

**Consent to Participate in a Research Study****ADULT**

Non-Invasive Diagnosis of Pulmonary Vascular Disease Using
Inhaled ^{129}Xe Magnetic Resonance Imaging: VITA

CONCISE SUMMARY

This is a research study to determine whether magnetic resonance imaging (MRI) using inhaled hyperpolarized ^{129}Xe gas can help visualize impaired lung function and detect changes over time in patients receiving treatment. ^{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 heart and lung disease. This visit will be 3-4 hours and will consist of taking a medical history and MRI.

There is no direct medical benefit to you for taking part of this study. Our ultimate goal is to predict how a particular patient might respond to a particular therapy and to observe such responses earlier than conventional tests. We anticipate that the images acquired in this study will provide more specific information about lung disease than standard lung function tests. The 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. Risks of the xenon gas are slight numbness in legs, nausea, a feeling of well-being, and mild tingling in fingertips. You will have pulmonary function testing for the study, you may experience breathlessness or dizziness during or immediately following these tests. There is also a small risk of collapsed lung in people with certain types of lung disease.

The information presented in this section may be discussed in greater detail later in the consent form. 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 are a patient with pulmonary arterial hypertension (PAH) or a patient with heart disease or a patient with lung disease. 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.

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, your doctors will be **Drs. Sudarshan Rajagopal, M.D, Joseph G Mammarappallil, M.D. Ph.D. and Bastiaan Driehuys, 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.

A grant from the National Institutes of Health (NIH)'s National Heart, Lung, and Blood Institute (NHLBI) will fund this study. Portions of Drs. Rajagopal, Mammarappallil, & Driehuys and their research team's salaries will be paid by this grant.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether magnetic resonance imaging (MRI) using inhaled hyperpolarized ¹²⁹Xe gas, can help visualize impaired lung function and detect changes over time in patients receiving treatment. ¹²⁹Xe 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 combined with images taken with injected contrast agents or other types of MRI may provide a better way to look at lung structure and function in patients with heart and lung disease. Our ultimate goal is to predict how a particular patient might respond to a particular therapy and to observe such responses earlier than conventional tests. 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 ¹²⁹Xe 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 127 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. The study involves the following study visits:

- **Screening Visit** – At the screening visit, you will be asked for your medical history, record of medications, and your vital signs including hemoglobin (optional) by finger sensor device 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:
 - If you are female of child-bearing potential, you will be required to undergo a urine pregnancy test and it must be negative before you can continue to participate in this study.
- **Visit 1 - Imaging Study Visit.** This visit may also occur at the same time as the screening visit or shortly after.

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Description of Imaging Study Visit

This visit will take about 3-4 hours. The visit will begin with a review of your relevant history, symptoms, medications and rescreening for eligibility to participate, including:

- a urine sample for pregnancy testing for women of child-bearing potential
- by finger sensor device for hemoglobin level the day of the MRI.

Either after screening or on a separate day you will undergo pulmonary function testing to assess your global lung function using standard clinical tests. If pulmonary function test results are already available from your medical record, the pulmonary function tests will not be done.

MRI using inhaled hyperpolarized ^{129}Xe gas

After pulmonary function testing you will participate in the MRI portion of the study. For the 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 measured 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.

- **Visit 2 - Imaging Study Visit.** For Chronic Thromboembolic Pulmonary Hypertension (**CTEPH**) subjects **ONLY**

If you give consent, you will need to return post-surgery for a second visit at least 4 weeks post-surgical to have another MRI. Before the MRI, females who are of child bearing potential will have a urine pregnancy test performed and must have a negative result. You will need to complete a MRI screening form. You will be in the MRI no more than 1hr.

Follow-up

You will be followed-up by a short phone contact no more than 30 minutes long approximately 24 hours later following study visit 1 and visit 2 (if applicable). You may be asked to return for a second scan in the study, at a time no earlier than 48hrs after your last xenon dose.

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Study Activities	Screening	Study Visit 1	Study Visit (2 *only for CTEPH subjects)	Follow Up/ Release (after last dose)	Follow-up contact w/in 24 hrs.
Informed Consent	X				
History re: Disease	X				
Medical History	X				
Pregnancy Test (urine)	(X)	(X)	(X)		
MRI Screening Form	X	(X)	X		
Imaging Session		X	X		
Adverse Events		X		X	X
Vital Signs Assessment with optional non-invasive, optical Hemoglobin measurement	X	X	X	X	

In addition, the team may obtain information from your DUHS medical record and use this data to analyze the MRI scans obtained as part of this study. 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.

HOW LONG WILL I BE IN THIS STUDY?

Your study involvement will last approximately 1 to 2 weeks depending on scheduling of the Visit 1 - Imaging Study Visit. CTEPH patients study involvement may last longer depending on scheduling of the post-surgical MRI scan.

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.

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.

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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 collected for this study are only used for research 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 ¹²⁹Xe) 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 will be done on the day of your MRI study, and it must be negative before you can continue in this 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 PVD.

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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 MRI scans of the lungs with gas. 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.

As part of the study, results of your study-related laboratory tests 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 NIH and the Duke University Health System Institutional Review Board. 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, and/or procedures performed. Some of these tests 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 **research data office at Duke** OR representatives and affiliates of **National Institutes of 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.

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.

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. This data will be de-identified, meaning minimal information about you will be shared with this external investigator. Data shared can include sex, ethnicity, birthdate and date

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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.

Certificate of Confidentiality:

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.

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.

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



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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.

WHAT ABOUT COMPENSATION?

You will be reimbursed up to \$100 for your expenses related to your participation in completion of Study Visits.

Screening visit \$50.00

Study visit 1 \$50.00

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. 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.

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.



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The sponsor or regulatory agencies may stop this study at any time 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.

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, weekends, and holidays please call the hospital to page Dr. Rajagopal at 919-684-8111.

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.



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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