

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

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Research Summary

1. Protocol Title: Non-Invasive Diagnosis of Pulmonary Vascular Disease Using Inhaled ^{129}Xe Magnetic Resonance Imaging

2. Purpose of the Study: To develop a novel, non-invasive means of comprehensively diagnosing and monitoring response to therapy in PVD using MR imaging (MRI). Our approach uses hyperpolarized ^{129}Xe (^{129}Xe)-MRI, a novel technology that images lung ventilation, microstructure, and gas exchange.

3. Background & Significance:

Pulmonary arterial 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. For example, patients with *mild to moderate* left heart disease or chronic obstructive pulmonary disease, which are common in older patients, technically cannot be diagnosed with PAH because *severe* left heart and lung disease can cause 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 concomitant heart disease, which can increase the filling pressures of the heart (the PCWP), or 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) ^{129}Xe (Xe) magnetic resonance imaging (MRI), for the diagnosis of PVD. Hyperpolarized ^{129}Xe MRI has been under active development and used in clinical research at Duke for over 7 years. It has been used in 5 IRB protocols, 3 of which are currently active. Over 250 patients and volunteers have undergone ^{129}Xe 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 ^{129}Xe -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 ^{129}Xe study demonstrated spectroscopic and imaging indices consistent with a barrier to diffusion of ^{129}Xe 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 ^{129}Xe 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, ^{129}Xe 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 ^{129}Xe 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 ^{129}Xe MRI could be used to non-invasively monitor response to therapy. If we are successful in demonstrating the applicability of HP ^{129}Xe MRI, this technology holds the promise of greatly improving the diagnosis and management of PVD.

4. Design & Procedures:

This study seeks to deploy several forms of ^{129}Xe MRI contrast as well as emerging conventional proton MRI techniques for imaging lung structure and perfusion. Specifically, the ^{129}Xe 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. The conventional ^1H MRI scans will include a free-breathing ultra-short echo time (UTE) scan that provides images similar to that of a CT scan. The overall aims of the study are as follows:

Aim 1. Perform ^{129}Xe MRI scans in cohorts of patients with PVD, isolated left sided heart failure and isolated lung disease:

- 1.1 Deploy and optimize ^{129}Xe gas exchange MR spectroscopy and imaging, ^{129}Xe ventilation MRI, structural ^1H UTE MRI, and breath-hold ^1H perfusion MRI.
- 1.2 Conduct comprehensive ^1H - ^{129}Xe MRI in 10 patients with pure PAH
- 1.3 Conduct comprehensive MRI in 10 patients with pure left heart failure
- 1.4 Conduct comprehensive MRI in 10 patients with pure lung disease but no pulmonary hypertension
- 1.5 Conduct comprehensive MRI in 5 patients with Chronic thromboembolic pulmonary hypertension (CTEPH) pre and post PTE surgery.

Aim 2. Develop diagnostic criteria for optimizing the sensitivity and specificity of ^{129}Xe MRI for the diagnosis of PVD:

- 2.1 Develop quantification/scoring methods based on PAH, left heart disease, and lung disease MRI
- 2.2 Develop reader training materials and train 3 expert readers
- 2.3 Begin prospective recruitment of 92 patients undergoing right heart catheterization for evaluation of PAH or other cardiac or pulmonary disease for MRI scans. These patients may be asked to return for a second scan in the study, at a time no earlier than 48hr after their last xenon dose.

Aim 3. Perform a larger, single-blind study testing the diagnostic accuracy of ^{129}Xe MRI for diagnosis of PVD:

- 3.1 Trained readers will evaluate ^{129}Xe MRI, while blinded to the subject's disease state and will determine the presence and severity of PVD
- 3.2 Diagnostic accuracy of ^{129}Xe MRI will be compared to the gold standard of hemodynamic and clinical criteria of PAH
 - 3.2.1 The primary focus of Aim 3 is to compare ^{129}Xe MRI capability to detect absence/presence of pre/post-capillary PH to the gold standard of RHC
 - a. For this PFTs are not necessary, so they are ancillary
 - b. However, they are a standard way to characterize patients for publications, etc, so we would like to get them if we can. Getting them from the medical record is perfectly adequate for this purpose.
 - i. If PFTs are not available from the medical record, they are not so critical as to prevent us from enrolling the subject. In publications we will simply acknowledge the realities of COVID for this missing data.

This will be a single-blinded, open-label study enrolling volunteers and patients with pure PAH (10 subjects), pure left heart disease (10 subjects), pure lung disease (10 subjects) and CTEPH (5 subjects) [Aim 1] followed by a larger cohort of 92 subjects who are undergoing right heart catheterization for evaluation of PAH or other cardiac or pulmonary disease. [Aim 2]. We plan to consent 127 subjects. No subject will be excluded from the study on the basis of gender or ethnicity. Female subjects of childbearing potential will undergo urine pregnancy testing before each MRI. The urine pregnancy test must be negative to continue participating in the study. To refine the precision of ^{129}Xe MRI for imaging gas transfer efficiency,

we will acquire a hemoglobin level by finger sensor device for each subject testing at each study visit. Informed consent will be obtained before a subject begins any study intervention. Subjects will undergo an approximately hour long comprehensive MRI protocol

Patients with PAH, CTEPH, left heart disease and lung disease will be recruited using minimally restrictive inclusion/exclusion criteria. The Duke Center for Pulmonary Vascular Disease sees approximately 150 patients for evaluation of PAH including CTEPH in a year. For the first phase of the study, whether patients are receiving approved therapies, enrolled in clinical trials, or receiving no therapy, all will be eligible for inclusion in this MRI study. For the second phase of the study, patients who have PAH and receiving approved therapies, patients who are being evaluated for PVD or other cardiac or pulmonary disease will be included in the study.

Each study session will begin with a collection of relevant patient history and symptoms, measurement of hemoglobin levels, and urine pregnancy testing (if applicable) and finally pulmonary function testing. Pulmonary function testing will include one or more of spirometry, lung volumes and DL_{CO}. Study team will use the PFTs that are available from the medical record. The subject will be escorted to the MRI suite where they will be fitted with a ¹²⁹Xe transmit-receive vest coil. They will then be positioned supine on the scanner bed. They will be coached about how to inhale HP ¹²⁹Xe from the dose delivery bags. Then the subject and bed will be moved into the scanner and they will undergo basic ¹H localizer and anatomical scans. Once localization is complete, subjects will undergo several MRI scans after inhalation of HP ¹²⁹Xe. 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. After completing the ¹²⁹Xe portion of the scan, the ¹²⁹Xe coil will be removed and patients fitted with a torso array ¹H coil. They will then undergo a free-breathing ultra-short-echo time ¹H MRI to delineate lung structure. This completes the MRI exam, after which subjects will be free to go home or continue with their standard clinical care. Altogether, the procedures will take approximately 3-4 hours.

5. Selection of Subjects:

We propose to recruit and consent 10 subjects with known PAH, 10 subjects with isolated left heart disease, 10 subjects with isolated lung disease (either chronic obstructive pulmonary disease or interstitial lung disease) and 5 patients with CTEPH, followed by 92 subjects undergoing or having undergone an evaluation for PAH over the course of this research. These subjects will undergo an approximately hour long comprehensive MRI protocol, including hyperpolarized ¹²⁹Xe administration. No subject will be excluded from the study on the basis of gender or ethnicity. Female subjects of childbearing potential will undergo pregnancy testing at study entry, and before each procedure. Informed consent will be obtained before a subject begins any study.

Definition of PAH: Mean PA pressure ≥ 25 mmHg with PCWP ≤ 15 mmHg and PVR ≥ 3 WU in the absence of significant left heart disease, lung disease, chronic pulmonary embolism, hemolytic anemia, sarcoidosis and cancer.

Definition of isolated left heart disease: Any of the following:

- 1) A mean PA pressure ≥ 25 mmHg with PCWP > 15 mmHg and PVR < 3 Woods units at right heart catheterization.
- 2) LVEF $\leq 40\%$ with mild or less RV enlargement and dysfunction on echocardiogram.
Evidence of diastolic dysfunction (as assessed by expert reader) with mild or less RV enlargement and dysfunction on echocardiogram.

Definition of isolated lung disease: A mean PA pressure < 25 mmHg at right heart Cath AND/OR an estimated right ventricular systolic pressure of < 40 on echocardiography AND/OR no diagnosis of heart

failure or pulmonary hypertension IN THE SETTING OF obstruction ($FEV1/FVC < 0.7$) on pulmonary function testing AND/OR radiographic evidence of lung disease.

Definition of CTEPH: Subjects with a history of a mean PA pressure ≥ 25 with evidence of chronic thromboembolic disease on imaging studies. Images may be obtained before and/or after pulmonary thrombendarterectomy (PTE) surgery for removal of blood clots from the lungs.

Inclusion criteria

1. Outpatients of either gender, age > 18
2. Willing and able to give informed consent and adhere to visit/protocol schedules. (Consent must be given before any study procedures are performed)
3. Women of childbearing potential must have a negative urine pregnancy test. This will be confirmed before participation in this investigational protocol.
4. Either have a diagnosis of PAH, isolated left heart disease or lung disease (chronic obstructive pulmonary disease or interstitial lung disease) or CTEPH using established clinical criteria.
5. Patients undergoing right heart catheterization for evaluation of PAH or other cardiac or pulmonary disease for MRI scans

Exclusion criteria

1. Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements
2. Conditions that will prohibit MRI scanning (metal in eye, claustrophobia, inability to lie supine)

6. Subject Recruitment & Compensation:

Patients will be recruited based on predetermined inclusion/exclusion criteria. They will be recruited in the pulmonary and cardiology clinics and inpatient services at Duke by their 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.

After informed consent is obtained, potential subjects will be screened to determine if they satisfy all inclusion and exclusion criteria. If subjects agree to participate, they will be consented into the study by the clinical coordinator in a private room. All potential subjects will be given a description of the procedures, have the opportunity to read the consent form, and to ask any questions. All subjects are free to decide whether or not to participate. It will be made clear to all subjects that their decision to participate or decline, will in no way affect their medical care. For all subjects, informed consent will be documented by having the patient sign a standard research consent form approved by the Duke IRB.

Dr. Driehuys is founder and chief technology officer of Polarean, Inc. a start-up company that seeks to commercialize hyperpolarized ^{129}Xe 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.

7. Consent Process: see Section 14 of the e-IRB submission form.

8. Subject's Capacity to Give Legally Effective Consent: Subjects without capacity to give consent will not be recruited into this study.

9. Study Interventions:

Hyperpolarized xenon will be administered in multiple doses in volumes up to 25% of subject TLC followed by a breath hold of up to 15 seconds. Subsequent ^{129}Xe doses will only be administered once the subject is ready to proceed. Hyperpolarized ^{129}Xe MRI will be used to acquire one or all of the following data:

1. ^{129}Xe calibration dose to test coil tuning and loading in each subject to permit optimal setting of imaging parameters.
2. ^{129}Xe distribution after inhalation and breath-hold as an indicator of regional pulmonary ventilation.
3. ^{129}Xe signal dissolved in the pulmonary interstitial spaces and capillary blood as an indicator of pulmonary gas exchange.
4. ^{129}Xe spectroscopy to follow the dynamics of gaseous and dissolved-phase ^{129}Xe .
5. Any of these ^{129}Xe exams may be repeated if deemed necessary by the study team.
6. Conventional ^1H MRI will be used to provide anatomical reference scans, as well as pulmonary perfusion. These will include some or all of the following:
7. 3-Plane Localizer
8. A variety of breath-hold 3D ^1H MRI scans to delineate the thoracic cavity
9. Free-breathing UTE ^1H MRI to image tissue density and edema

Study Visit Schedule

Protocol Activities	Screening (V0)	Study Visit (V1)	Study Visit ($^6\text{V2}$) only for CTEPH subjects)	Follow Up/Release (after last dose)	Follow-up contact w/in 24 hr
Informed Consent	X				
History re: Disease	X				
Medical History	X				
Pregnancy Test ¹	(X)	(X)	(X)		
MRI Screening ² Form	X	(X)	X		
Imaging Session ³ .		X	X		
Pulmonary Function Testing ⁴	(X)	(X)			
Adverse Events ⁵		X		X	X
Vital Signs Assessment with optional non-invasive, optical Hemoglobin measurement	X	X	X	X	

¹ for women of child bearing potential, a urine pregnancy test will be performed on the day of the MR examination. The test must be negative before MRI. The pregnancy test will be conducted and interpreted by study personnel who have completed competency training from the Duke Office of Clinical Research (DOCR).

² An MRI screening form will be completed at the screening session and will be verified prior to starting the imaging session. If a MRI is performed on a different day from the screening session, subject will need to complete a new MRI screen form.

³The MRI session will be conducted on the CAMRD research MRI scanner. Hyperpolarized ^{129}Xe is produced and delivered by the study team. Macrocyclic contrast agents are available at the scanner.

During the 1-hr MRI session, a qualified medical professional (MD, DO, PA, LNP, RN, RT or MT) will be on hand to monitor subjects during MRI and note any symptoms related to xenon MRI or contrast administration.

⁴ PFTs may not be acquired if subjects are undergoing scans for technical development purposes only or have such data available in their medical record.

⁵ Based on the known pharmacokinetics of xenon, no additional effects are expected after subject is released from the imaging study. However, subjects will be contacted 24 hours after their participation to enable them to report any additional effects or events.

⁶ Subjects will CTEPH will be ask to return for a second MRI. The second MRI will done post-surgically.

10. 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 ^{129}Xe 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 ^{129}Xe without oxygen. This is necessary to preserve good image quality, because O_2 is paramagnetic and depolarizes the HP ^{129}Xe . Administration of a single anoxic 1-liter breath has been well tolerated by subjects undergoing both ^3He and ^{129}Xe MRI because for a single breath, the residual oxygen in the subject's lungs is sufficient to maintain blood O_2 saturation during the breath-hold. Numerous studies have now been published demonstrating the safety and tolerability of hyperpolarized ^{129}Xe MRI.

Hyperpolarized ^{129}Xe 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 ^{129}Xe 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 ^{129}Xe 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. All MRI will be conducted in the presence of a qualified healthcare professional trained and certified in the American Heart Association's Advanced Cardiac Life Support (ACLS) training. This individual will be present in the MRI suite during ^{129}Xe administration and will monitor all aspects of the subjects well-being 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 de-identified 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.

11. Costs to the Subject:

There are no additional costs to the subject for the MRI examination. Subjects will be compensated \$100.00 for travel/parking and time for each study visit via a ClinCard. This does not include the screening visit.

12. Data Analysis & Statistical Considerations:

Sample size

Our sample size calculation is based on testing whether the proposed diagnostic test based on Xe MRI has accuracy comparable to imaging diagnostic procedures in clinical practice, such as mammography. To this end, we propose to test the hypotheses H₀: AUC = 0.72 vs. H₁: AUC > 0.85, where AUC is a summary measure of diagnostic accuracy obtained as the area under the receiver operating characteristic (ROC) curve which displays the tradeoff between sensitivity and specificity for our proposed Xe MRI based diagnostic test. Here AUC = 0.72 represents a moderately accurate test while AUC = 0.85 represents accuracy comparable to clinical mammography. Based on a one sided, one sample test with variances approximated using the binormal model, we estimate a minimum sample size of 46 normals and 46 with disease will be required to test the above hypotheses at a significance level of 5% with 80% power.

Correlation

Our preliminary Xe MRI studies on patients with PAH, in combination with our previous experience with normals as well as those with other diseases, have helped us formulate quantitative metrics based on Xe MRI studies with high diagnostic potential for PAH. These metrics include the proportion of voxels with low RBC/Gas transfer and the amplitude of the wave seen in Xe MRI based spectroscopy. In Aim 2, our goal is to identify a combination of these metrics which optimally correlates with the current diagnostic standard for PAH which is based on measurements obtained from right heart catheterization, in a training set of 30 patients with and without the disease. The optimal combination will be obtained using discriminant analysis, in which the Xe MRI based metrics will be used as predictors and the diagnosis obtained from right heart catheterization as outcome. To identify the optimal combination and associated thresholds, we will consider all possible combinations of predictors, as well as a variety of discriminant analysis techniques, such as linear discriminant analysis and support vector machines. To avoid optimistic bias from overfitting, we will use leave out one cross validation to obtain an unbiased estimate of prediction error in the training set, which will be used to rank the most predictive discriminant rules. The actual diagnostic accuracy will be evaluated on a separate validation set of 92 patients in Aim 3.

13. Data & Safety Monitoring:

All of the protocols in this proposal trial will be approved by Institutional Review Boards and reviewed periodically (every 12 months). Furthermore, all protocols are submitted as part of our investigational new drug application (IND# 109,490). 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 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.

14. 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.