The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

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

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

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Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

The study results will be retained in your research record forever. Any research information in your medical record will also 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 TO YOU?
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. Rajagopal and study team**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

Procedures performed solely for research purposes, such as research blood collection, vital sign assessments, and the ^{129}Xe MRI, will be done with no cost to you.

WHAT ABOUT COMPENSATION?
You will receive $100 compensation for each completed visit for your expenses related to your participation. In addition, if you need to travel 50 miles or more (one way) for a visit, you will be reimbursed for
your mileage according to IRS guidelines. If you travel 100 miles or more (one way) and need to stay overnight for a visit, you will be reimbursed up to $150 for your lodging per night, inclusive of taxes

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and hotel fees, validated by receipt, and will require approval by the study staff. You will also be reimbursed for meals during your hotel stay up to a maximum of $50 per day.

Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual exceeds $600 in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research subject payments to a non-employee of Duke University exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples.

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., or your Duke physicians 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. Sudarshan Rajagopal*** at ***919-684-6237*** during regular business hours and After hours and on weekends and holidays, please page the on-call doctor from Center of Pulmonary Vascular Disease at 919-970-2783.

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

Duke Health
Pulmonary Vascular Disease Center
Division of Pulmonary, Allergy & Critical Care
DUMC 102531.
Durham NC 27710

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

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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 any time without your consent. 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 https://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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Rajagopal at 919-684-6237 during regular business hours. After hours and on weekends and holidays, please page the on call doctor from Center of Pulmonary Vascular Disease at 919-970-2783.

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
_____		
Print Name of Person Signing Subject		
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time
_____		
Print Name of Person obtaining Consent		